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Copper dyshomeostasis and cardiovascular disease: Molecular mechanisms and new strategies for targeted intervention with cuproptosis (Review)

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Abstract. Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide and their pathological mechanisms have remained a major focus of research. Notably, copper has an essential role in maintaining cardiovascular homeostasis and disruption of copper metabolism can lead to a range of pathological consequences. The present review summarizes the dynamic balance of copper metabolism, clarifies its regulatory network encompassing intestinal absorption, intracellular transport, tissue storage and excretion, and emphasizes the molecular associations between copper dyshomeostasis and CVDs, including atherosclerosis and stroke. Notably, cuproptosis, a newly identified mode of regulated cell death, provides novel insights into the role of copper-induced cell death in the cardiovascular system. Based on current research progress, the current review also discusses the value of therapeutics that target copper metabolism, such as copper chelators, ionophores and dietary interventions. Furthermore, key unanswered questions are identified, particularly those regarding the specific molecular pathways linking copper homeostasis to cardiovascular function.

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Abbreviations: AMI, acute myocardial infarction; α-LA, α-lipoic acid; AS, atherosclerosis; ATOX1, antioxidant 1; ATP7A, copper-transporting ATPase α; ATP7B, copper-transporting ATPase β; ATTM, ammonium tetrathiomolybdate; Aβ, amyloid-β; CAD, coronary artery disease; CCS, copper chaperone for superoxide dismutase; CHF, chronic heart failure; COX, cytochrome c oxidase; COX11, cytochrome c oxidase copper chaperone 11; COX17, cytochrome c oxidase copper chaperone 17; CP, ceruloplasmin; CTR1, copper transporter 1; CuO NPs, copper oxide nanoparticles; CVD, cardiovascular disease; DCM, dilated cardiomyopathy; DLAT, dihydrolipoamide S-acetyltransferase; DSF, disulfiram; ECM, extracellular matrix; EPCs, endothelial progenitor cells; FDX1, ferredoxin 1; Fe-S, iron-sulfur; GSH, glutathione; HF, heart failure; HFHC, high-fat, high-cholesterol; HIF-1, hypoxia-inducible factor 1; I/R), ischemia-reperfusion; IHF, ischemic heart failure; IMS, intermembrane space; LIAS, lipoic acid synthetase; MD, Menkes disease; MI, myocardial infarction; MT, metallothionein; mtETC, mitochondrial electron transport chain; ROS, reactive oxygen species; SCO, synthesis of cytochrome c oxidase; SOD1, superoxide dismutase 1; STZ, streptozotocin; TCA, tricarboxylic acid; TETA, triethylenetetramine; TGN, trans-Golgi network; TTM, tetrathiomolybdate; WD, Wilson disease

Key words: copper, CVD, copper metabolism, cuproptosis, copper chelator

Contents

1. Introduction

As a crucial trace element in the human body, copper serves an essential role in human pathophysiology. Copper is not only involved in hemoglobin synthesis, supporting the immune system and neurotransmitter biosynthesis, but also has powerful antioxidant properties, as well as being involved in the formation of bone and connective tissue (1). These physiological functions render copper vital for disease prevention and the maintenance of health. Copper exhibits dose-dependent dual effects on the cardiovascular system: i) Copper prevents cardiovascular diseases (CVDs) through antioxidant effects, protecting endothelial function and maintaining vascular connective tissue structure (2); ii) however, in CVDs, copper overload interferes with lipid metabolism, and leads to oxidative stress, mitochondrial dysfunction and endothelial cell dysfunction (3). Therefore, maintaining an appropriate intake of copper is essential to protect the heart and blood vessels.

In recent years, the discovery of cuproptosis, a newly identified form of copper-induced cell death, has provided novel perspectives for resolving the molecular associations between copper dyshomeostasis and CVDs. Tsvetkov *et al* (4) revealed that treatment of human cell lines (such as the lung carcinoma line A549 and the immortalized kidney line 293T) with the copper ionophore elesclomol induced cell death and that pharmacologically inhibiting all other known cell death pathways failed to inhibit elesclomol-induced cell death; this novel form of cell death was named cuproptosis. Furthermore, it has been demonstrated that copper ions can induce aberrant aggregation by targeting mitochondrial lipoylated proteins and, alongside the loss of iron-sulfur (Fe-S) clusters, trigger uncoupling of oxidative phosphorylation, ultimately leading to the collapse of cellular energy metabolism (4). Bioinformatics studies have revealed the extensive involvement of cuproptosis in the progression of CVDs (5-7).

The present review aimed to elucidate the dynamic balance of copper absorption-transportation-storage-excretion in the human body, and to outline the mechanism underlying the regulation of cuproptosis. Furthermore, the review summarizes the molecular pathways linking copper to CVDs, including atherosclerosis (AS) and heart failure (HF), and critically appraises the roles of copper chelators [such as tetrathiomolybdate (TTM) and triethylenetetramine (TETA)], copper ionophores (including elesclomol) and therapeutics developed based on cuproptosis in the treatment of CVDs, according to the progress of current research. The aim was to clarify the causal relationship between copper and CVD, and to inform the development of prevention and treatment strategies based on precise regulation of copper homeostasis.

2. Copper metabolism

Copper metabolism encompasses the absorption, distribution, storage, utilization and excretion of copper. These processes are essential for maintaining copper homeostasis, thereby supporting the physiological functions of copper. As shown in Fig. 1, copper metabolism involves multiple organs and systems, primarily including intestinal absorption, hepatic storage and release, and excretion through bile and urine. Abnormalities in any of these processes can result in disturbances in copper metabolism, thereby affecting health.

Copper absorption. In the body, the primary forms of copper are Cu^+ and Cu^{2+}, which account for 95 and 5% of the total intracellular and extracellular copper, respectively (8). Copper in the human body is primarily derived from dietary sources, and is absorbed in the duodenum and proximal small intestine (9,10). Copper transporter 1 (CTR1) is the main transport channel for Cu^+. Since most dietary copper is Cu^{2+} and is not directly translocated by CTR1, duodenal cytochrome b and STEAP reduce Cu^{2+} to Cu^+, which is subsequently transported into intestinal epithelial cells via CTR1. The transport activity of CTR1 is also affected by K^+ levels, extracellular pH and other factors (11-13). When CTR1 availability is limited, divalent metal transporter-1 may serve a compensatory role; together, they maintain intestinal copper absorption through an interdependent regulatory network (14). CTR1 expression is feedback-regulated in a copper-dependent manner; it is downregulated under copper overload and upregulated during copper deficiency (15). After entering the intestinal epithelium, Cu^+ is transported to the basolateral membrane via antioxidant 1 (ATOX1), then exits the intestinal epithelium via copper-transporting ATPase α (ATP7A) and enters the portal circulation, where it binds to soluble chaperones such as transcuprein, histidine, albumin and macroglobulin, thereby preventing the cytotoxic effects of free Cu^{2+}. It is then taken up and utilized by other tissues or organs (16). Recent evidence has suggested that zinc transporter protein 1 not only transports zinc out of cells but also functions in copper uptake (17).

Copper transportation and storage. In the cytoplasm, the transportation of copper is precisely regulated by a network of high-affinity copper chaperones (16). Copper enters the cell and forms complexes with reduced glutathione (GSH), metallothionein (MT), ATOX1 and copper chaperone for superoxide dismutase (CCS) (11,18). ATOX1, which is conserved across species, acquires Cu^+ from CTR1 through its classical metal-binding site (19) and subsequently transports Cu^+ via ATP7A and copper-transporting ATPase β (ATP7B) to the trans-Golgi network (TGN) for the synthesis of tyrosinase, lysyl oxidase and ceruloplasmin (CP), thereby sustaining copper homeostasis inside the cell (20-23). CCS, a copper chaperone protein, facilitates the transport of Cu to certain proteins, including superoxide dismutase 1 (SOD1), located in the cytoplasm and mitochondrial intermembrane space (IMS), thereby neutralizing mitochondria-derived superoxide radicals (24,25). Cellular copper levels inversely regulate CCS expression (26). Moreover, CCS modulates the localization of SOD1 between the IMS and cytosol in an oxygen-dependent manner, preserving the stability of reactive oxygen species (ROS) *in vivo*, thereby preventing oxidative damage caused by copper overload (27). In addition, CCS facilitates the transport of Cu^+ to mitogen-activated protein kinase 1, hence modulating its activity and influencing cellular proliferation (28). The delivery of Cu^+ to mitochondria primarily relies on the cytochrome c oxidase (COX) copper chaperone 17 (COX17), which facilitates copper transport into the IMS for COX synthesis. Additionally, the literature has indicated that copper can be transported to mitochondria through a non-proteinaceous anionic ligand (CuL) (29). COX comprises two core subunits, COX1 and COX2, which bind copper at the conserved Cu_B and Cu_A sites, respectively (16,30). Within the IMS, COX17 transfers Cu^+ to synthesis of COX (SCO)1 and SCO2 for the assembly of COX subunits. Cu^+ is subsequently conveyed to COX2, contributing to its structure; alternatively, it is transported by COX17 to the COX copper chaperone 11 (COX11) and then to COX1 for use in its assembly (12,31).

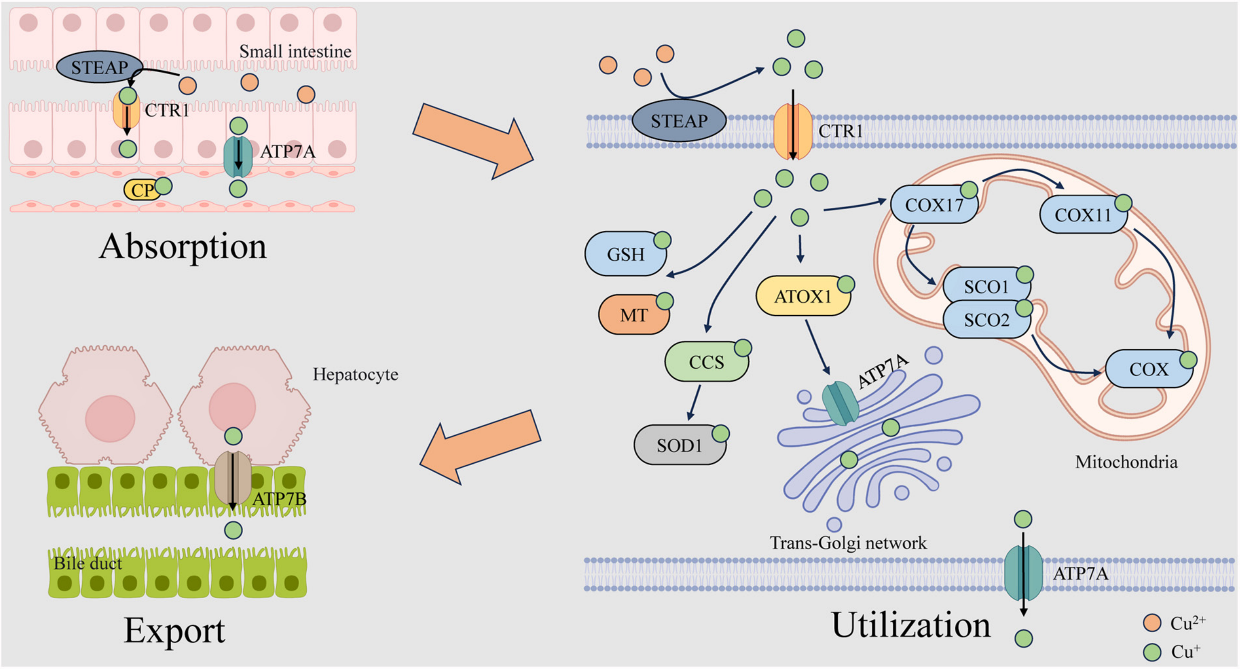

Figure 1. Dietary copper ions are absorbed into the bloodstream through the small intestinal epithelium, and transported to the liver and other tissues by binding to soluble chaperones. The absorption of copper ions is mediated by CTR1, while its excretion is co-regulated by ATP7A and ATP7B. Intracellular copper ions can form complexes with GSH and MT for storage, or be targeted to subcellular structures via specific chaperones (such as CCS, SOD1, ATOX1 and COX17) to participate in enzyme assembly. Ultimately, copper ions are excreted from the body through bile. CTR1, copper transporter 1; ATP7A, copper-transporting ATPase α; ATP7B, copper-transporting ATPase β; GSH, glutathione; MT, metallothionein; CCS, copper chaperone for superoxide dismutase; SOD1, superoxide dismutase 1; ATOX1, antioxidant 1; COX17/11, COX copper chaperone 17/11; COX, cytochrome c oxidase; SCO, synthesis of COX.

The liver serves as the main organ responsible for copper metabolism and storage within the human body. Upon reaching the liver, copper in the bloodstream is delivered to designated structures by copper chaperone proteins, including ATOX1, CCS and COX17. Excess copper is sequestered by MT and GSH for hepatic storage, thereby preventing cytotoxicity (16,32).

Copper excretion. Biliary excretion represents the principal pathway for hepatic copper elimination. ATP7A and ATP7B are the primary transporters of Cu^{+} within cells. Their regulatory roles in copper absorption and excretion depend largely on their subcellular localization (33,34). Under physiological copper concentrations, these ATPases predominantly localize to the TGN, where they transfer Cu^{+} into the TGN lumen (23). When intracellular copper rises, these transporters relocalize from the TGN to vesicular compartments, subsequently fusing with the plasma membrane to facilitate Cu^{+} export. Once homeostatic copper levels are restored, the transporters are recycled back to the TGN (35). ATP7A is widely expressed in most tissues and organs, excluding the liver, whereas ATP7B is primarily expressed in the liver (23). After being absorbed by the intestinal epithelium, copper is released into the bloodstream by ATP7A and thereafter enters the portal circulation, where it is absorbed by hepatocytes. It is then pumped into the TGN by ATP7B and delivered to the plasma membrane to form CP, and then secreted into the bloodstream through exocytosis. In cases of excessive copper accumulation, ATP7B is relocated from the TGN to the canalicular membrane of hepatocytes, facilitating the excretion of surplus copper from the cytoplasm into the bile and ultimately out of the body. Copper excreted into bile forms complexes with bile salts, preventing its intestinal reabsorption (34,36). Copper homeostasis in the body is maintained through absorption in the duodenum and small intestine, as well as excretion via the biliary system (37,38).

3. Copper homeostasis

Copper homeostasis refers to the tightly regulated balance among copper absorption, transport, storage and excretion (39). It is crucial for appropriate physiological processes, as it participates in enzyme activity, cellular respiration, iron metabolism, and the development and maintenance of nervous system function. Copper dyshomeostasis can result in oxidative stress, cellular damage and even illness, such as Wilson disease (caused by ATP7B mutations leading to copper accumulation) and Menkes disease (due to ATP7A deficiency causing systemic copper deficiency). An imbalance in copper homeostasis is a well-established clinical characteristic of these inherited disorders. Moreover, copper levels can serve as a predictive indicator for certain conditions; for example, elevated copper levels are associated with advanced stage and poor prognosis in prostate, bladder and renal cancers (11).

Copper homeostasis and disease. Copper homeostasis, largely governed by the transporters ATP7A and ATP7B, is essential for human health. Dysfunction of these two transporters may result in severe illnesses. Menkes disease (MD) results from mutations in the ATP7A gene. The dysfunction of ATP7A in intestinal epithelial cells results in copper accumulation inside these cells and a reduced transfer of copper into the bloodstream, culminating in a notable systemic copper deficit.

Patients present with characteristic clinical features, such as intellectual disability, hypothermia, neuronal degeneration, bone fractures, and anomalies of the hair, skin and vasculature (16). Wilson's disease (WD) results from mutations in the ATP7B gene. Impaired ATP7B function hinders the efficient elimination of Cu^+ from cells, causing persistent copper accumulation in the liver, brain and other tissues, which results in copper toxicity and organ damage in patients. Patients may present with hepatic manifestations, including acute liver failure, jaundice and chronic hepatitis, as well as neurological conditions, such as tremors, Parkinsonism, ataxia, dystonia, dysarthria, spasticity and a lack of motor coordination (16).

Copper dyshomeostasis is closely associated with the development and progression of numerous diseases. Emerging evidence has suggested that copper dyshomeostasis contributes to the pathogenesis of coronary heart disease. Furthermore, copper deficiency may result in myocardial diastolic dysfunction and a diminished β-adrenergic response, and can lead to HF. By contrast, copper overload disrupts the mitochondrial electron transport chain (mtETC), which contributes to HF by impairing the antioxidant defense, ROS accumulation and activation of ischemic/hypoxic signaling pathways via CP (40). Copper overload may result in vascular dysfunction by elevating nitric oxide generation and endothelial oxidative stress (41). Copper dyshomeostasis in neurological illnesses is associated with the etiology of Alzheimer's disease. Copper can facilitate the aggregation of amyloid-β peptides and induce neurotoxicity (16). Abnormal alterations in copper levels, specifically elevated serum copper and increased urinary copper excretion, have been observed in patients with diabetic nephropathy (42). In addition, cancer cells have a markedly higher demand for copper compared with normal cells (43); notably, copper levels in tumor tissue and/or serum are significantly elevated in patients with various types of cancer, including prostate, bladder and renal cell carcinoma, compared with in healthy controls, and are associated with tumor growth and progression (39). Furthermore, copper can promote cancer metastasis by activating enzymes, such as lysyl oxidase, and signaling pathways, including MEK-ERK, both of which drive tumor invasion and dissemination (16). These findings provide new insights into the diagnosis and management of disorders associated with copper homeostasis.

Copper homeostasis and medicine. As research advances on copper dysregulation and associated diseases, an increasing number of pharmaceuticals are being identified and utilized. In instances of severe systemic copper deficiency in patients with MD, Cu-histidine may be injected into the blood to circumvent intestinal absorption, facilitating the distribution of Cu^{2+} to various tissues and organs, thereby aiding in restoring systemic copper levels in affected individuals. Conversely, to mitigate the continuous copper accumulation in the brain, liver and other tissues of individuals with WD, oral zinc may be employed to decrease copper absorption, while copper chelators such as D-penicillamine and TTM can be utilized to lower copper levels in the body. Free α-lipoic acid (α-LA) is a cuproptosis enhancer; however, it has been shown that α-LA can mitigate cytotoxicity caused by copper overload through chelation and improve the copper-induced oxidative stress environment (44).

Serum and tumor tissue copper levels in patients with cancer are notably higher than those in healthy individuals, and copper serves a crucial role in tumor angiogenesis (45). Consequently, the accumulation of copper in tumor tissue may serve as a target for the formulation of anticancer agents. Two main methods exist for triggering apoptosis through copper targeting. The first strategy involves employing copper chelators, such as D-penicillamine and TTM, to bind Cu directly, hence diminishing its bioavailability, which may inhibit tumor proliferation in both cellular and animal tumor models (46). Copper chelators may inhibit collagen fiber cross-linking by blocking the copper-dependent lysyl oxidase family, therefore preventing renal fibrosis (47,48). Notably, copper chelators also exhibit anti-metastatic effects, primarily by inhibiting the recruitment of endothelial progenitor cells (EPCs), which are essential for angiogenesis and the establishment of metastatic niches (49). Copper chelators are also used to treat Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease (16). The alternative approach involves elevating intracellular copper levels through the use of copper ionophores, such as disulfiram (DSF), to generate ROS, inhibit proteasomes and trigger apoptosis (50). Nonetheless, some studies have suggested that copper ionophores eliminate cancer cells by a distinct process rather than through apoptosis, necrosis or oxidative stress (46,51,52). Furthermore, cuprous oxide nanoparticles can destabilize the copper chaperones ATOX1 and CCS, consequently producing an anticancer impact (11).

4. Cuproptosis

Beyond its initial identification, Tsvetkov *et al* (4) further elucidated the underlying mechanism of cuproptosis. Notably, cell death triggered by copper ionophores is strongly dependent on mitochondrial respiration. Cells relying on oxidative phosphorylation are ~1,000 times more sensitive to copper ionophores than glycolytic cells (4), thus indicating that cuproptosis specifically targets active mitochondrial metabolism. The morphological hallmarks of cuproptosis encompass mitochondrial shrinkage, rupture of the cell membrane, and damage to the endoplasmic reticulum and chromatin (53).

In cells treated with the copper ionophore elesclomol, the levels of tricarboxylic acid (TCA) cycle intermediates increase over time, highlighting a robust association between cuproptosis and mitochondrial metabolism. In mitochondria, ferredoxin 1 directly binds to lipoic acid synthetase, promoting the post-translational lipoylation of dihydrolipoamide S-acetyltransferase (DLAT), a key E2 subunit of the pyruvate dehydrogenase complex. This lipoylation is essential for the structural integrity and enzymatic activity of DLAT within the TCA cycle (54,55). It subsequently facilitates the dissociation of Cu^{2+} from elesclomol, and reduces Cu^{2+} to Cu^+ (56). Cu^+ exhibits a high affinity for the disulfide pentane ring structure within the lipoyl group (57). When excess Cu^+ binds to lipoylated proteins such as DLAT, it disrupts their native conformational stability, inducing abnormal cross-linking and irreversible aggregation in these enzymes that should normally assemble in an ordered, polymeric form. The resulting protein aggregation leads to inactivation of the pyruvate dehydrogenase complex, suppressing acetyl-CoA and α-ketoglutarate oxidation, and causing a sharp decline in ATP synthesis. Additionally, copper can replace

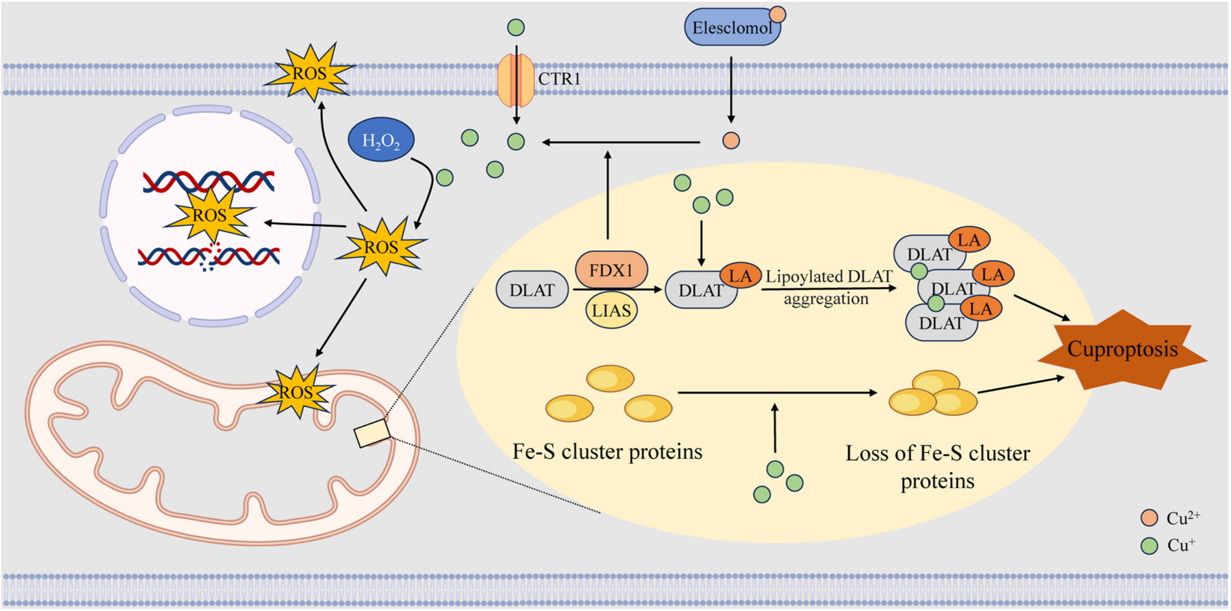

Figure 2. Copper ionophores, such as elesclomol, form complexes with extracellular copper ions through chelation and deliver them to various areas within cells. Intracellular copper overload causes aggregation of lipoylated mitochondrial enzymes in the tricarboxylic acid cycle (such as DLAT) and promotes the loss of Fe-S clusters, thereby causing proteotoxic stress and cell death. Copper ions also catalyze the Fenton reaction to generate ROS, induce cell membrane lipid peroxidation, damage the inner mitochondrial membrane to disrupt the mitochondrial electron transport chain, and destroy the DNA double helix structure, thereby triggering cell death. CTR1, copper transporter 1; DLAT, dihydrolipoamide S-acetyltransferase; FDX1, ferredoxin 1; LIAS, lipoic acid synthetase; LA, lipoic acid; Fe-S, iron-sulfur; ROS, reactive oxygen species.

iron in Fe-S clusters or disrupt their synthesis, leading to the inactivation of Fe-S-dependent enzymes, and further disturbing metabolic and redox balance. These events collectively trigger protein toxicity stress, ultimately resulting in cell death (4). Drug inhibition of the electron transport chain and pyruvate uptake can reverse elesclomol-induced cell death, providing compelling evidence for this process (4). Furthermore, excessive copper promotes ROS formation via the Fenton reaction, damages mitochondrial and plasma membranes, disrupts DNA integrity and broadly impairs cellular functions (58). The process of cuproptosis is illustrated in Fig. 2.

Cuproptosis and ferroptosis are two metal ion-dependent modes of regulated cell death that have attracted considerable attention, particularly in cancer research. Although their mechanisms are distinct, ferroptosis being driven by iron-dependent lipid peroxidation, the two processes are metabolically interconnected.

During cuproptosis, degradation of Fe-S clusters releases free iron ions, which elevate intracellular oxidative stress and can subsequently promote ferroptosis. Conversely, during ferroptosis, depletion of GSH and mitochondrial injury compromise cellular copper chelation and export, resulting in copper accumulation and the induction of cuproptosis. This self-reinforcing feedback loop between copper and iron metabolism has been exploited in several nanotherapeutic approaches to enhance anticancer efficacy (59-61).

5. Copper and CVD

Mechanism

Oxidative stress. Copper participates in the Fenton reaction, continuously generating hydroxyl radicals during the transformation of Cu^{2+} to Cu^{+}. This potent oxidant can directly induce DNA strand breakage and base oxidation (62). Excessive copper-induced systemic oxidative stress can disrupt lipid metabolic balance and facilitate lipid accumulation in the intima of vessels; this mechanism markedly propels the progression of AS (3). Copper-induced oxidative stress also increases the oxidation of GSH (63). Experimental evidence clarifying the toxic mechanism of copper oxide nanoparticles (CuO NPs) has been demonstrated through studies involving animal models and cellular experiments. These studies have revealed that CuO NPs induce oxidative stress in a stepwise manner, encompassing ROS burst, compensatory upregulation of heme oxygenase-1, mtETC dysfunction, and aberrant secretion of proinflammatory and profibrogenic cytokines (64,65). The copper chelator TTM can markedly alleviate cardiovascular damage associated with CuO NPs by chelating excess Cu (66). This multilayered oxidative damage represents a key pathophysiological mechanism in copper-related CVD.

Mitochondrial dysfunction. Mitochondria serve as the energy-producing organelles in eukaryotic cells and regulate cellular metabolic activities, including oxidative phosphorylation. Cuproenzymes in mitochondria are essential to this process. COX, the major mitochondrial cuproenzyme, utilizes most of the mitochondrial copper pool, accounting for 20-25% of the total copper content of the cell. Another important cuproenzyme, SOD1, is situated in the IMS of the mitochondria and its primary role is to facilitate the breakdown of superoxide generated by the mitochondrial respiratory chain (29). Copper deficiency impairs the delivery of Cu to SCO1/SCO2 and COX11 through COX17, which in turn reduces the synthesis of COX. Copper deficiency can also induce the production of the peroxisome proliferator-activated receptor-γ coactivator-1α protein, thereby altering mitochondrial ultrastructure, and leading to abnormal mitochondrial proliferation and dysfunction. This series of changes is closely associated with myocardial dysfunction (3).

Regulation of angiogenesis. Hypoxia-inducible factor 1 (HIF-1) functions as a crucial transcription factor in the regulation of angiogenesis (3). Copper can regulate the HIF-1 signaling pathway in multiple ways. Copper can enhance the stability of HIF-1α in the nucleus under normoxic conditions, causing the expression of HIF-1-dependent genes (67). CCS mediates the effect of copper on HIF-1 activity (68).

Furthermore, copper-dependent lysyl oxidases are vital for maintaining the structural integrity of blood vessel walls by catalyzing the covalent cross-linking of elastin and collagen, which confer tensile strength and elasticity to connective tissues (69). Abnormal lysyl oxidase expression levels or enzyme activity are associated with pathological processes such as CVD. Under copper deficiency, reduced lysyl oxidase synthesis and activity cause abnormal collagen degradation, which may cause serious complications such as destruction of the vascular matrix and rupture of the intima (3,69).

AS. AS is a chronic cardiovascular disorder characterized by the progressive formation of atherosclerotic plaques, leading to luminal narrowing and impaired vascular function. Accumulation of the oxidized form of low-density lipoprotein (LDL) in cells in the subendothelial space is a key factor in AS formation (70). In parallel, *in silico* screening has demonstrated that natural compounds derived from *Chlorella vulgaris* and *Boesenbergia rotunda* possess the potential to inhibit key early steps of AS, such as foam cell formation, by targeting proteins such as cholesteryl ester transfer protein, lectin-like oxidized LDL receptor-1, CD36 and acyl-CoA:cholesterol acyltransferase 1 (71,72). Separately, accumulating evidence has implicated copper dyshomeostasis in AS pathogenesis, with increased levels of copper being strongly linked to AS (73) and blood copper levels positively linked with subclinical carotid plaques (74). Furthermore, increased urinary levels of copper have been reported to be associated with a heightened 10-year risk of atherosclerotic CVD (75). Copper-related DNA methylation alterations are also associated with an elevated risk of acute coronary syndrome, potentially resulting from aberrant lipid metabolism and inflammation (76), which are associated with copper-mediated ROS formation, elevated CP, expansion of arterial endocardium and narrowing of the arterial lumen (40).

In aging patients with AS, the copper levels in their arteries decrease (77). Notably, although arterial copper content declines in AS, circulating copper levels often rise, suggesting that elevated serum copper may reflect impaired tissue utilization rather than systemic copper overload (78). This underscores that serum copper concentration alone may not accurately reflect systemic copper status or tissue distribution. Supporting this complexity, a short-term copper supplementation trial in healthy young women reported no beneficial effects on cardiovascular risk markers despite increased intake (79), and crucially did not assess arterial copper content, vascular structure or clinical outcomes, thus limiting its relevance to AS pathophysiology. Notably, the results across different studies are inconsistent. A previous study indicated that increased copper consumption was associated with a higher incidence of AS in non-diabetic individuals; however, there was a negligible association between dietary copper intake and the prevalence of AS in patients with diabetes (80). However, this previous study did not consider the impact of zinc intake. Conversely, another study indicated that a high dietary Zn:Cu ratio was favorably associated with the carotid intima-media thickness in individuals with type 2 diabetes (81). Therefore, the impact of copper on AS may not be determined by its absolute intake, but rather by the zinc-copper balance and individual metabolic status. Both insufficient and excessive intake may potentially promote AS. Therefore, advocating copper supplementation without rigorous evidence may be premature and could potentially pose risks under specific physiological contexts. ATOX1 is important in the pathogenesis of AS; it translocates to the nucleus in response to activation by inflammatory cytokines or exogenous copper. Similarly, in inflamed atherosclerotic aortic endothelial cells, ATOX1 is located in the nucleus. ATOX1-deficient mice demonstrate reduced AS progression (82), whereas TNF receptor-associated factor 4 (TRAF4) can markedly impede ATOX1 nuclear translocation and ROS generation. The ATOX1-TRAF4 axis represents a promising therapeutic target for vascular inflammatory diseases, including AS (83). Recent bioinformatics analyses have identified three cuproptosis-related genes, SLC31A1, SLC31A2 and SOD1, as potential diagnostic biomarkers for AS (7). However, the specific process of copper dyshomeostasis and cuproptosis in AS is still unclear.

Stroke. Currently, stroke ranks as the second most common cause of death worldwide, following ischemic heart disease. Stroke disrupts cerebral perfusion, leading to ischemic brain injury and subsequent neurological impairment (84). A large case-control study in the USA indicated that elevated dietary copper consumption was associated with a reduced risk of stroke (84). However, dietary copper intake does not necessarily reflect systemic or circulating copper levels, which complicates the interpretation of these findings. Several studies have shown that while plasma copper levels are not notably associated with the first hemorrhagic stroke, there is a positive association between plasma copper levels and the risk of the first ischemic stroke (85,86). A case-control study further reported that elevated plasma copper, along with certain trace metals such as molybdenum and titanium, was associated with higher ischemic stroke risk (87). Similarly, multiple meta-analyses have revealed a favorable association between elevated circulating copper levels and stroke incidence (88,89). This apparent contradiction may be explained by the marked elevation of serum non-CP-bound copper observed in patients with acute ischemic stroke. As free copper unbound to CP, it exhibits strong pro-oxidant properties. The increase in blood copper during the acute stroke phase may also partially stem from a stress response, meaning elevated blood copper serves both as a risk factor and potentially as a pathological consequence. Collectively, the impact of copper appears to be context-dependent, varying with inflammatory status and disease stage, and may follow a non-linear dose-response relationship.

The precise biological pathway by which copper impacts stroke remains unidentified. Notably, copper contributes to the synthesis of SOD, which mitigates ROS generated by ischemic stroke and diminishes cellular damage following such events (90). Conversely, copper can exacerbate ischemic stroke. EPCs can improve endothelial function and promote angiogenesis in ischemic brain tissue, whereas thrombospondin-1 serves as a principal inhibitor of EPC activity. Research findings have suggested that copper exposure in mice can lead to elevated thrombospondin-1 levels, hence exacerbating ischemic stroke in these subjects (3). Copper may influence stroke risk indirectly through its modulation of lipid metabolism, a hypothesis that warrants confirmation in prospective cohort studies (91).

Ischemia/reperfusion (I/R) injury. I/R injury refers to tissue damage caused by the restoration of blood flow after a period of ischemia, primarily driven by oxidative stress (92). This process generates excessive ROS and provokes a robust inflammatory response, a major pathogenic mechanism underlying various diseases, such as acute kidney injury, particularly in the context of kidney transplantation (93). Following I/R-induced myocardial infarction (MI), substantial remodeling of the extracellular matrix (ECM) occurs, leading to interstitial fibrosis, scarring and cardiac dysfunction. The increased copper-dependent lysyl oxidase subtype following MI may facilitate cardiac ECM remodeling and dysfunction (40).

The copper-dependent enzyme Cu/Zn-SOD mitigates oxidative stress-induced cellular edema during reperfusion (94). When Cu/Zn-SOD is upregulated in coronary vascular cells, the heart becomes more resistant to I/R injury (95,96). A meta-analysis showed that regular exercise can elevate levels of GSH peroxidase and Cu/Zn-SOD, and enhance cardiac function after myocardial I/R injury (97). Nonetheless, the mechanistic links between copper dyshomeostasis, cuproptosis and myocardial I/R injury remain to be fully elucidated.

HF. HF is prevalent among adults, and has high morbidity and mortality rates worldwide. Both acute HF (AHF) and chronic HF (CHF) is linked to heightened oxidative stress resulting from the elevated generation of ROS and compromised clearance mechanisms (98). Furthermore, the Cu:Zn ratio is important in HF. A prospective study conducted in 2022 demonstrated that for every 1-unit increase in serum Cu:Zn ratio, the risk of HF was increased by 63%, and this association exhibited a linear dose-response relationship. Incorporating the Cu:Zn ratio into traditional HF risk prediction models may improve risk stratification efficacy (99). However, the Cu:Zn ratio as a single biomarker may be driven by confounding factors, such as inflammation, liver function or inadequate zinc intake, and may not necessarily reflect a causal relationship. In a study of 125 patients, serum copper levels were elevated and serum zinc levels were decreased in patients with both AHF and CHF (100). This has been confirmed in several studies (99,101-103). Although elevated serum copper is frequently observed in inflammatory states, it does not necessarily indicate copper overload. Conversely, evidence regarding the impact of copper deficiency or excess on HF remains limited and inconsistent. Patients with ischemic and non-ischemic HF showed differences in dietary zinc and copper intake, but the median zinc and copper status biomarkers did not show a notable difference between the two groups (104), suggesting that the serum Cu:Zn ratio may be regulated by homeostasis during the chronic stable phase of HF and thus lose the ability to distinguish between ischemic and non-ischemic etiologies. A Mendelian randomization investigation analysis also indicated that dietary copper was not markedly associated with the risk of cardiovascular and metabolic diseases (105). Although observational studies have repeatedly reported elevated serum Cu:Zn ratios in patients with HF (99,106,107), their clinical significance is highly dependent on disease stage, inflammatory status and zinc-copper balance. Single-cell transcriptome sequencing of immune cells in epicardial adipose tissue from patients with HF has revealed disturbed zinc and copper metabolism (108). Prior studies have also shown that elevated blood copper levels in patients with HF are linked to higher mortality and morbidity rates (99,100,109). Nonetheless, certain studies have indicated that shortages in zinc and copper may elevate the risk of coronary heart disease, valvular regurgitation, myocardial lesions and myocardial hypertrophy (110). Supplementation with several nutrients, including copper, may serve as a viable therapeutic method for individuals with HF (111,112). Some experiments have even shown that the serum copper levels of patients with CHF are similar to those in a healthy control group (102). In summary, the current evidence linking zinc and copper status to CVD remains fragmented and inconsistent. Neither zinc nor copper levels should be used alone for diagnosing HF or guiding supplementation therapy. Additional research is needed to determine whether the detection of diseases relies on the degree of association between zinc and copper content and CVD (110).

Antioxidant mechanisms serve a regulatory role in HF pathology. In end-stage HF, increased oxidative stress may specifically upregulate catalase gene expression (113), while copper dyshomeostasis exacerbates this pathological process. In a study involving diabetes-induced HF, patients with diabetes had impaired cardiac mitochondrial copper regulation, with reduced COX17, COX11, CCS and SCO1 expression, and mitochondrial translocation in the myocardium, thus affecting copper transport to the mitochondria and COX assembly, resulting in a decrease in COX activity of ~27%. Notably, TETA treatment could restore COX activity to normal, improving cardiac function (114). Non-pharmacological interventions also have regulatory potential. In patients with CHF, 12 weeks of aerobic exercise training (cycling at 50% of peak oxygen uptake for 45 min, four times/week) has been shown to increase the expression of Cu/Zn-SOD and GSH peroxidase, and thus improve cardiac function (115). A previous transcriptome analysis has indicated that genes associated with cuproptosis regulate the immunological microenvironment in ischemic HF (116). However, the mechanism of cuproptosis in HF is currently unclear.

6. Copper-related therapeutic approaches for CVDs

Copper chelators. Copper chelators are agents capable of binding copper ions, thereby preventing their intracellular accumulation, or depleting excessive copper to modulate redox homeostasis and induce cell death (117). An increasing body of preclinical and clinical evidence has suggested that copper chelation therapy holds therapeutic potential in CVDs. As shown in Table I (114,118-132), various copper chelators have been evaluated in different animal models and patient populations.

Table I. Applications of copper chelators in cardiovascular diseases.

A, ATTM

First author, year	Type of model/subject	Treatment	Mechanism	(Refs.)
Johnson, 2024	Surgical-induced myocardial infarction in female large white pigs	6 mg/kg administered intravenously before reperfusion, followed by 18 mg/kg/h intravenous infusion for 1 h	Reduced infarct size	(118)
Dyson, 2017	Surgical-induced myocardial, cerebral or systemic ischemia/reperfusion in rats, and hypoxic/reoxygenated cardiomyocytes *in vitro*	In rat models of surgical-induced myocardial and cerebral ischemia/reperfusion: 10 mg/kg IV bolus immediately prior to reperfusion, followed by 10 mg/kg/h IV infusion for 1 h (total dose 20 mg/kg); in global I/R model in male Wistar rats: 10 mg/kg IV bolus plus 2.5 mg/kg added to reinfused blood (total dose 12.5 mg/kg); *in vitro*: 0.055-5.5 mM ATTM during reoxygenation	Notable reduction in infarct size and levels of related biomarkers; reduction in oxidative stress and systemic inflammation; improved survival, increased cell viability and reduced mitochondrial superoxide production	(119)

B, TTM

First author, year	Type of model/subject	Treatment	Mechanism	(Refs.)
Chen, 2024	Spontaneously hypertensive rats	10 mg/kg/day orally for 2 weeks	Reduced myocardial hypertrophy, fibrosis and cuproptosis, improved mitochondrial structure and cardiac function	(120)
Bogaard, 2012	Exposure to SU5416, and chronic hypoxia-induced vascular proliferative pulmonary arterial hypertension and right ventricular dilatation and hypertrophy in rats	10 mg/kg intraperitoneal injection every 2 days for 10 days	Opened blocked pulmonary blood vessels, reduced pulmonary artery pressure and induced right ventricular remodeling	(121)
Wei, 2012	HFHC Western-type chow diet-induced atherosclerosis in ApoE$^{-/-}$ mice	HFHC diet containing 33 ppm TTM for 2 weeks, followed by HFHC diet containing 66 ppm TTM for 8 weeks	Reduced the availability of copper and vascular inflammation, and inhibited atherosclerosis	(122)
Ambi, 2023	Genetic edit-induced cerebral amyloid angiopathy in rats	10 mg/kg intraperitoneal injection 3 times per week for 6 months	Copper was not removed from vascular amyloid-β aggregates, and it promoted the development of disease pathology in cerebral amyloid angiopathy	(123)

Table I. Continued.

B, TTM

First author, year	Type of model/subject	Treatment	Mechanism	(Refs.)
Mandinov, 2006	Pigs with stents implanted in the coronary artery	5 mg/kg orally twice daily for 2 weeks before stent implantation	Reduced the bioavailability of copper, inhibiting inflammatory responses and in-stent restenosis	(124)
C, TETA				
Zhang, 2020	STZ-induced DCM in rats	20 mg/day in drinking water for 8 weeks (~68 mg/kg/day)	Restored myocardial copper homeostasis, antioxidant defense function and related metabolic processes, and improved cardiac function in diabetic rats	(114)
Cooper, 2009	Patients with type 2 diabetes	600 mg twice daily orally for 12 months	Reduced left ventricular mass	(125)
Zhang, 2014	STZ-induced DCM in rats	20 mg/day in drinking water for 8 weeks (~68 mg/kg/day)	Reversed the local copper deficiency in the left ventricular myocardium caused by diabetes in rats, and improved the structural and functional defects of the left ventricle	(126)
Zhang, 2013	STZ-induced diabetes in rats	30 mg daily in drinking water for 7 or 8 weeks after STZ injection	Restored the decline in myocardial copper levels caused by diabetes, prevented the development of cardiac dysfunction and maintained normal cardiac contractility	(127)
D, EDTA				
Lamas, 2024	Patients aged ≥50 years with diabetes and MI ≥6 weeks before recruitment	Up to 3 g intravenously weekly for 30 infusions	Ineffective in reducing cardiovascular events in stable patients with CAD who had diabetes and a previous MI	(128)
Lamas, 2013	Patients aged ≥50 years with diabetes and MI ≥6 weeks before recruitment	Up to 3 g 30 weekly infusions, followed by 10 infusions at intervals of 2-8 weeks (total of 40 infusions)	Moderately reduced the composite risk of adverse cardiovascular outcomes in stable patients with a history of MI	(129)
Knudtson, 2002	Patients aged ≥21 years with CAD or a documented MI and stable angina	40 mg/kg (up to 3 g) twice a week for 15 weeks, then once a month for 3 months (total of 33 infusions)	No evidence from this study supports a positive effect of EDTA chelation therapy over placebo in patients with ischemic heart disease, stable angina and a positive treadmill test	(130)

Table I. Continued.

D, EDTA

First author, year	Type of model/subject	Treatment	Mechanism	(Refs.)
Anderson, 2003	Patients aged ≥21 years with CAD or a documented MI and stable angina	40 mg/kg (up to 3 g) twice a week for 15 weeks, then once a month for 3 months (total of 33 infusions)	No additional benefits were provided regarding abnormal vasomotor responses in patients with CAD	(131)
Escolar, 2014	Patients aged ≥21 years with MI ≥6 weeks before recruitment	Up to 3 g 30 weekly infusions for 30 weeks, followed by 10 infusions at intervals of 2 weeks-2 months	Reduced the risk of cardiovascular events in patients aged ≥50 years with diabetes after MI	(132)

ApoE, apolipoprotein E; ATTM, ammonium TTM; CAD, coronary artery disease; DCM, dilated cardiomyopathy; HFHC, high-fat, high-cholesterol; IV, intravenous; MI, myocardial infarction; STZ, streptozotocin; TETA, triethylenetetramine; TTM, tetrathiomolybdate.

TTM exhibits a high affinity for copper and has the ability to selectively bind to copper ions. Notably, it is extensively employed in treating WD. In comparison to conventional therapies, such as D-penicillamine and trientine, which increase urinary copper excretion but may provoke paradoxical neurological worsening, TTM may prevent copper-induced harm to the blood-brain barrier and demonstrate an improved safety profile (133,134). TTM can specifically form a TTM-copper-ATOX1 complex with ATOX1, thus obstructing copper transport to the TGN and its subsequent synthesis of cuproprotein, or diminishing copper bioavailability and vascular inflammation to prevent AS in apolipoprotein E-deficient mice (135). The second-generation TTM analog (ATN-224; choline TTM) inhibits SOD1 within both tumor cells and endothelial cells, thus decreasing endothelial cell proliferation *in vitro* (136), and TTM can reduce the proliferation of human pulmonary microvascular endothelial cells (121). Intravenous injection of ammonium TTM (ATTM) has been shown to protect the heart in an MI-reperfusion model in a drug-exposure-dependent manner (118). Notably, ATTM may function as an inorganic sulfide-releasing molecule (119). Intervention with TTM has been reported to markedly inhibit the aggregation of DLAT oligomers and enhance ATP7A expression in the hearts of spontaneously hypertensive rats, thereby diminishing cuproptosis and mitochondrial damage (120).

TETA acts as a selective copper chelator and has a bidirectional regulatory function in the cardiovascular system. In copper-deficient myocardial hypertrophy model tissues, TETA can serve as a copper chaperone to promote the transport of copper ions to cardiomyocytes. Under copper overload conditions, excess copper ions are removed by chelation (40). TETA may inhibit the rise in serum copper levels and efficiently reduce the heightened CP activity during MI (137). Abnormal ECM Cu^{2+} accumulation and a defect in intracellular Cu^+ supply can lead to copper dyshomeostasis in the myocardium. TETA can restore the balance of copper distribution in the myocardium and effectively maintain the integrity of the heart structure (127). In addition, TETA has been reported to enhance myocardial function in the hearts of diabetic rats by reinstating myocardial copper transport routes (114,126), and it may serve as a possible therapeutic agent for diabetic heart disease (125). However, neither TTM nor TETA has been systematically evaluated in large-scale clinical trials or meta-analyses.

EDTA can bind to a range of metals. The results of the TACT randomized trial showed that individuals with type 1 and type 2 diabetes who had previously suffered from MI experienced a reduction in the recurrence of cardiovascular events following EDTA-based injections (129). However, EDTA chelation proved ineffective in reducing cardiovascular events among stable patients with coronary artery disease who also had a history of diabetes and MI (128). Therefore, current evidence does not support its routine clinical use in CVD management. A meta-analysis demonstrated that there is currently insufficient evidence to determine whether chelation therapy is effective in improving clinical outcomes in patients with atherosclerotic CVD (138). More high-quality randomized controlled trials are needed to evaluate the effects of EDTA chelation therapy on CVD.

Although several copper chelators have shown promise in preclinical models and selected patient populations, their clinical efficacy remains limited, largely due to poor cellular permeability. Moreover, these agents pose risks of off-target toxicity and oxidative stress (139). Prolonged administration may further result in copper deficiency, myelosuppression, nephrotoxicity or imbalances in trace elements (140). Therefore, indicators of copper metabolism should be carefully monitored throughout treatment.

Copper ionophores. Copper ionophores are compounds that bind copper ions and promote their transport across cellular membranes, thereby increasing intracellular copper concentrations. Among these agents, elesclomol and DSF are the most extensively studied (141). Elesclomol is an antineoplastic agent that targets mitochondrial metabolism. It can inhibit cancer by facilitating the delivery of copper ions into cells, thereby triggering copper-mediated apoptosis (142). DSF can markedly elevate intracellular copper levels and inhibit angiogenesis through a number of routes, thereby exerting an anticancer impact (143). Despite these promising findings in oncology, no copper ionophore has yet been applied to CVD therapy. Moreover, carrier-mediated copper delivery may aggravate cardiovascular injury due to its pro-oxidative effects, and its safety and tissue specificity remain notable challenges.

Dietary copper supplementation. Dietary copper supplementation serves as a non-specific approach to restore systemic copper homeostasis. Among Chinese adults participating in the China Health and Nutrition Survey, a U-shaped association exists between dietary copper consumption and the incidence of new-onset hypertension; the inflection point is ~1.57 mg/day (144). Furthermore, it has been suggested that dietary copper supplementation may reverse pressure overload-induced cardiac hypertrophy (145). Prolonged supplementation with multiple micronutrients, including copper, can enhance cardiac function in older individuals with HF (112). Furthermore, a notable association exists between lower copper intake in the diet and a higher occurrence of abdominal aortic calcification (146). Longitudinal and cross-sectional studies in the US population have suggested that moderately increasing dietary copper intake may confer cardiovascular protective effects (147,148). By contrast, a prospective cohort study in the Chinese population indicated that high copper intake (>2.45 mg/day) may increase the risk of all-cause and CVD mortality (149). These findings indicate that the effects of copper follow a U-shaped or J-shaped curve, both excessively low and excessively high levels are detrimental, with the optimal range varying depending on the individual, dietary patterns and baseline health status. Nevertheless, Mendelian randomization analyses have not demonstrated a marked causal relationship between dietary copper intake and CVDs or metabolic diseases (105). This may be due to methodological limitations that failed to detect such complex relationships. Currently, there is a lack of precise copper status assessment tools for patients with CVD, and indiscriminate copper supplementation carries potential risks. Further studies are warranted to clarify the role of dietary copper in CVD prevention and management.

Cuproptosis. Although research on the molecular mechanisms of cuproptosis in cardiovascular cells is still at an early stage, current evidence has indicated a high degree of tissue specificity. Compared with other tissues, cardiomyocytes, which are highly dependent on mitochondrial energy supply, are markedly sensitive to the stability of lipoylated proteins (150). Cuproptosis in the cardiovascular system does not occur in isolation; instead, it reflects systemic copper homeostasis dysregulation involving coordinated interactions among the liver, kidneys and heart. Elevated blood copper levels, often associated with hepatic or renal dysfunction, may increase copper uptake by cardiomyocytes. At the molecular regulatory level, sirtuin 3 maintains intracellular copper homeostasis by modulating the interaction between copper transporters and the autophagy-related protein LC3B, which suppresses cuproptosis in cardiomyocytes (151). In vascular endothelial cells, MT2A preserves mitochondrial and vascular function by chelating free copper, effectively blocking the cuproptosis pathway (152). In cardiomyocytes, TTM reverses cuproptosis caused by copper overload (153). In a diabetic cardiomyopathy model, advanced glycation end products have been shown to markedly upregulate CTR1 mRNA and protein levels, while downregulating the copper efflux transporters ATP7A and ATP7B; this leads to intracellular copper accumulation, thereby inducing or exacerbating cuproptosis (154). As shown in Table II (5-7,116,155-162), bioinformatics and multi-omics analyses have suggested that cuproptosis serves a broad role in CVD pathogenesis. Nevertheless, experimental validation of the functional relevance of these genes remains limited. For example, although ATP7B has been proposed as a cuproptosis-associated biomarker in ischemic cardiomyopathy (6), its direct participation in copper-induced cardiomyocyte death remains to be experimentally verified. Furthermore, several genes appear to have dual or context-dependent roles, underscoring the need for further mechanistic studies. Future studies should move beyond correlative findings toward causal validation.

CTR1, SOD1 and ATOX1 are the most common copper-related biomarkers. In human tumor research, substantial evidence has supported the clinical value of CTR1. Although animal models have revealed the role of CTR1 in CVDs (163), human clinical studies remain extremely limited (164,165). In a model of I/R injury, dysfunction of CTR1 in cardiomyocytes can lead to excessive copper ion accumulation, inducing cuproptosis (166). In addition to potentially serving as a biomarker and target in cancer treatment, CTR1-induced regulation of intracellular copper levels to influence cuproptosis offers novel therapeutic approaches for various diseases. However, the complexity of its regulation poses challenges for clinical translation (167). SOD1 has demonstrated clear clinical value in neurodegenerative diseases (168). Bioinformatics research has indicated that SOD1 may serve as a potential diagnostic biomarker for AS (7), but evidence directly linking it to cuproptosis remains lacking in the field of CVD. Furthermore, its application is constrained by functional complexity and insufficient tissue specificity (169). ATOX1, as a copper chaperone and potential transcription factor, occupies a pivotal position in the cuproptosis-regulated network. In oncology, ATOX1 expression is upregulated across multiple types of cancer, with its upregulation associated with poor patient prognosis (170). However, high-quality human clinical evidence remains scarce in the CVD field. Its potential value lies in reflecting copper metabolic status and serving as a prognostic indicator in both cancer and CVDs. The primary limitations stem from its complex regulatory network, which may compromise the specificity of ATOX1 as a standalone biomarker and complicate activity assessment (171). As key molecules in copper metabolism and oxidative stress pathways, as well as biomarkers for specific disease subtypes, these three substances require unified detection standards and large-scale prospective clinical validation in the future to prove their predictive or prognostic value. Precision medicine should be achieved by constructing precision classification models based on copper homeostasis pathways through multi-omics integration, and drugs for targeted therapy should also be developed.

Reagents for CVDs based on cuproptosis have been formulated. When exposed to aging conditions, copper and iron atoms accumulate in their lower-oxidized states, triggering a cascade of cuproptosis and ferroptosis. D-handed $PtPd_2CuFe$ can alleviate the effects of aging in multiple aging models and has notable therapeutic capabilities in AS, a disease that involves multiple types of senescent cells (172). Conversely,

Table II. Roles of cuproptosis-related genes in cardiovascular diseases.

First author, year	Disease	Gene	Function	(Refs.)
Lin, 2024	DCM	SEPTIN1, CLEC11A, ISG15, P3H3, SDSL and INKA1	Novel diagnostic biomarkers in DCM, suggesting the potential involvement of cuproptosis in the immune regulation of DCM	(155)
Chen, 2024	Diabetic heart failure	HSDL2, BCO2, CORIN, SNORA80E (core cuproptosis-related genes); LOXL2 (differentially expressed, linked to fibrosis)	HSDL2/BCO2/CORIN/SNORA80E potentially regulate cuproptosis in cardiomyocytes through immune system modulation; LOXL2 is implicated in myocardial fibrosis	(5)
Zhou, 2024	AMI	SLC31A1 (key), PDHB, GLS and CDKN2A	Used to construct a diagnostic model for AMI; SLC31A1 (the key gene) is upregulated in AMI and is associated with immune cell infiltration	(156)
Wang, 2024	AMI	CBLB and ZNF302	Cuproptosis-related biomarkers validated in patients with AMI and mouse models; form a high-performance diagnostic signature for AMI	(157)
Fang, 2024	AMI	DLST	Downregulated cuproptosis-related gene in AMI; identified as a risk factor in a cuproptosis-immune infiltration-based predictive model	(158)
Zhang, 2025	AMI	GZMA, GIMAP7, GIMAP5, GIMAP6, and TRAF3IP3	Serve as key immune-related genes, and may participate in the occurrence and development of AMI through multiple immune signaling pathways	(159)
Chen, 2024	IHF	MTF1, FDX1, DLAT, LIPT1, GLS, PDHB, LIAS, DLD and PDHA1	Core regulators or effectors of cuproptosis, showing dysregulated expression in IHF and collectively serve as a diagnostic signature	(116)
Tan, 2024	Ischemic cardiomyopathy	DLST, ATP7B, FDX1, SLC31A1 and DLAT	Closely related to ischemic cardiomyopathy and are potential biomarkers for it	(6)
Wang, 2023	Primary cardiomyopathy	FDX1, MAP2K1 and SLC31A1	May be a prospective biomarker for diagnosing primary cardiomyopathy and identifying its molecular subtypes	(160)
Wang, 2023	Atrial fibrillation	SLC31A1 and LIAS	HOXA9 and TET1 may regulate SLC31A1 and LIAS, linking cuproptosis to altered immunocyte infiltration in atrial fibrillation	(161)
Chen, 2023	AS	SLC31A1, SLC31A2 and SOD1	Potential diagnostic biomarkers and therapeutic targets for AS	(7)
Zhang, 2023	CAD	F5, MT4, RNF7, S100A12 and SORD	Potential diagnostic biomarkers for CAD	(162)

AMI, acute myocardial infarction; AS, atherosclerosis; CAD, coronary artery disease; DCM, dilated cardiomyopathy; IHF, ischemic heart failure.

the mitochondrial-targeted triphenylphosphonium-modified Cu^{2+} bis(diethyldithiocarbamate) can markedly increase copper accumulation in mitochondria, and severely impair mitochondrial morphology and functions. Therefore, it may serve as a mitochondrial-targeted cuproptosis inducer to selectively eliminate diseased cells (173).

7. Challenges and prospects

Studies in animal models have shown that targeting CTR1 during I/R injury reduces intracellular copper accumulation, thereby suppressing cuproptosis. This intervention also alleviates inflammation, oxidative stress and mitochondrial injury in cardiomyocytes, ultimately providing protection against I/R-induced damage (166). Serum copper levels are often elevated in patients with CHF, potentially enhancing copper deposition in cardiomyocytes. This may lead to cardiomyocyte loss via cuproptosis and contribute to ventricular remodeling. However, the clinical relevance of this association is complicated by multiple confounding factors. In arterial walls, copper catalyzes Fenton-like reactions that promote oxidized LDL formation. Moreover, studies have linked copper dysregulation to the progression of AS, implying that cuproptosis may participate in AS pathogenesis (82,122). The molecular pathways underlying cuproptosis in cardiomyocytes, endothelial cells and vascular smooth muscle cells have not yet been fully elucidated. In addition, both direct clinical evidence and clinically applicable copper ionophores are still lacking. Nevertheless, targeting cuproptosis holds promise as a novel therapeutic strategy for refractory conditions such as AS and cardiomyopathy.

Copper modulation strategies have demonstrated therapeutic potential in animal models of atherosclerosis (in apolipoprotein E-deficient mice fed a high-fat, high-cholesterol Western-type diet) (122), ischemia/reperfusion injury (in rats subjected to surgical induction of myocardial, cerebral or systemic ischemia/reperfusion) (119) and myocardial infarction (in female Large White pigs subjected to surgical induction) (118), yet their translation to clinical applications remains challenging. Major obstacles include interspecies differences in copper metabolism, toxicity risks arising from the dual biological roles of copper, the absence of reliable biomarkers and clearly defined clinical endpoints, and variability due to individual genetic and environmental factors. Collectively, these limitations hinder the clinical validation of safety and efficacy. Future research should focus on developing specific inhibitors targeting cuproptosis pathways to reduce toxic side effects, utilizing biomarkers to assess disease risk or treatment response, and establishing reliable technologies for monitoring copper homeostasis dynamics.

Cuproptosis and ferroptosis, as two novel forms of programmed cell death, display distinct yet overlapping molecular mechanisms, regulatory pathways and therapeutic implications. Simultaneously inducing cuproptosis and ferroptosis can produce synergistic cytotoxic effects, and multiple nanotherapeutic strategies (such as DSF@HMCIS-PEG-FA nanoparticles, which enable a self-accelerating ferroptosis-cuproptosis cycle; HA@CuCo-NC nanoconjugates, which hijack Fe-S clusters; and dual-responsive NSeMON-P@CuT/LipD platforms that disrupt copper metabolism) have been designed to exploit this effect (59-61). Their combined use can overcome single-pathway drug resistance in tumors and enhance tumor targeting; however, the mechanisms underlying cuproptosis are not yet fully elucidated, and potential clinical applications must carefully address toxicity and translational limitations.

8. Conclusion

The present review provides an overview of copper metabolism, highlights the mechanisms linking copper dysregulation to CVDs, and summarizes therapeutic strategies that target copper homeostasis. The recently identified form of regulated cell death, termed cuproptosis, provides novel insights into the role of copper in CVD. However, the mechanisms through which copper dysregulation drives the onset and progression of CVD remain to be elucidated and warrant validation through well-designed experimental studies. Current evidence linking cuproptosis to CVD is largely derived from bioinformatics and multi-omics analyses, with limited experimental validation in cellular and animal models. The development of safe and effective modulators of copper homeostasis represents a key focus for future research aimed at restoring copper homeostasis in patients with CVD. Furthermore, therapies targeting cuproptosis and other copper-mediated cell death pathways may provide promising new options for treating CVDs.

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Authors' contributions

PL and YL wrote the manuscript, and made substantial contributions to the conception and design, literature search, and analysis and interpretation of the literature. QM and JW drew the figures and tables, and contributed to the literature search and the analysis and interpretation of the literature. SY and KW revised the manuscript. Data authentication is not applicable. All authors read and approved the final 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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