An emerging double-edged sword role of ferroptosis in cardiovascular disease (Review)

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Abstract. The pathophysiology of cardiovascular disease (CVD) is complex and presents a serious threat to human health. Cardiomyocyte loss serves a pivotal role in both the onset and progression of CVD. Among various forms of programmed cell death, ferroptosis, along with apoptosis, autophagy and pyroptosis, is closely linked to the advancement of CVD. Ferroptosis, a mechanism of cell death, is driven by the buildup of oxidized lipids and excess iron. This pathway is modulated by lipid, amino acid and iron metabolism. Key characteristics of ferroptosis include disrupted iron homeostasis, increased peroxidation of polyunsaturated fatty acids due to reactive oxygen species, decreased glutathione levels and inactivation of glutathione peroxidase 4. Treatments targeting ferroptosis could potentially prevent or alleviate CVD by inhibiting the ferroptosis pathway. Ferroptosis is integral to the pathogenesis of several types of CVD and inhibiting its occurrence in cardiomyocytes could be a promising therapeutic strategy for the future treatment of CVD. The present review provided an in-depth analysis of advancements in understanding the mechanisms underlying ferroptosis. The present manuscript summarized the interplay between ferroptosis and CVDs, highlighting its dual roles in these conditions. Additionally, potential therapeutic targets within the ferroptosis pathway were discussed, alongside the current limitations and future directions of these novel treatment strategies. The present review may offer novel insights into preventive and therapeutic approaches for CVDs.

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Contents

1. Introduction

Cardiovascular disease (CVD) is a leading cause of mortality worldwide, accounting for >50% of deaths related to noncommunicable diseases, according to the World Economic Forum (1). It has been estimated that by 2030, CVD will be responsible for >22.2 million deaths annually worldwide. Furthermore, the American Heart Association estimates that 1.1 trillion dollars will be devoted to managing CVD by 2035 (2). As a major public health challenge, CVD is characterized by high mortality rates and escalating healthcare expenditures, underscoring the importance of understanding its underlying mechanisms and identifying therapeutic targets. Regardless of the specific pathways involved, cardiomyocyte damage in CVD ultimately results in cell death.

CVD is associated with several cell death mechanisms, including ferroptosis, pyroptosis and autophagy (3,4). Ferroptosis, first proposed by Dixon *et al* (5), represents a unique form of cell death, distinct from apoptosis, autophagy and necroptosis, with defining morphological, biochemical and immunological characteristics governed by specific regulatory genes or proteins. Morphologically, it is marked by mitochondrial shrinkage, increased density of the double-layered membranes and the loss of mitochondrial crests. Biochemically, the depletion of glutathione reduces the activity of glutathione peroxidase 4 (GPX4), impairing the breakdown of lipid peroxides. Consequently, divalent iron converts lipids into reactive oxygen species (ROS), triggering ferroptosis. In immunological contexts, damage-associated molecular patterns (DAMPs) release pro-inflammatory mediators such as HMGB1 (high mobility group box 1). Genetic research has focused on mutations that regulate iron metabolism and lipid degradation (5,6). Excess iron accumulation leads to irreversible tissue damage and organ failure (7). Ferroptosis is primarily characterized by oxidative damage caused by mitochondrial dysfunction, driven by iron-dependent lipid peroxidation (8). The mechanisms of

ferroptosis are closely linked to physiological processes such as iron, amino acid and lipid metabolism.

Ferroptosis is a key contributor to the development and progression of CVD (9,10). Evidence indicates that ferroptosis significantly influences the progression of various CVD types (3,4,9,10). The present review aimed to offer a succinct overview of the molecular mechanisms underlying ferroptosis and its relevance to CVD. Therapeutic strategies designed to inhibit ferroptosis have been reported to be effective in protecting cardiomyocytes from cell death. Furthermore, the present review highlighted novel perspectives on the potential for emerging clinical treatments that target ferroptosis specifically within the cardiovascular system.

2. Molecular mechanisms of ferroptosis

Several signaling molecules and metabolic pathways are involved in the regulation of ferroptosis. The present review highlighted the key aspects of iron, amino acid and lipid metabolism that drive the progression of ferroptosis (Fig. 1).

Lipid metabolism and ferroptosis. The uncontrolled peroxidation of lipids is a hallmark of ferroptosis (11), with lipid-ROS-induced membrane damage serving a central role in this process (5). Polyunsaturated fatty acids (PUFAs) in their free form and PUFA-containing membrane phospholipids (PUFA-PEs) are highly susceptible to peroxidation due to their unique molecular structure, making them particularly prone to oxidative damage (12). Peroxidation can be triggered either by enzymatic activity or non-enzymatic autoxidation. Lipid peroxides are primarily generated through lipoxygenases (LOXs), key enzymes in this process. Simultaneously, iron promotes non-enzymatic lipid autoxidation via the Fenton reaction (13-15).

Lipid peroxidation catalyzed by enzymes. Arachidonic acid (AA) and adrenic acid (ADA), two PUFAs present in membrane lipids, are precursors of PUFA-PE (16,17). Lysophosphatidylcholine acyltransferase 3 (LPCAT3) and acyl-CoA synthetase long-chain family member 4 (ACSL4) are key enzymes involved in phospholipid biosynthesis (18). ACSL4 acylates PUFAs to produce PUFA-acyl-coenzyme A (PUFA-CoA), which LPCAT3 then re-esterifies to form PUFA-PEs through their reaction with phosphatidylethanolamines (PEs). LOXs further oxidize PUFA-PEs into harmful lipid hydroperoxides, such as PE-AA-OOH and PE-ADA-OOH. Peroxidation predominantly occurs in plasma membranes and the endoplasmic reticulum (ER), where ACSL4 is most active (17). ACSL4, a critical regulator of PUFA-CoA production, serves as a marker for ferroptosis susceptibility (18). Knockdown of ACSL4 reduces PUFA-PE synthesis and prevents RSL3-induced ferroptosis. Additionally, thiazolidinediones, such as Rosiglitazone and Troglitazone, may inhibit ACSL4, protecting cells from ferroptosis-associated damage (19). LOXs, as non-heme iron-dependent dioxygenases, contribute to ferroptosis by oxygenating membrane PUFAs (20).

Lipid peroxidation mediated by autoxidation. The autoxidation process can be divided into three fundamental stages (21). The initiation phase begins with the abstraction of a bisallylic hydrogen atom from PUFA chains in phospholipid bilayers, generating a carbon-centered radical. This radical then reacts with oxygen to form a peroxyl radical, which, in turn, propagates the chain reaction by reacting with another substrate molecule. In the termination phase, two peroxyl radicals combine to form an alcohol, a carbonyl molecule and oxygen, although this process competes with the ongoing propagation reactions. During the Fenton-like reaction, lipid alkoxyl or hydroxyl radicals can be produced through the one-electron reduction of lipid hydroperoxides. Ferrous iron or other redox-active metals can serve as the reductant for this process. The progression of these free-radical-mediated reactions accelerates ferroptosis by compromising membrane integrity. The intense lipid oxidation disrupts ion balance within the cell, leading to reduced membrane flexibility, increased permeability and the formation of protein-based pores. Lipid peroxidation byproducts such as malondialdehyde and 4-hydroxynonenal are particularly harmful to cells (22). Typically, GPX4 mitigates oxidative damage by reducing lipid hydrogen peroxides, which are produced during cellular metabolism, into lipid alcohols. However, lipid metabolism imbalances that result in excessive accumulation of lipid hydrogen peroxides directly diminish GPX4 activity, further exacerbating ferroptosis.

Iron metabolism and ferroptosis. Iron is a vital nutrient for humans, is primarily involved in synthesizing hemoglobin and myoglobin and serves a key role in various physiological processes, including mitochondrial respiration, intracellular enzymatic activities and oxygen transport and storage (23). Imbalances in iron metabolism can disrupt these processes, leading to pathological conditions. A strong connection exists between ferroptosis and iron-dependent lipid peroxidation. The body sources most of its iron from an individual's dietary intake or through the natural breakdown of red blood cells during the aging process. Transferrin (TF) binds extracellular Fe^{3+} to form TF-Fe^{3+}, which is then absorbed by cells through transferrin receptor 1 (TFR1). Inside the cell, Fe^{3+} is released from endosomes by divalent metal transporter 1 (DMT1) after being reduced by six-transmembrane epithelial antigen of prostate 3 and enters the cytosol (24,25). Ferroportin 1 facilitates the release of Fe^{2+} from ferritin molecules. When the balance between iron absorption, utilization and recycling is disrupted, ferroptosis is triggered. This occurs as free Fe^{2+} reacts with hydrogen peroxide, generating highly reactive lipid peroxides that drive the process of ferroptosis (25). Several proteins and regulatory factors involved in iron metabolism contribute to ferroptosis. TFR1, which serves a critical role in iron transport, increases cellular iron uptake and sensitivity to ferroptosis when upregulated by hypoxia-inducible factor-1 and iron regulatory protein (IRP). Limiting iron intake can prevent ferroptosis (26). In cases where TFR1 is absent, the metal cation transporter solute carrier family 39 member 14 can also facilitate iron entry into cells, leading to ferroptosis (27). Additionally, autophagy and ferroptosis are closely interconnected. Nuclear receptor coactivator 4 (NCOA4) serves a key role in breaking down ferritin through a process known as ferritinophagy. This mechanism helps maintain intracellular iron homeostasis by regulating the degradation of ferritin (28). However, when NCOA4 mediates ferritin autophagy, cells

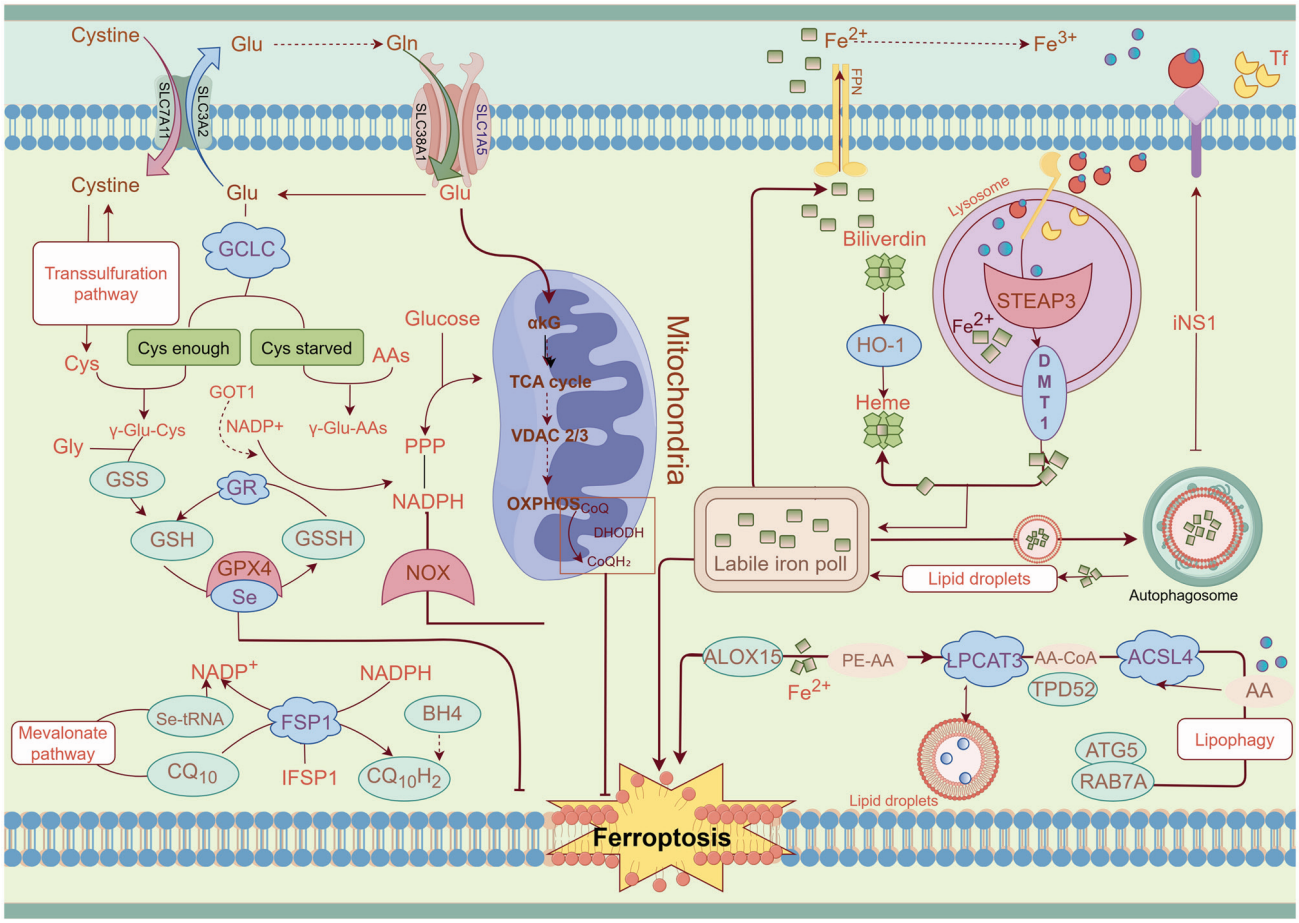

Figure 1. Molecular mechanisms underlying ferroptosis. The primary molecular pathways encompass iron metabolism, amino acid metabolism and lipid metabolism. The pointed arrows represented activation of the process. The flat-head arrows represented the inhibition of the process. AA, arachidonic acid; ACSL4, acyl-coa synthetase long chain 4; ALOX15, 15-lipoxygenase; DMT1, divalent metal transporter 1; Erastin, ferroptosis inducer; FSP1, ferroptosis suppressor protein1; FPN, ferroportin; Glu, glutamate; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSH, glutathione disulfide; Gln, Glutamine; HO-1, heme oxygenase 1; IPP, isopentane pyrophosphate; LPCAT3, lysophosphatidyl acyltransferase 3; NCOA4, nuclear receptor coactivator 4; PE, phosphatidylethanolamine; PUFA, polyunsaturated fatty acid; ROS, Reactive Oxygen Species; SLC3A2, Solute transporter family 3 members 2; SLC7A11, Solute transporter family 7 member 11; SLC1A5, Solute transporter family 1 member 5; SLC38A1, Solute transporter family 38 members 1; SystemXc-, The cystine/glutamate antiporter system; STEAP3, six-transmembrane epithelial antigen of the prostate 3; SAT1, spermidine/spermineN1acetyltransferase 1; Tf, transferrin; TFR1, transferrin receptor 1; VDAC, voltage-dependent anion channel.

become more prone to ferroptosis due to the increased release of free iron (29). Mitochondrial iron transport is regulated by CDGSH iron sulfur domain 1 (CISD1) and CISD2. Suppression of CISD1 enhances erastin-induced ferroptosis and iron-dependent mitochondrial lipid peroxidation (30). Similarly, inhibition of CISD2 increases mitochondrial Fe^{2+} levels and lipid ROS, further accelerating sulfasalazine-induced ferroptosis (31). These findings underscore the pivotal role of iron metabolism in regulating ferroptosis.

Amino acid metabolism and ferroptosis. L-g-glutamyl-L-cysteinylglycine, commonly known as glutathione (GSH), is a tripeptide found in nearly all cells of the body (32). The synthesis of GSH is catalyzed by γ-glutamylcysteine synthetase, which converts glutamate and cysteine into γ-glutamylcysteine. GSH serves a critical role in protecting cells from ferroptosis by converting potentially harmful lipid hydroperoxides, generated during cellular metabolism, into less toxic lipid alcohols (33,34). GSH exists in two forms: Reduced glutathione and oxidized glutathione disulfide (32). There are several pathways for GSH synthesis. Of these pathways, one method involves the enzyme glutathione reductase, which uses NADPH to reduce glutathione disulfide to its active form, NADH. Another method involves synthesizing GSH from intracellular cysteine, glycine and glutamate with the help of specific enzymes (35,36). Cysteine is essential for GSH synthesis and can be acquired through methionine production via the transsulfuration pathway or through exogenous cysteine uptake. The Xc complex (also known as System Xc^-), a glutamate-cystine antiporter composed of solute carrier family 3 member 2 and solute carrier family 7 member 11 (SLC7A11), is responsible for importing cystine into cells, which is then reduced to cysteine. Glutaminase 2 converts glutamine to glutamate, while transporters, such as solute carrier family 38 member 1 and solute carrier family 1 member 5, import glutamine into cells. The primary role of GSH in cells is to neutralize potentially toxic lipid hydrogen peroxides by converting them into less toxic lipid alcohols, thereby preventing oxidative damage (37).

Research into the amino acid metabolic pathways regulating ferroptosis has typically focused on key components such as GPX4 and cysteine. The availability of cysteine is

regulated by multiple pathways, with significant attention given to the role of SLC7A11 (37). In HT-1080 fibrosarcoma cells, overexpression of SLC7A11 was found to increase resistance to ferroptosis, while its knockdown made cells more susceptible to ferroptosis (38). The tumor suppressor gene p53 also serves a critical role in regulating ferroptosis, metabolism and neurodegeneration, with its effects depending on tissue type and genotoxic stress levels (39-41). By downregulating SLC7A11, p53 can inhibit cystine uptake through the system Xc^- transporter, reducing cellular antioxidant capacity, increasing lipid ROS and inducing ferroptosis. Another key regulator of lipid peroxidation and ferroptosis is nuclear factor erythroid 2-related factor 2 (Nrf2), which controls genes involved in iron metabolism and oxidative stress, such as heme oxygenase-1 (HO-1) and quinone oxidoreductase 1 (NQO1). The Nrf2-HO-1 axis enhances cellular resistance to ferroptosis by upregulating system Xc^- expression. Additionally, p62 prevents Nrf2 degradation, allowing Nrf2 to accumulate and further protect against ferroptosis. Knockdown of p62, NQO1, HO-1 and ferritin heavy chain 1 through RNA interference exacerbates erastin-induced ferroptosis (42,43). The p53/p21 axis also delays ferroptosis by reducing GSH consumption, although more research is needed to clarify how p21 promotes GSH production (44). Erastin impairs cystine uptake through system Xc^-, leading to decreased GSH levels and reduced GPX4 activity, which weakens cellular antioxidant defenses, increases lipid ROS and induces ferroptosis. Furthermore, Ras synthetic lethal 3 (RSL3) directly inhibits GPX4 enzymatic activity, exacerbating ferroptosis.

Mitochondria and ferroptosis

Voltage-dependent anion channels (VDACs) mediate ferroptosis. VDACs are ion channels formed by porin proteins located on the outer mitochondrial membrane (45). These channels serve a pivotal role in regulating the exchange of ions and metabolites, such as respiratory substrates, ADP and phosphate, between the cytosol and mitochondria (46). In the open state, VDACs permit the entry of these critical molecules into the mitochondria, facilitating cellular respiration. However, when VDACs are closed, this transport is inhibited. Microtubulin can regulate mitochondrial metabolism and ion transport by obstructing VDACs, leading to reduced mitochondrial function and a subsequent decrease in ROS production. Paradoxically, this mechanism enhances mitochondrial metabolism, reduces glycolysis and increases ROS levels (47-49). Further research has shown that reducing the expression of VDAC2 or VDAC3 via RNA interference confers resistance to erastin and alters cell membrane permeability (50). Erastin-induced ferroptosis is linked to the opening of VDACs, which results in diminished glycolysis and elevated ROS generation, causing mitochondrial oxidative stress (51).

ER stress response with ferroptosis. In eukaryotic cells, the ER serves a pivotal role in protein synthesis, folding, assembly and transport, as well as maintaining calcium homeostasis and cholesterol synthesis (52). Misfolded or unfolded proteins can accumulate within the ER under stress conditions, such as inflammation, hypoxia, glucose deprivation and oxidative stress, triggering the unfolded protein response (UPR) and inducing ER stress. The UPR is a protective mechanism aimed at restoring normal protein folding or initiating cell death if stress persists. A previous study showed that erastin and Sorafenib, in addition to their effects on ferroptosis in HT1080 cells, also activated the ER stress response (53). A critical factor linking ER stress to ferroptosis is activating transcription factor 4 (ATF4), which regulates genes involved in amino acid metabolism and antioxidant defenses and is expressed across various human tissues (54-57).

Other pathways that regulate ferroptosis. Recent studies have identified ferroptosis suppressor protein 1 (FSP1) as a potent anti-ferroptosis factor, independent of the glutathione pathway (58,59). Following myristoylation, FSP1 localizes to the plasma membrane, where it functions as an oxidoreductase, converting NADPH to coenzyme Q10, which acts as a lipid-soluble antioxidant (58,59). Coenzyme Q10 helps inhibit ferroptosis by neutralizing lipid peroxidation in cell membranes. Fin56, a type 3 ferroptosis inducer, promotes ferroptosis partly by depleting coenzyme Q10, which serves as an endogenous ferroptosis inhibitor (60). Additionally, it has been reported that doxorubicin (DOX) may trigger FSP1 translocation in the heart by inducing lipid peroxidation products (61). However, the specific role of FSP1 in cardiac tissue remains poorly understood. Conditional deletion of Fsp1 in mice could provide further insights into the underlying mechanisms of its function in the heart.

3. Ferroptosis: A double-edged sword in CVD

Pathogenic role of ferroptosis in CVD. A concise overview of the link between ferroptosis and various CVDs was summarized (Fig. 2).

Atherosclerosis (AS). Ferroptosis has been implicated in several CVDs, including AS, a lipid metabolism disorder characterized by inflammation, smooth muscle proliferation, endothelial dysfunction and the formation of foam cells and lipid plaques. Pro-inflammatory processes in AS are closely tied to ferroptosis, which is also associated with altered blood iron levels. During ferroptosis, excess iron catalyzes the Fenton reaction, leading to the production of lipid ROS. These ROS oxidize low-density lipoprotein (LDL), contributing to lipid deposition, foam cell formation and endothelial dysfunction. This cascade ultimately weakens endothelial function, enhances white blood cell adhesion and increases the vulnerability of plaques, promoting new blood vessel growth within the plaques and even causing intraplaque hemorrhaging (62). Iron overload is a key factor in the early development of AS, damaging endothelial mitochondria and altering macrophage phenotypes. Iron-catalyzed free radical reactions oxidize LDL in endothelial and smooth muscle cells, exacerbating the progression of AS. Furthermore, iron excess and foam cell formation are commonly seen as central to AS pathology. According to Xiao *et al* (63), iron ions accelerate AS by generating free radicals, which induce endothelial cell apoptosis and oxidize LDL, promoting macrophage uptake.

Kiechl *et al* (64) reported a correlation between higher serum ferritin levels and an increased risk of carotid AS development. In apolipoprotein E (ApoE)-deficient mice fed a high-fat diet, ferroptosis, characterized by iron-dependent lipid peroxidation, contributes to AS. Suppressing iron levels

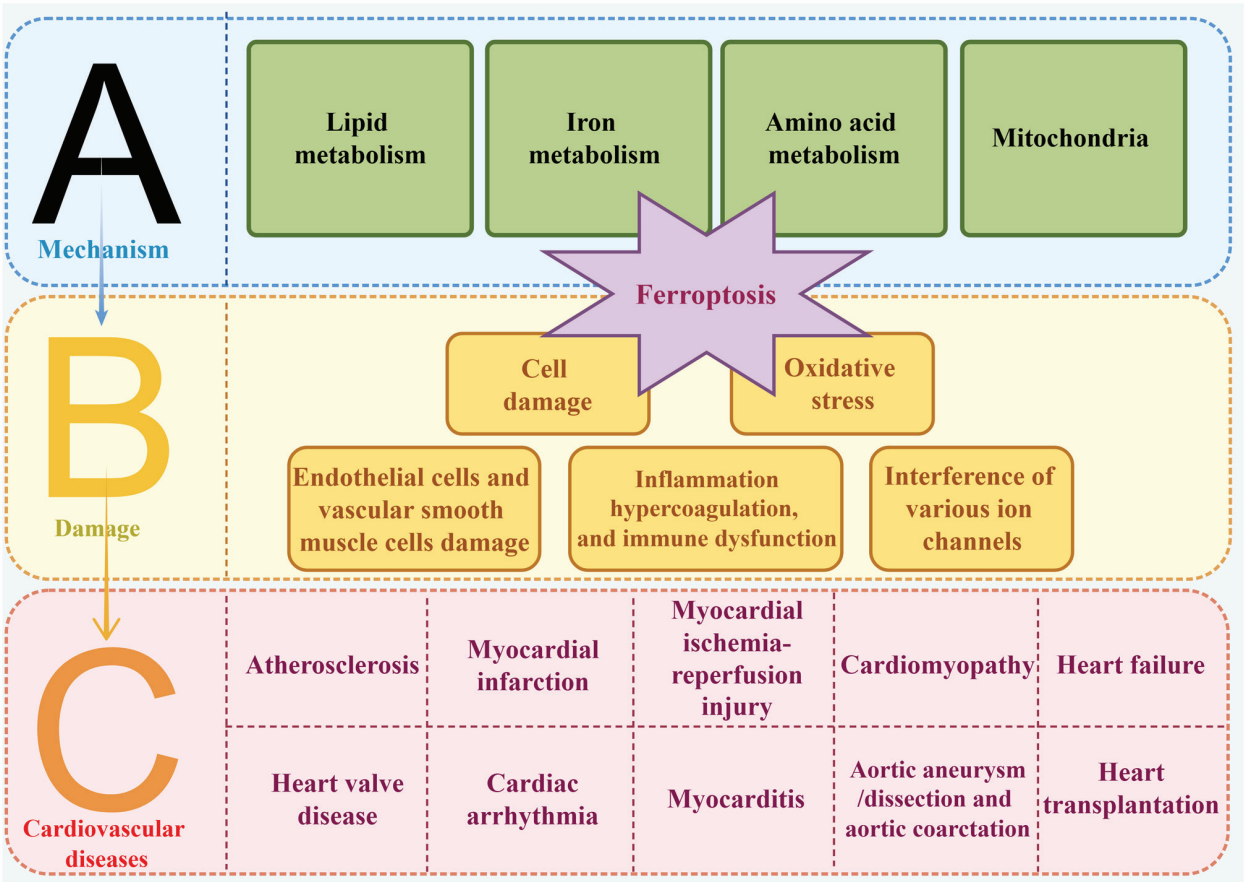

Figure 2. A pathogenic role of ferroptosis in cardiovascular disease. (A) Molecular mechanisms of ferroptosis. (B) Pathological changes caused by ferroptosis. (C) Cardiovascular diseases associated with ferroptosis-induced pathological changes.

has been shown to reduce lipid peroxidation and improve small artery endothelial function impaired by LDL, restoring cell viability and inhibiting both ferroptosis and arteriosclerosis progression. Moreover, dietary iron intake has been linked to increased inflammatory marker production. Hou (65) reported that glycolysis serves a role in the polarization of M1 macrophages in response to iron load, which accelerates AS by promoting inflammation and enhancing glycolysis. In experiments comparing $ApoE^{-/-}$ mice with normal ferruginous acid levels to iron-loaded $ApoE^{-/-}$ FPNwt/C326S mice, the latter group experienced significantly worsened AS, indicating that iron overload may contribute to AS progression. Iron accumulation in the tunica media of arteries is associated with plaque formation, oxidative stress in blood vessels and impaired vascular function. Endothelial dysfunction is closely linked to ferroptosis, with the activation of the p53-xCT (the substrate-specific subunit of system Xc^-)-glutathione (GSH) axis serving a pivotal role in inducing ferroptosis in endothelial cells, thereby contributing to endothelial dysfunction (66).

Myocardial infarction (MI). MI is a leading cause of death among individuals with CVDs. In a mouse model of MI, proteomic analysis revealed a significant reduction in GPX4 protein levels, a change strongly associated with increased lipid peroxidation and ROS accumulation. These processes are central to the onset of ferroptosis, which primarily occurs during the early and middle phases of MI. To counteract this, the Nrf2 pathway is activated, serving as a defense mechanism to inhibit ferroptosis (67). Cardiomyocytes from mice with mTOR knockdown displayed elevated ROS production and increased cell death. Conversely, cardiomyocytes with enhanced mTOR expression showed resistance to ferroptosis when exposed to erastin or RSL3. The upregulation of TfR1 and ferroportin in mice with mTOR overexpression indicates that ferroptosis is mitigated by maintaining intracellular iron balance, suggesting that targeting this pathway could offer a novel therapeutic approach for MI (68). Furthermore, exosomes derived from human umbilical cord blood mesenchymal stem cells were administered to mice following MI, effectively preventing cardiomyocyte death from ferroptosis and reducing heart damage. Detailed analysis showed that these exosomes targeted DMT1 and delivered microRNA (miR)-23a-3p, which inhibited ferroptosis, offering a promising potential treatment for MI (9).

Myocardial ischemia-reperfusion injury. Apoptosis, necrosis and autophagy-related cell death have typically been considered the primary contributors to the pathophysiology of ischemia/reperfusion (I/R) injury (69). However, previous studies suggest that processes occurring during I/R, such as the release of ROS leading to lipid peroxidation (70) and the accumulation of intracellular iron (71), are closely linked to ferroptosis. Researchers have observed elevated levels of ACSL4, a key marker of ferroptosis, in the hearts of rats after I/R or hypoxia-reoxygenation. Furthermore, a study reported that ferroptosis can be inhibited by treatments such as iron

chelation with desferrioxamine or by blocking glutamine metabolism (72). A previous study confirmed that ferroptosis serves a significant role in cardiac I/R injury (73), emphasizing its importance in this context.

Several studies have focused on uncovering the exact mechanisms by which ferroptosis contributes to I/R injury. First, ferroptosis occurs at specific phases of the I/R process. A previous study reported that ferroptosis is most prominent during reperfusion, as interventions targeting ferroptosis primarily reduce reperfusion-related damage but do not significantly affect ischemia-related injury (74). The distinct characteristics of the ischemia and reperfusion phases explain this difference in cell death mechanisms. While ischemia-induced cell death follows a certain pattern, reperfusion of ischemic tissue triggers a significant surge in ROS production, which is referred to as the oxidative burst. This phase of reperfusion is more strongly linked to ferroptosis and is characterized by lipid peroxidation, as the oxidative burst can exacerbate I/R injury (75). Thus, the reperfusion phase is more closely associated with ferroptosis compared with the ischemic phase. Ferroptosis also contributes to I/R injury due to its role in inducing ER stress (ERS). ERS triggers apoptosis through mechanisms involving p53 upregulated modulator of apoptosis and C/EBP homologous protein (CHOP) binding and its activation has been linked to ferroptosis (76). The interaction between ERS and ferroptosis can be explained in three phases. First, ERS frequently occurs alongside ferroptosis. Ferroptosis inducers can trigger the UPR, which activates the eukaryotic translation initiation factor 2 α kinase 3 (PERK)/eukaryotic translation initiation factor 2α/ATF4/CHOP pathway, leading to ERS. Upon activation, PERK dimerizes in the cytoplasm, and the downstream CHOP molecules, upregulated by ATF4 translation, promote apoptosis and cellular damage (77). Second, ferroptosis may exacerbate ERS by affecting system Xc^-, a critical transporter involved in cystine import and glutathione synthesis, thus aggravating oxidative stress and ERS (53). Finally, ROS, produced during ferroptosis can initiate the ERS response (78). The generation of phospholipid oxidation products during ROS accumulation, as observed in intrarenal injury models, further supports this connection (60). In rats, CHOP-mediated ERS has been shown to contribute to I/R damage (53), indicating that ferroptosis-induced ERS may serve as a key link between ferroptosis and the exacerbation of I/R injury.

Cardiomyopathy. Cardiomyopathy is a progressive cardiac disorder with multiple causes, leading to a heightened risk of mortality. Recent advances have enhanced the understanding and classification of cardiomyopathy (79,80). According to the European Society of Cardiology, cardiomyopathy is defined as a condition in which the heart muscle exhibits structural and functional abnormalities that cannot be attributed to coronary artery disease, hypertension, valvular disease or congenital heart defects (79). The cardiomyopathies discussed in the present review were selected for their clinical significance and the wealth of currently published data. All forms of cardiomyopathy involve the loss of cardiomyocytes, with damaged tissue being replaced by non-contractile fibrotic tissue (80). This loss of cardiomyocytes leads to abnormal ventricular remodeling and, ultimately, heart failure.

Causes of cardiomyopathy. i) Chemotherapy-related cardiomyopathy. Anthracyclines, including DOX, daunorubicin, epothilone and idarubicin, are widely used in the treatment of cancers, such as breast cancer and leukemia (81). However, their clinical use is often limited by severe cardiotoxic side effects, including irreversible cardiomyopathy and heart failure (82). Ferroptosis, a regulated form of cell death, has been identified as a key mechanism of cardiomyocyte loss in models of DOX-induced cardiotoxicity. It has been shown that inhibiting ferroptosis significantly reduces DOX-induced cardiomyocyte death. Sequencing analysis showed that DOX increases free iron release and promotes cardiomyocyte heme degradation via the NRF2/heme oxygenase 1 (HMOX1) pathway, triggering ferroptosis (73). Mice pre-treated with iron chelators and then exposed to DOX-induced myocardial damage exhibit improved cardiac function compared with untreated controls (73). Additionally, the mitochondria-targeted antioxidant MitoTEMPO was found to effectively reduce DOX-induced cardiomyopathy (DIC) by preventing oxidative damage to mitochondria and inhibiting ferroptosis-induced cardiomyocyte injury (73). These observations suggest that mitochondria-specific Fe^{2+} chelators could offer a novel approach to treating DIC. Further studies highlight the role of mitochondrial GSH depletion in DOX cardiomyopathy. The outer mitochondrial membrane protein FUN14 domain containing 2 binds to and stabilizes the mitochondrial GSH transporter protein solute carrier family 25 member 11, regulating its stability and preventing ferroptosis (83). Melatonin, a potent mitochondrial antioxidant, has also been shown to protect against DOX-induced cardiotoxicity by modulating Yes-associated protein expression and suppressing ferroptosis (84). Protein arginine methyltransferase 4 (PRMT4), accelerates ferroptosis by inhibiting the NRF2/GPX4 pathway, thereby exacerbating DIC (85). In neonatal rat ventricular cardiomyocytes treated with DOX, researchers reported an elevated expression of methyltransferase 14, N6-adenosine-methyltransferase non-catalytic subunit (METTL14), a factor that induces ferroptosis by increasing TFR expression and suppressing miR-7-5p levels. Furthermore, the inhibition of miR-7-5p forms a positive feedback loop that enhances METTL14 expression, thereby promoting ferroptosis (86). These findings provide a deeper understanding of the molecular mechanisms underlying DOX-induced cardiotoxicity and suggest potential therapeutic targets to mitigate its effects.

ii) Radiation-induced cardiomyopathy. Radiation therapy (RT) is commonly used to treat solid tumors and hematologic malignancies (87), but it can lead to cardiovascular complications, particularly radiation-induced heart disease (RIHD) (88). A prevalent form of RIHD is radiation-induced cardiomyopathy, characterized by endothelial damage, myocardial fibrosis and long-term cardiac dysfunction (87). Previous studies reported that radiation can trigger various forms of cell death, including necrosis, autophagy and apoptosis (89,90). Subsequent research has identified vascular injury and endothelial dysfunction as key contributors to the development of radiation-induced cardiomyopathy (91,92), primarily due to the heightened sensitivity of endothelial cells to radiation (92).

Mechanistically, ROS are likely the main drivers of endothelial dysfunction and cell death following radiation

exposure (93-95). Radiation is reported to enhance ROS production by increasing the activity of NADPH oxidase 2 (NOX2) and NOX4 (87,96). Additionally, it has been reported that ionizing radiation leads to increased expression of ACSL4, a key enzyme that contributes to the initiation of ferroptosis (97). This upregulation heightens the susceptibility of PUFAs to oxidation, thereby promoting ferroptosis (98). Specifically, a dose of 2 Gy of radiation therapy has been shown to activate the cyclic GMP-AMP synthase-stimulator of interferon genes protein pathway in HCECest2 cells, which line the coronary arteries (99). Although patients may remain asymptomatic for nearly a decade following radiation treatment, radiation-induced cardiac fibrosis can still develop and be detected later (100).

iii) Septic cardiomyopathy (SCM). SCM, a form of myocardial dysfunction resulting from septic shock, can lead to severe outcomes such as heart failure or death. Recent studies suggest that ferroptosis exacerbates heart damage in patients with sepsis (101). Gong *et al* (101) used bioinformatics to identify cyclin dependent kinase inhibitor 1A, NFE-2 like BZIP transcription factor 2, RELA proto-oncogene, NF-κB subunit, prostaglandin-endoperoxide synthase 2 (Ptgs2) and Vim5 as key genes interacting with ferroptosis. Islet cell autoantigen 69 (ICA69), a major regulator of the inflammatory response, is also elevated in the hearts of lipopolysaccharide (LPS)-treated mice, along with markers of ROS and ferroptosis. Knockdown of ICA69 significantly reduced the expression of ferroptosis markers, suggesting ICA69 as a potential therapeutic target for septic cardiomyopathy (102).

iv) Coronavirus disease 2019 (COVID-19)-related cardiomyopathy. The global outbreak of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been associated with numerous cardiovascular complications, including chest pain, myocarditis, palpitations, stress cardiomyopathy, postural tachycardia, arrhythmias and MI (103-107). SARS-CoV-2 can inhibit the production of certain selenoprotein mRNAs and reduce the activity of GPX4 in patients with COVID-19, thereby exacerbating oxidative stress (108). Additionally, the viral protein ORF3a recruits Kelch-like ECH associated protein 1 (Keap1) to degrade NRF2, diminishing the cell's oxidative stress defense and promoting ferroptosis (109). The virus can also activate ACSL4, further inducing ferroptosis, and inhibiting ACSL4 has been shown to reduce viral replication (110). This highlights ferroptosis as a potential therapeutic target for managing COVID-19. Notably, SARS-CoV-2 infection can trigger ferroptosis in sinoatrial node cells, leading to their dysfunction. Antiviral agents like iron chelators and tyrosine kinase inhibitors have demonstrated protective effects by reducing viral infection and ferroptosis-related damage (111,112).

v) Diabetic cardiomyopathy. Diabetic cardiomyopathy, characterized by myocardial fibrosis, hypertrophy and diastolic dysfunction, is primarily caused by insulin resistance, type 2 diabetes and hyperinsulinemia (113). Oxidative stress serves a significant role in the progression of diabetic cardiomyopathy (114). In diabetic retinopathy, ferroptosis has been identified as the primary cause of death in pigment epithelial cells, while autophagy provides a protective mechanism (115). Moreover, ferroptosis inhibitors have shown efficacy in preventing cardiomyocyte dysfunction induced by high glucose levels, indicating ferroptosis is a key driver in the development of diabetic cardiomyopathy (116). Curcumin, a natural antioxidant, has been found to mitigate heart damage caused by ferroptosis and improve cardiac function by promoting NRF2 nuclear translocation and increasing GPX4 and HO-1 levels (117). However, HO-1 activation, which involves the breakdown of heme to release ferrous iron, can elevate mitochondrial iron levels and enhance ferroptosis (118,119). Curcumin may also regulate ferroptosis by increasing ferritin and SLC7A11 levels and activating NRF2 to inhibit ferroptosis (120).

vi) Hypertensive cardiomyopathy. Hypertensive heart disease, which arises from prolonged, untreated hypertension, leads to structural and functional heart alterations and is a major contributor to heart failure. The apelin receptor, abundantly present in cardiac microvascular endothelial cells (CMVECs), interacts with its ligand, elabela. Angiotensin II (Ang II) significantly reduces elabela levels in rats. Elabela and ferrostatin-1 have been shown to mitigate myocardial remodeling and ultrastructural damage in Ang II-induced hypertension by enhancing xCT/GPX4 signaling and inhibiting IL-6/STAT3 signaling, which reduces iron content and lipid peroxidation in the heart. These reports suggest that elabela may slow the progression of hypertensive cardiomyopathy by blocking Ang II-induced ventricular remodeling and CMVEC ferroptosis (121).

vii) Sickle cell disease (SCD)-induced cardiomyopathy. SCD-induced cardiomyopathy is a complication of SCD characterized by excessive hemolysis (122). Ferroptosis serves a key role in the pathogenesis of this cardiomyopathy. The breakdown of heme by HMOX1 releases iron into the bloodstream, promoting ferroptosis. In an SCD mouse model, rising heme levels were correlated with increased ferroptosis markers and worsening cardiomyopathy. Notably, treatment with ferroptosis inhibitors improved cardiac function and previous research suggests that activating or inhibiting Hmox1 can respectively enhance or reduce cardiac ferroptosis (122).

viii) Hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy is another common cardiac complication that can progress to heart failure. In individuals with inherited hemochromatosis, the most frequent cause of death is heart damage resulting from iron overload, which is associated with cardiac hypertrophy and decreased left ventricular ejection fraction (123). In a hemochromatosis mouse model, researchers found that cardiac iron levels increased with age, suggesting iron deposition and oxidative stress (124). Ferroptosis is reported to contribute to heart enlargement in certain patients. A diet high in iron leads to reduced GSH levels and increased lipid peroxidation, causing significant heart damage and the development of hypertrophic cardiomyopathy. Treatment with ferrostatin-1 reversed these changes, suggesting the role of ferroptosis in ventricular hypertrophy (125). In cardiomyocytes exposed to Ang II, hypertrophy was induced by the downregulation of xCT mRNA and protein expression levels. Impairment of xCT function exacerbates the progression of heart hypertrophy and dysfunction. Compounds such as ferrostatin-1 and elabela have shown potential in reducing cardiac remodeling by inhibiting ferroptosis (121,126). Cardiac hypertrophy is also linked to dysfunction of the small blood vessels within the heart (127).

Interferon regulatory factor 3 (IRF3) inhibition promotes ferroptosis by downregulating SLC7A11 transcription. Conversely, docosahexaenoic acid enhances IRF3 expression, protecting endothelial cells from pressure overload. This suggests that increasing IRF3 levels may offer new therapeutic strategies for treating heart failure and ventricular hypertrophy (128). In both human and animal models of hypertrophic heart disease, apelin-13 injections increased mitochondrial iron deposition in the heart and upregulated the expression of NCOA4 and sideroflexin 1 (SFXN1). Apelin-13 was found to reduce cardiac hypertrophy and reverse mitochondrial iron overload by decreasing SFXN1 and NCOA4 expression. Furthermore, NCOA4 mediates autophagy and ferroptosis, which are crucial in the development of cardiac hypertrophy, and functions upstream of SFXN1 (129,130). Mice supplemented with iron exhibited increased iron accumulation in lung tissue, elevated pulmonary artery resistance and right ventricular hypertrophy. Losartan, an Ang II-1 receptor blocker, effectively prevented vascular remodeling, pulmonary hypertension and right ventricular hypertrophy caused by iron overload (131).

ix) Dilated cardiomyopathy. Dilated cardiomyopathy (DCM) is the most prevalent form of nonischemic cardiomyopathy, affecting ~1/2,500 individuals (132). Heart failure is a major symptom of this disease, and for those with severe DCM, heart transplantation often becomes the only viable treatment option (132,133). The causes of DCM can be genetic, with ~20-30% of cases linked to hereditary factors, while the majority arise from other forms of cardiomyopathy (134,135). Both genetic and non-genetic forms of DCM share pathways with hypertrophic cardiomyopathy, particularly in terms of mechanisms leading to ferroptosis (136).

x) Post-transplant cardiomyopathy. Heart transplantation offers a treatment option for severe heart failure, but transplant recipients face significant risks of both immediate and long-term complications, particularly graft degradation and failure. I/R injury is recognized as a primary contributor to graft dysfunction (GD) in the early post-transplant period (137). Sterile inflammation, driven by neutrophil-mediated tissue damage, is a key mechanism of GD (138,139). Neutrophil recruitment is triggered by the release of DAMPs from dead cells, which bind to Toll-like receptors (TLRs) on innate immune cells (139,140). Ferroptosis is thought to serve a pivotal role in this process, as it induces cardiomyocyte death and promotes the release of DAMPs (141). Research by Li *et al* (139) showed that the ferroptosis inhibitor Fer-1 reduced levels of hydroperoxy-arachidonoyl-PE and decreased both ferroptosis and cardiomyocyte death in a mouse heart transplantation model, suggesting that ROS are a key factor in cardiomyocyte death. Endothelial dysfunction, a defining feature of GD, is closely associated with cardiac allograft vasculopathy (CAV), a condition that affects the entire cardiac vasculature (142). Ferroptosis has been linked to endothelial dysfunction in CAV (143,144). A previous study reported that natural killer cells contribute to the development of CAV through a $CD8^+$ T-cell-mediated process (145). $CD8^+$ T-cells secrete IFN-γ, which can reduce SLC7A11 expression, thereby promoting ferroptosis (146). Post-transplant cardiomyopathy is a complex condition involving multiple pathways (147). While it is evident that ferroptosis contributes to the immune responses in post-transplant cardiomyopathy, further research is needed to fully understand the various mechanisms involved and to develop targeted interventions.

xi) Iron overload cardiomyopathy. Iron overload cardiomyopathy arises when excess iron accumulates in the heart muscle, leading to systolic or diastolic dysfunction (148,149). This condition is particularly common in patients with thalassemia and primary hemochromatosis. Early stages of iron overload cardiomyopathy typically show preserved systolic function; however, as the disease progresses, systolic dysfunction worsens and ventricular dilation occurs (149,150). Excess free iron in cardiomyocytes catalyzes the production of ROS, causing damage to intracellular lipids, proteins and DNA (151). Mitochondrial damage and oxidative stress occur as the mitochondria struggle to clear the excess iron effectively (152). Iron overload cardiomyopathy can develop when non-transferrin-bound iron enters cardiomyocytes through type I Ca^{2+} channels, competing with calcium ions. The increasing Fe^{2+} concentration further disrupts Ca^{2+} flow, leading to reduced contractile activity (153,154). Male and female mice exhibit differing risks for iron overload cardiomyopathy as males were less affected by iron overload and females benefitted more from the iron injection treatments (155). This finding could have considerable consequences in clinical practice. First, it highlights the importance of considering sex as a biological variable when assessing patient risk for iron overload cardiomyopathy. Female patients may inherently be at lower risk for developing this condition, even under conditions of iron overload, which could influence diagnostic algorithms and preventive strategies. Conversely, male patients may require more vigilant monitoring and earlier intervention to mitigate the development of cardiomyopathy. Secondly, the observed sex-specific differences in response to iron injection treatments suggest that therapeutic approaches may need to be tailored to the patient's sex. In female patients, who appear to be protected from iron-overload cardiomyopathy, treatments aimed at reducing iron levels might need to be less aggressive to avoid potential side effects without conferring significant additional benefit. By contrast, male patients, who are more susceptible, may require more robust iron-reducing therapies to effectively manage their risk of developing cardiomyopathy. Finally, the identification of estrogen as a potential protective factor against iron-overload cardiomyopathy opens new avenues for therapeutic intervention. Estrogen replacement therapies or estrogen-mimetic drugs could be explored as potential treatment options for male patients or for postmenopausal female patients who may no longer benefit from their estrogen levels. Additionally, understanding the molecular mechanisms underlying the protective effects of estrogen could lead to the development of novel therapies that target these pathways, providing new strategies to prevent and treat iron overload cardiomyopathy in both sexes (156).

Heart failure. Heart failure (HF) represents the final stage of many CVDs, often linked to disturbances in iron metabolism, whether it be deficiency or overload. Iron homeostasis in the heart requires ferritin H, and its absence disrupts this balance. Conversely, overexpression of Slc7a11, which increases GSH levels, protects against cardiac ferroptosis in ferritin H-deficient animals, suggesting a critical role for ferritin H in preventing HF (125,157). Additionally,

research has identified that adipose tissue macrophages release miR-140-5p in their extracellular vesicles, which may contribute to obesity associated with a high-fat diet. miR-140-5p targets SLC7A11, reducing GSH production and promoting ferroptosis in cardiomyocytes (158). Further studies by Chen *et al* (130) using bioinformatics analysis revealed a connection between ferroptosis, autophagy, TLR4 and NOX4. TLR4 binding to NOX4 triggers the production of superoxide anions, hydrogen peroxide and cardiomyocyte ferroptosis. In heart failure models, knockdown of TLR4 and NOX4 expression using small interfering RNA lentivirus reduced cardiomyocyte death and improved ventricular remodeling by delaying the onset of autophagy and ferroptosis. This suggests that the TLR4-NOX4 axis is a potential therapeutic target for treating heart failure (130). The primary mechanisms leading to heart failure following an I/R injury are ventricular remodeling and the eventual development of cardiac fibrosis, both of which are closely related to ferroptosis and autophagy. These findings underscore the importance of targeting pathways involved in oxidative stress and ferroptosis to prevent or treat heart failure.

Heart valve disease. The heart valves serve a critical role in protecting the electrical conduction system from the laminar shear stress caused by blood flow. However, hemodynamic abnormalities, such as those caused by hypertension or extreme stress, can lead to extracellular matrix injury and the rupture of the basement membrane. These issues, along with reduced laminar stress and increased mechanical strain, can contribute to valve damage. A common consequence of valve injury is lipid infiltration at the damaged basement membrane, leading to the formation of dispersed lipid deposits beneath the endothelium. These lesions are often accompanied by high levels of oxidized LDL and the presence of activated inflammatory cells (159). Pathological calcification of the valve is frequently associated with the accumulation of ROS (159). Iron likely contributes to oxidative stress, which is linked to calcification in both the valves and blood vessels. Ferroptosis, a type of cell death driven by iron-dependent lipid peroxidation, may be involved in calcification-associated valve degeneration, particularly in cases involving intraleaflet hemorrhage (ILH), abnormalities in iron metabolism and ROS production. ILH and interstitial iron deposition can lead to inflammation in valve tissue and promote the development of osteogenic cells, which contribute to calcium accumulation in the valve. In degenerative aortic stenosis, ILH is a recognized risk factor for valve calcification (160) and a previous study has reported that the extent of calcification correlates with iron accumulation (161). Heme iron has been shown to catalyze oxidative damage to DNA, proteins and lipids through Fenton and Haber-Weiss reactions, which generate ROS (162). Moreover, the Nrf2/HO-1 axis serves a regulatory role in ferroptosis during heart valve calcification (163). Nrf2 regulates several oxidative processes, and under normal conditions, it is ubiquitinated and degraded upon binding to the Keap1 protein. However, changes in the redox state stabilize Nrf2, allowing it to enter the nucleus and regulate gene transcription related to oxidative stress (164).

Cardiac arrhythmia. Atrial fibrillation (AF) is a prevalent arrhythmia that has been linked to a significant number of clinical deaths. The incidence of AF has doubled over the past 50 years (165). Several pathogenic factors contribute to AF, including the potential activation of ferroptosis. For example, heavy and frequent alcohol consumption has been linked to increased AF incidence, partly by triggering ferroptosis. However, ferroptosis inhibitors have shown the potential to reduce AF risk (166), indicating that ferroptosis serves a role in AF progression. Suppression of ferroptosis has been found to reverse AF-related changes in various models, whereas activation of ferroptosis significantly increased susceptibility to AF in endotoxemia models, fast atrial pacing canines and mice with chronic iron overload (167-169). Additionally, patients with beta thalassemia, who experience cardiac iron deposition, have a higher incidence of AF (170). In these individuals, iron chelators may help prevent AF. Overall, ferroptosis inhibitors represent promising therapeutic targets for the prevention and treatment of AF across a range of health conditions.

Myocarditis. Sepsis-induced myocarditis is closely linked to ferroptosis, with LPS commonly used to model toxemia. LPS triggers inflammatory pathways in cardiomyocytes, leading to oxidative stress and apoptosis, which ultimately result in cardiac damage (171). LPS elevates NCOA4 expression and increases intracellular Fe^{2+} levels. This rise in cytoplasmic Fe^{2+} further enhances the presence of SFXN1 on the mitochondrial membrane, facilitating Fe^{2+} transfer into mitochondria, promoting ROS production and leading to mitochondrial iron accumulation (24). Additionally, LPS stimulates Ptgs2 production and raises lipid ROS levels, processes inhibited by Fer-1 and dexrazoxane (172). While Fer-1 alleviates LPS-induced cardiomyocyte damage, erastin and sorafenib exacerbate it. Excessive iron accumulation, linked to immune dysregulation, inflammation and hypercoagulability, is also reported to serve a significant role in the pathogenesis of COVID-19 (173). Evidence of myocardial lipid peroxidation in a patient with COVID-19 suggests ferroptosis may contribute to the cardiac damage associated with the virus (174). These findings suggest that targeting ferroptosis could represent a promising therapeutic approach for preventing and managing myocarditis.

Aortic aneurysm/dissection and aortic coarctation. Abdominal aortic aneurysms (AAAs) are characterized by progressive segmental aortic dilation, thinning of the aortic wall, and eventual rupture (175). As the diameter of the artery increases, the risk of rupture escalates (176). Age is another key factor, with the likelihood of vasodilation, AAA formation and rupture increasing over time and rupture leading to death in up to 90% of cases (177). A critical pathological feature of AAA is the loss of vascular smooth muscle cells (VSMCs) in the medial artery wall (178). VSMCs are particularly vulnerable to smoking-induced cell death, which is exacerbated by lipid peroxidation and depletion of GSH. Ferroptosis, a form of regulated cell death, has been identified as a potential therapeutic target for preventing AAA, as inhibitors of ferroptosis can protect VSMCs from smoking-induced damage (179). Neutrophils contribute to AAA development through the release of neutrophil extracellular traps (NETs), which carry bactericidal proteins. Elevated levels of NET markers have been detected in the bloodstream of patients with AAA. Research indicates that NETs promote AAA progression by inducing ferroptosis in VSMCs through suppression of the PI3K/AKT pathway. Notably, extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) can inhibit the release of

NETs, making MSC-EVs a promising therapeutic target for AAA treatment (180). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, widely used to lower cholesterol, may also influence AAA progression. Bioinformatics analysis of human AAA tissue revealed an upregulation of PCSK9 expression, negatively correlated with GPX4, suggesting that PCSK9 could promote ferroptosis by regulating lipid metabolism (181).

Aortic dissection (AD), a severe and often fatal vascular condition, is characterized by degeneration of the medial aortic wall, including the death of smooth muscle cells (SMCs) and rupture of elastic fibers (182). AD occurs when the intima and lining of the aorta are damaged, leading to the formation of true and false lumens. Studies have shown decreased expression of SLC7A11, GPX4 and FSP1 in the aortic tissues of individuals with Stanford type A AD, reinforcing the association between AD and ferroptosis (182). Methylation of m6A RNAs, regulated by the enzyme methyltransferase-like 3 (METTL3) (183), has been linked to many CVDs. In human aortic smooth muscle cells, METTL3 promotes ferroptosis by suppressing SLC7A11 and FSP1 expression. In mice with METTL3 knockdown, aortic degeneration and Alzheimer's disease progression are slowed (182). BRD4770 (a histone methyltransferase G9a inhibitor), when administered to a mouse model of Alzheimer's disease, reduced AD progression by decreasing inflammatory cell infiltration and preventing ferroptosis in SMCs (184).

Heart transplantation. The outcomes for individuals with late-stage HF have significantly improved with the global rise in heart transplantation (HT). However, new challenges have emerged, particularly I/R injury, which causes aseptic inflammation and leads to complications. Primary graft dysfunction, resulting from I/R injury, accounts for difficulties and mortality in up to 28% of patients who underwent a heart transplant (185). It has been reported that using ferroptosis inhibitors may enhance post-transplant prognosis by mitigating I/R injury. Studies confirm that this process is distinct from necrosis, with Fer-1 shown to improve outcomes following HT (139). Similar protective effects were observed in animal models of myocardial I/R, where inhibiting ferroptosis improved recovery after coronary artery ligation. In a multicenter clinical study involving 103,299 heart transplants from 1982 to 2011, cardiac allograft vasculopathy (CAV) was identified as the leading cause of graft failure and mortality, affecting between 20-65% of transplant recipients (186). CAV primarily stems from endothelial dysfunction due to allograft damage. Ferroptosis, a key contributor to endothelial cell dysfunction, is linked to damage across the cardiac vascular system, including intimal thickening and plaque formation (142,187). Consequently, using ferroptosis inhibitors during heart transplantation may reduce inflammation and improve patient outcomes.

A protective role of intervention based on ferroptosis in cardiovascular disease. Ferroptosis, characterized by iron accumulation, lipid peroxidation and inflammation, serves a key role in various CVDs. Therefore, inhibiting ferroptosis represents an effective therapeutic strategy for treating cardiac disorders associated with this form of cell death. Various substances and treatments that target ferroptosis were summarized (Fig. 3).

Therapies targeting for excess iron. Iron homeostasis and quantity within cells are regulated by mRNA-binding proteins IRP1 and IRP2. Patients with conditions such as hereditary hemochromatosis often undergo chelation therapy to manage excess iron. The Food and Drug Administration (FDA) has approved three iron chelators for removing iron from the heart: deferasirox, deferiprone and deferoxamine (DFO) (188). DFO, a non-toxic chelator, is commonly used to treat beta thalassemia and other iron overload disorders. Studies have shown that DFO-treated mice exhibit reduced ROS in cardiomyocytes, while patients with coronary heart disease experience improved endothelium-dependent vasodilation (189-191). In patients recovering from thalassemia and undergoing bypass surgery, Paraskevaidis *et al* (192) reported enhanced heart function following DFO treatment. In another previous study aimed at preventing I/R injury in perfused hearts, Jiang *et al* (72) combined L-glutamine, a glutaminase inhibitor, with DFO, demonstrating the protective effects of chelators and ferroptosis inhibitors by lowering iron levels. Additionally, the FDA-approved iron chelator dexrazoxane protects patients with cancers from DOX-induced cardiotoxicity, primarily by inhibiting ferroptosis (73). A novel iron chelator, MitoFerroGreen, has shown promising cardioprotective effects in mice treated with DOX, further highlighting the potential of iron chelation strategies to mitigate ferroptosis-related heart damage (193). These findings underscore the therapeutic potential of iron chelators and ferroptosis inhibitors in protecting against heart injury in various clinical contexts.

Antioxidants. Ferroptosis, a form of cell death driven by the oxidation of phospholipids, can be mitigated by introducing compounds that inhibit this oxidation process. Liproxstatin-1, a member of the lipophilic radical-trapping antioxidants, effectively halts the spread of lipid peroxyl radicals and reduces myocardial infarction and I/R injury. This compound has demonstrated significant efficacy in ferroptotic models (194). Another approach to chemically counteract lipid peroxidation involves deuterium substitution at the bis-allylic carbon of PUFAs. Deuterated PUFAs have been shown to suppress ferroptosis effectively, while monounsaturated fatty acids have also been identified as potent inhibitors, suggesting a promising therapeutic strategy (195). Omega-3 fatty acids, known for their cardioprotective properties, have been linked to a 25% reduction in cardiovascular events, further supporting their potential in improving cardiovascular outcomes (196).

Statins, such as fluvastatin, lovastatin and simvastatin, are widely used to lower blood cholesterol by inhibiting the enzyme HMG-CoA reductase, which regulates cholesterol synthesis. In addition to lowering cholesterol, statins also block the production of isopentyl pyrophosphate in the mevalonate pathway, leading to reduced synthesis of selenoproteins such as GPX4 and coenzyme Q10. This disruption promotes ferroptosis in MSCs, indicating that statins may indirectly influence ferroptosis-related cardiovascular conditions (197,198). Nucleotide pyrophosphatase 2, a lipid kinase, has been shown to reduce the generation of ROS and protect cardiomyocytes from erastin-induced ferroptosis (199). GSH, a key antioxidant, is essential for preventing ferroptosis. A previous clinical study has suggested that GSH

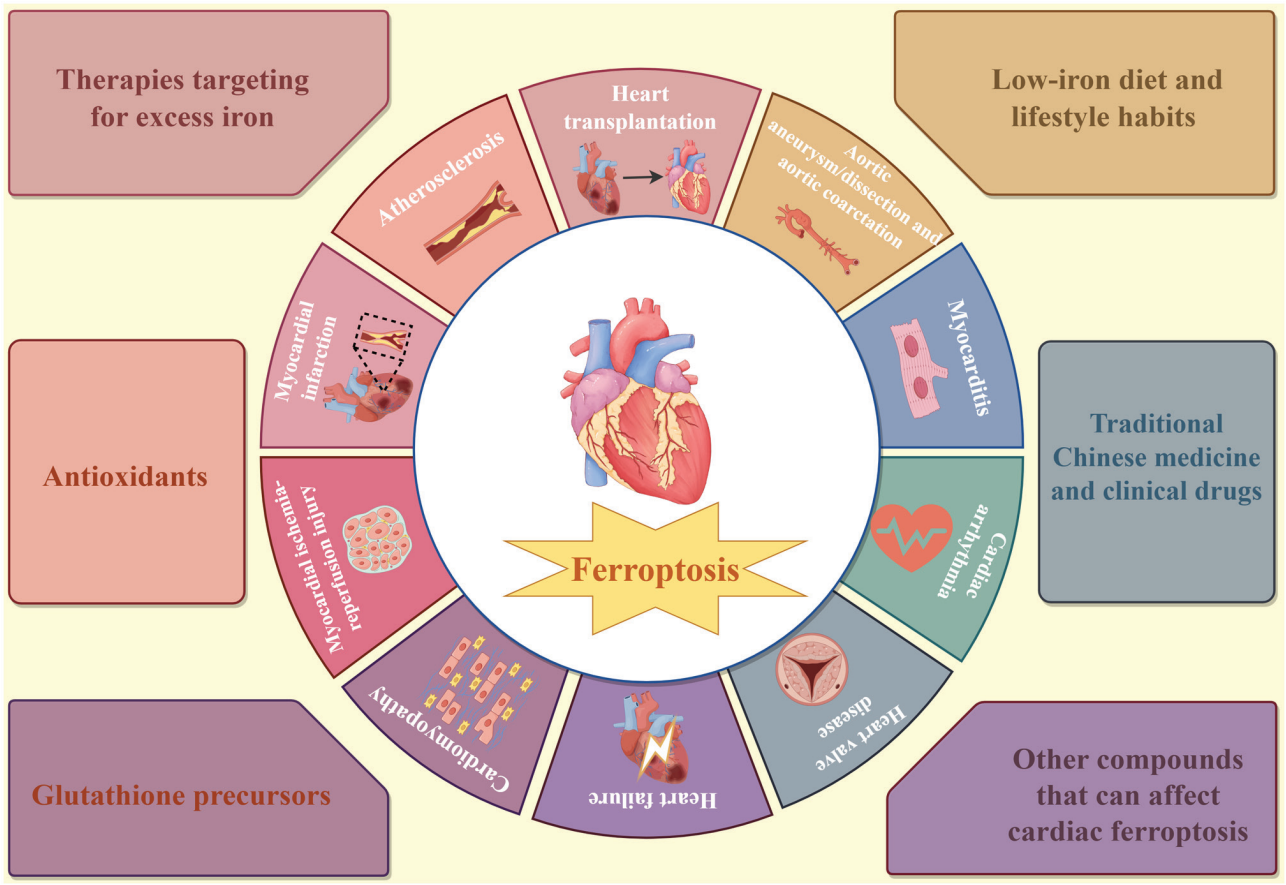

Figure 3. Protective role of interventions based on ferroptosis in cardiovascular disease.

supplementation, along with thiol compounds, improves endothelial dysfunction by enhancing nitric oxide (NO) activity (200). Antioxidant-rich natural compounds, including vitamins, have been found to inhibit ferroptosis and exert cardioprotective effects (201). Specifically, vitamin E may protect against atherosclerosis by preventing LDL oxidation, highlighting its role in reducing ferroptosis-related damage in CVDs (202-205).

Cystine, a key precursor for glutathione synthesis, is imported into cells by the system xc^- in its reduced form. *In vitro* studies have demonstrated that supplementing cell cultures with cystine or cysteine inhibits ferroptosis (72). To enhance cysteine bioavailability, N-acetyl cysteine (NAC) was developed, which has shown positive effects on heart function (206,207). Research on ferroptosis induced by cysteine depletion or system xc^- inhibition has demonstrated that NAC exhibits anti-ferroptotic properties (5,208). Another study found that NAC treatment reduced myocardial ischemia-reperfusion injury in diabetic rats, suggesting its potential for treating human cardiac conditions (209).

Fer-1, a potent ferroptosis inhibitor, reduces cell damage by suppressing ROS and has shown promise in the treatment of cardiovascular disorders (29). Fer-1 protects against myocardium damage in conditions such as septic cardiomyopathy and DIC (73,210). Additionally, Fer-1 has been linked to reduced total creatine kinase release and neutrophil recruitment following heart transplantation, further supporting its cardioprotective role (139). Another ferroptosis inhibitor, liproxstatin-1 (LIP-1), has demonstrated potential cardioprotective effects by reducing the expression of voltage-dependent anion channel 1, thereby preserving mitochondrial integrity and mitigating myocardial infarction severity (211). MitoTEMPO, a mitochondria-targeted superoxide scavenger, alleviates heart dysfunction and mitochondrial damage by reducing lipid peroxides, further highlighting the critical role of antioxidants in managing CVD (73). While these studies underscore the therapeutic potential of antioxidants like NAC, Fer-1, LIP-1 and MitoTEMPO in treating cardiovascular conditions, further research is necessary to clarify their full therapeutic applications and optimize their use.

Traditional Chinese Medicine (TCM) and clinical drugs. TCM has a history spanning nearly 2,000 years, emphasizes holistic balance and healing using a range of natural substances, including herbs, animal products, medicinal minerals and mineral extracts (212). TCM's multifaceted approach to disease treatment, particularly through the regulation of ferroptosis, has garnered interest in CVD research (213,214). The natural substances in TCM are reported to have a wide range of therapeutic targets and minimal side effects, making them potentially valuable for the study of future cardiovascular treatments (215).

TCM compounds can act as natural antioxidants and regulate ferroptosis. Notable examples include artemisinin (216), curculigoside (217), curcumin (117) and glycyrrhiza (218). These substances have been explored for their cardioprotective effects, given their ability to modulate ferroptosis pathways.

For instance, baicalin has been reported to enhance cell resistance to ferroptosis by inhibiting erastin-induced GPX4 degradation and suppressing ACSL4 expression (219). Other TCM compounds, such as betulinic acid and ginsenoside Rd, protect against I/R injury by reducing oxidative stress through the NRF2/HO-1 signaling pathway (220,221). Resveratrol has also demonstrated cardioprotective effects by upregulating GPX4 and ferritin heavy chain (FTH) (222).

The QiShenYiQi dripping pill (QSYQ) has been recommended by Cao *et al* (223) for the treatment of ischemic heart disease due to its ability to enhance blood circulation and alleviate discomfort. In a mouse model of MI, QSYQ has been shown to prevent ferroptosis by reducing mitochondrial ultrastructural damage, promoting mitochondrial biogenesis and maintaining dynamic homeostasis (224). Additionally, it upregulates the naringenin-NRF2/System Xc-/GPX4 axis, suppressing ferroptosis and protecting against I/R injury (225). The plant-based compound hederagenin (HDG) possesses a range of medicinal properties, including anti-inflammatory effects, cancer prevention, inhibition of cell death and protection against conditions such as gliomas and Alzheimer's disease (226). Zhao *et al* (226) demonstrated through molecular docking studies that HDG inhibits ALOX5, which in turn alleviates cardiac dysfunction caused by I/R injury by reducing oxidative stress and ferroptosis in cardiomyocytes.

Although progress has been made, further research is needed to understand how TCM regulates ferroptosis and other cardiovascular conditions. For example, the NAD^+-dependent class III histone deacetylase SIRT1 has shown potential in managing cardiovascular disorders (227,228). Fisetin, through the SIRT1/NRF2 pathway, has been shown to reduce DIC (229). Additionally, 6-Gingerol, a polyphenol from ginger extract, possesses antioxidant, anti-inflammatory and anti-apoptotic properties, and protects against DCM by blocking ferroptosis and reducing ROS via the NRF2/HO-1 pathway (230). Puerarin, commonly used in the treatment of CVDs, exhibits notable antioxidant properties (231). Additionally, it inhibits ferroptosis and decelerates the progression of heart failure by elevating the levels of FTH1 and GPX4, while simultaneously lowering LIP and ROS levels (232).

Low-iron diet and lifestyle habits. The average human body contains 3-5 g of iron under normal physiological conditions. Deviations from this range, whether due to iron deficiency or excess, can lead to adverse health outcomes (233). Notably, a review of cohort studies has indicated that the risk of death from CVDs rises with increased haem iron consumption, suggesting that reducing haem iron intake could help lower the risk of premature mortality from CVDs (234,235). Consequently, following a low-iron diet may be an effective preventive strategy against ferroptosis-related cardiovascular conditions. There is a link between frequent heavy alcohol consumption and an elevated risk of AF, compared with infrequent heavy drinking. Given that ferroptosis serves a role in alcohol-induced AF, inhibiting ferroptosis could potentially reduce AF vulnerability in these cases (166). Additionally, research has shown that Beclin1 haploinsufficiency improves contractile dysfunction and cardiac remodeling induced by acute ethanol exposure through a ferroptosis-mediated mechanism (236). In rat VSMCs, cigarette smoke extract (CSE) has been found to trigger key features of ferroptosis, such as lipid peroxidation, depletion of intracellular GSH and increased PTGS2 mRNA expression. A previous study reported that the use of iron chelators and specific ferroptosis inhibitors can completely prevent CSE-induced cell death in these cells (179). Moreover, cigarette tar accelerates atherosclerosis by promoting macrophage ferroptosis through the NF-κB-activated hepcidin/FPN/SLC7A11 pathway (237). Natural ferroptosis inhibitors, such as vitamin E, cyanidin-3-glucoside and baicalin, are found in a variety of fruits and vegetables (219,238). Therefore, lifestyle changes, including quitting smoking and excessive alcohol consumption, along with increased intake of fruits and vegetables, may help mitigate the risk of CVDs linked to ferroptosis.

Additional compounds affecting cardiac ferroptosis. Cardiac ferroptosis can be inhibited by several compounds that target mechanisms beyond those typically discussed. In mice, zinc protoporphyrin IX, a competitive inhibitor of HO1, reduces ferroptosis and DOX-induced iron accumulation in the heart by preventing haem breakdown and the release of free iron (73). Additionally, compound 968, an inhibitor of glutaminolysis, has been shown to reduce cardiac I/R injury *in vitro* by limiting glutamine availability, which is essential for cysteine deprivation-induced ferroptosis (72). Another protective agent, P22077, inhibits ubiquitin-specific protease 7, activates p53 and subsequently lowers TFR1 levels, thereby suppressing ferroptosis and protecting the heart from I/R damage (239). Dexmedetomidine, an α2-adrenergic receptor agonist used in clinical sedation, has been found to reduce sepsis-induced cardiac damage by upregulating the ferroptosis suppressor GPX4 (240). Puerarin, an isoflavone from kudzu root, has also been shown to mitigate pressure-induced heart failure in rats and protect cardiomyocytes from ferroptosis induced by erastin and isoprenaline (232). Moreover, atorvastatin has demonstrated potential in preventing hypertrophic cardiomyopathy by improving isoprenaline-induced ventricular dysfunction and remodeling through inhibition of ferritinophagy-mediated ferroptosis (241). Additionally, some commonly prescribed heart medications may possess previously unrecognized anti-ferroptotic effects. Carvedilol, widely used for treating hypertension and heart failure, has been found to inhibit ferroptosis (242,243), likely due to its capacity to scavenge lipid peroxides and bind iron (244).

4. Conclusions and future perspectives

CVD represents a significant threat to human health and longevity. Maintaining cardiac function and preventing heart failure depends largely on reducing cardiomyocyte death. Over the past decade, substantial experimental evidence has emerged indicating that ferroptosis, a regulated form of cell death driven by iron, serves a critical role in the progression of CVDs. Characterized by lipid oxidation, ferroptosis has been associated with various cardiovascular conditions and is increasingly viewed as a potential therapeutic target. Unlike other forms of cell death, ferroptosis is marked by the accumulation of intracellular iron, lipid peroxides and mitochondrial changes. However, the precise

mechanisms underlying many CVDs remain only partially understood, and current knowledge of ferroptosis is insufficient to develop comprehensive treatment strategies. Furthermore, multiple pathways of regulated cell death, including ferroptosis, are often interconnected rather than isolated. Greater clarity is required regarding the relationship between ferroptosis and other cell death mechanisms that have recently gained attention. Investigating these interactions could provide deeper insights into the progression of biological processes and lead to more effective therapeutic interventions. Empirical evidence has highlighted the potential of inhibiting ferroptosis as a novel therapeutic approach for a range of CVDs. Iron chelation therapy, in particular, shows promise for patients with iron overload-related cardiomyopathy. Encouraging preclinical results suggest that ferroptosis-specific antagonists could be developed for various clinical applications (72,73,193,240). Despite this potential, significant challenges remain in addressing both CVDs and ferroptosis concurrently. Research must prioritize uncovering the precise pathways linking ferroptosis to CVDs to identify new treatment targets. Moreover, the current body of clinical research involving human participants is limited, with most studies on ferroptosis and CVDs focusing on cellular or animal models. Additional clinical trials are essential to confirm the efficacy of ferroptosis inhibitors in treating CVDs. Furthermore, it is essential to explore the potential adverse effects of these inhibitors on other organs, as their long-term impact remains unclear. The relationship between ferroptosis and inflammation also requires further investigation. While ferroptosis can exacerbate inflammation and ROS production, these processes are not always harmful; in certain contexts, they may be benign or even beneficial. It is crucial to assess whether ferroptosis activators could be used to modulate inflammation or ROS levels in specific cases. Given the widespread use of anti-inflammatory drugs in CVD treatment, large-scale, multicenter clinical trials could establish a stronger link between ferroptosis modulation and inflammation management in cardiovascular therapy.

In the previous studies, Hong *et al* (245) reviewed the role of ferroptosis, a newly discovered form of programmed cell death characterized by iron-dependent lipid peroxidation, in cardiovascular diseases (CVDs). The aforementioned review discusses the mechanisms involved in ferroptosis, including iron metabolism disorder and lipid peroxidation and summarized the research progress on ferroptosis in CVDs, suggesting its potential as a therapeutic target for CVD prevention and treatment (245). Similarly, Chen *et al* (25) focused on the role of ferroptosis in CVDs, emphasizing the involvement of different organelles in regulating ferroptosis and the relationship between autophagy and ferroptosis. This review also discusses the specific mechanisms by which ferroptosis contributes to the development of CVDs and summarizes current research on ferroptosis-related pathway inhibitors and clinically beneficial cardiovascular drugs (25). Additionally, Fang *et al* (246) provided an in-depth review of the mechanisms and regulations of ferroptosis in CVDs, including its involvement in various cardiovascular conditions such as myocardial infarction, atherosclerosis, heart failure and I/R injury. The aforementioned review discussed the latest research on the role of ferroptosis in CVDs and its relationship with iron metabolism, lipid peroxidation and amino acid metabolism, aiming to provide new insights and treatment targets for CVDs (246). Based on the above articles, the present review provided a more comprehensive and updated review of ferroptosis in CVDs compared with the aforementioned previous reviews. The present review not only covered the basic mechanisms and regulations of ferroptosis but also delved deeper into the specific double-edged sword roles of ferroptosis in various CVDs, such as myocardial infarction, myocardial ischemia-reperfusion injury and hypertrophic cardiomyopathy, etc. Additionally, it discussed emerging therapeutic strategies targeting ferroptosis, including iron chelation therapy, antioxidants and other compounds that can affect cardiac ferroptosis. The present review also highlighted the potential of low-iron diets and lifestyle changes as preventive measures against ferroptosis-related CVDs. By evaluating the clinical potential of these strategies, the present review provided insights that could guide future research and clinical trials in this area. Important research gaps and future directions in the field of ferroptosis and CVDs were highlighted, and areas were identified where further investigation is needed. Additional clinical studies are required to validate the efficacy of ferroptosis inhibitors in human subjects. Overall, the present review offered a broader perspective on ferroptosis in CVDs and suggested novel therapeutic avenues for future research.

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SQ and CZ reviewed the literature and wrote the manuscript. CC and ZS collected and analyzed the existing data from the previously published research articles. YC reviewed and critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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