mtDNA replacement therapy (MRT) is to use enucleated donor embryos as healthy mtDNA to replace undesired defective/mutated mtDNA to prevent mitochondria from being maternally inherited. MRT is a form of in vitro fertilization (IVF) that includes spindle transfer (ST), prokaryotic transfer (PNT) and polar body transfer (PBT) [103]. In fact, embryos from human nuclear transfer can contain low levels of mutated mtDNA, which may be suitable for treating degenerative diseases caused by mtDNA mutations [104]. This opens up the possibility of MRT for CVDs, a chronic noncommunicable degenerative disease. Hyslop et al. developed a PNT protocol that promotes efficient development at the blastocyst stage, keeping mtDNA residues as low as possible [105]. At present, there have been successful cases of applying MRT strategies [106,107], and offspring will not suffer from mtDNA mutation–related diseases. Therefore, hypertrophic cardiomyopathy, dilated cardiomyopathy, genetically related coronary heart disease and other CVDs can be considered using MRT, as an auxiliary means of human reproduction, to solve the problem from the embryo. However, the scientific knowledge related to MRT is still being explored, and the risks and ethical issues of this technology remain to be resolved [108]. 3.2. Mitophagy Therapy in CVDs Mitophagy clears dysfunctional mitochondria under normal physiological conditions, and in response to pathological stress [15]. Currently, there are three mechanisms of mitophagy, including mitochondrial outer membrane receptor–mediated, Pink1/Parkin pathway, and lipid receptor–mediated mechanisms (Figure 2) [109]. Notably, the mech– anism mediated by the Pink1/Parkin pathway is the most extensively studied. Under normal circumstances, the content of Pink1 is extremely low. When oxidative stress occurs and mitochondria damage is induced, Pink1 is activated and recruits Parkin to the mito– chondrial outer membrane for phosphorylation. The phosphorylated Parkin ubiquitinates the substrate protein on the mitochondrial membrane [110]. These ubiquitinated proteins subsequently recruit specific autophagy–related receptors to interact with LC3–II to form autophagosomes [111]. Mitophagy maintains cardiovascular homeostasis and performs significant functions in mitochondrial quality control. It has been shown that phosphorylation of Ser495 in Pink1 by AMPKα2 is necessary for effective mitotic inhibition of the progression of heart failure [15]. Ophiopogonin D' (OPD') is toxic to mitochondria, and OPD'–induced mitosis and mitochondrial damage in cardiomyocytes are partly mediated by the dysregulation of the Pink1/Parkin pathway, preventing excessive mitochondrial autophagy [112]. In a study on the improvement of cardiac function by berberine, it was found that the coordinated action of berberine and the Pink1/Parkin pathway enhances mitochondrial phagocytosis and protects patients with heart failure [16]. Ulk1/Rab9–dependent alternative mitophagy is activated during chronic high–fat diet depletion as an important mitochondrial quality control mechanism to protect the heart from the obesity effects of cardiomyopathy [81]. In conclusion, the control of mitophagy has an important role in the clearance of abnormal mitochondria and the protection of cardiomyocytes (Figure 2). In addition, when abnormal mitochondria undergo fission, they can trigger cardio– vascular dysfunction [113,114]. Cytoplasmic GTPase dynamics related protein 1 (Drp1) regulates mitochondrial fission by interacting with proteins located at fission sites such as mitochondrial fission 1 (Fis1), mitochondrial fission factor (Mff), and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51) [115]. A study identified mito– chondrial fission inhibitor (mdivi–1) as a cell–permeable quinazolinone derivative inhibitor of Drp1 [116]. In cardiomyocytes treated with

mdivi−1, proteolytic cleavage of the OPA1 isoform and decreased expression of Mfn2, altered complex I and complex II protein expres− sion of OXPHOS, and increased superoxide production were observed, which resulted in mitochondrial respiration defects and macro−autophagy inhibition [117]. Taken together, it is speculated that targeting mitochondrial fission or Drp1 may be useful for CVDs therapy. Int. J. Mol. Sci. 2022, 23, 16053 8 of 16 Figure 2. Three mechanisms of mitophagy and the ways they intervene in treating CVDs. Three mechanisms of mitophagy include mitochondrial outer membrane receptor−mediated (such as Bnip3, Nix and Fundc1), Pink1/Parkin pathway, and lipid receptor−mediated mechanisms (such as MtCK, NDPK−D). The LC3 is located in the phagophore and binds to the corresponding receptor. The LC3 can bind to substances of different mitophagy mechanisms. To demonstrate the mitophagy occurring in CVDs, cardiomyocytes (CM) and Pink1/Parkin pathway were used to intervene in heart failure (HF) and myocardial hypertrophy (MH) by inhibitors. In Pink1/Parkin−dependent mitophagy, the Pink 1 accumulated on the damaged mitochondria is activated and recruits Parkin for phosphorylation. The phosphorylated Parkin binds to the ubiquitin attached to outer OMM, and finally binds to LC3 for mitophagy. The Bnip3 and Nix can directly bind LC3 and promote mitophagy. MtCK and NDPK−D as specific transporters can also directly bind LC3 for mitophagy to eliminate damaged mitochondria. The inhibitor acts on Pink1/Parkin pathway, and then prevents excessive mitophagy and improves mitochondrial function, thereby maintaining the healthy levels of cells associated with CVDs. OMM, outer mitochondrial membrane; IMS, inter membrane space; IMM, inner mitochondrial membrane. 3.3. Mitochondrial OXPHOS Reduction and Treatment in CVDs 3.3.1. Small Molecule Compounds Enhance Mitochondrial Function SIRT3 is a mitochondrial protein deacetylase that regulates mitochondrial function and is considered as an emerging drug target for CVDs [118]. SIRT3 can make mitochondrial metabolic pathways and ROS detoxification activate, and increase ATP production [119]. Resveratrol improves mitochondrial OXPHOS in diabetic hearts and prevents the decline of SIRT3 activity in the heart by increasing ETC activity and mitochondrial function [120]. The polyphenolic compound polydatin can initiate SIRT3−regulated mitophagy to prevent MI [84]. Notably, proteolytic targeting chimera technology, as a new strategy of targeted inhibitors, makes it possible to potently target small molecule compounds to enhance mitochondrial function, which may be more beneficial to the treatment of CVDs caused by mitochondrial dysfunction. When mtDNA is damaged at high levels, increased Poly(ADP−ribose) polymerase (PARP) activity leads to a decrease in NAD+ levels, resulting in impaired NAD+ −dependent SIRT3 activation and ultimately cardiac mitochondrial dysfunction [121]. Therefore, tar− geted improvement of mitochondrial function through nutritional supplementation NAD+ Int. J. Mol. Sci. 2022, 23, 16053 9 of 16 or ketoesters may be useful in patients with heart failure [87]. NAD+ supplementation with nicotinamide riboside (NR) promotes mitophagy in a Pink1−dependent manner [122]. NR can reduce ROS production and maintain normal mitochondrial function in the presence of inflammatory triggers [123]. The effect of nicotinamide mononucleotide (NMN) on the generation of ROS was investigated and it was finally found that NMN can reduce mito−chondrial oxidative stress in brain microvascular endothelial cells and improve primary cerebro−microvascular endothelial cell membrane potential and mitochondrial respiration in a sirtuin−dependent manner [124]. Similarly, NMN improves the aorta by reducing oxidative stress [125]. Taken together, it

can be seen that NR, NAD+ , and NMN have cer- tain therapeutic potential in the treatment of CVDs caused by mitochondrial dysfunction. Among them, NR and NMN still require further preclinical and clinical studies to ensure the safety of the drug [83]. 3.3.2. Nanomaterials Targeted Mitochondria to Improve Mitochondrial Function Many drugs cannot precisely bind to damaged mitochondria, and they are even toxic to other tissues in the body. To solve these problems, precise targeted therapy has at- tracted much attention. Modification of nanoparticles with different components facilitates mitochondrial directed drug penetration [126]. A team has constructed a non invasive aerosol inhalation delivery system based on antioxidant nano drugs, which can target damaged mitochondria, clear ROS, and improve the targeting ability of nano-drugs to my- ocardium [85]. Artificial hybrid nanozymes created by protein reconstruction technology and nanotechnology can target mitochondria and scavenge ROS, thereby reducing mito- chondrial oxidative damage [127]. Improved formulation of negatively charged peptide nanoparticles enables efficient localization of the drug to mitochondria [128]. Therefore, the novel nano drug delivery system in the human body to effectively treat human CVDs by targeting mitochondria will bring another bright future. 3.4. Reduction or Elimination of Mitochondrial-Derived ROS in CVDs ROS acts as highly active molecules in vivo, and antioxidants can effectively reduce or eliminate ROS. The in vitro hypoxia/reoxygenation model of H9c2 cells could simulate myocardial ischemia-reperfusion injury, and it found that the experimental group sup- plemented with vitamin D could inhibit the production of ROS in cardiomyocytes [129]. Melatonin is an indole heterocyclic compound produced by pineal cells in the pineal gland. It can effectively lower ROS production, thereby reducing oxidative stress and VSMC loss, preventing the deterioration of thoracic aortic aneurysm and dissection [32]. Fullerenol nanoparticles are introduced into an alginate hydrogel to form a fullerenol/alginate hy- drogel with antioxidant activity. This injectable cell delivery vector can treat myocardial infarction by effectively reducing ROS levels [130]. Cardioprotection of tetrahedral DNA nanostructures can significantly decrease oxidative stress and play a positive role in pro- tecting against myocardial ischemia-reperfusion injury [131]. However, the clinical effects of ROS scavengers in CVDs are not always significant, probably because antioxidants can indiscriminately remove some physiological ROS. Therefore, finding drugs to target damaged mitochondria will improve the clearance of pathological ROS. Fortunately, the antioxidant CoQ10 has been used in the clinical treatment of CVDs and has good curative effect. Ubiquinone, the oxidized form of CoQ10, transports electrons in the mitochondrial ETC and plays a crucial role in mitochondrial energy production. CoQ10 can transport H+ to thermally dissipate chemosmotic gradients via uncoupling proteins (UCP-1, 2 and 3). After uncoupling, the reduction level of electron carriers is reduced, thereby reducing the production of ROS [132]. Moreover, the reduced form of CoQ10 is also an active agent involved in antioxidant function, which can scavenge ROS production due to mitochondrial dysfunction [133]. Meanwhile, CoQ10 helps recycle other antioxidants such as radical forms of vitamin C and vitamin E [134]. CoQ10 has been shown to increase ATP production in cardiomyocytes, enhance oxidative effects, and improve endothelial function and lipid profile [135]. Comparing CoQ10 with placebo, the therapeutic effect Int. J. Mol. Sci. 2022, 23, 16053 10 of 16 of CoQ10 was more significant in the long term [136]. In addition, substantial clinical evidence suggests that CoQ10 supplementation (≥200 mg/day) contributes to cardiac

health in patients affected by coronary heart disease and heart failure [90]. The safety profile of CoQ10 can be used as adjunctive therapy in congestive heart failure and may be helpful in patients who cannot tolerate mainstream drugs [137]. CoQ10 supplementation is safe and well tolerated with few drug interactions and side effects [138]. Similarly, the MitoQ was clinically demonstrated for its antioxidant effects on mitochondrial-derived ROS. The MitoQ can increase the resistance of aging mice to mitochondrial-derived ROS and protect against the imbalance of mitochondrial homeostasis due to aging. It is a novel strategy to treat and prevent age-related CVDs [139]. Of course, the task of applying more safe and effective new antioxidants to the clinical treatment of CVDs is a long way to go and needs to be continuously explored. 4. Conclusions and Perspective As an important component of the cell, mitochondria contain genetic material, produce energy, and participate in a wide variety of metabolic activities in the cell. It can be seen that if the mitochondrial dysfunction occurs, the normal replication of mtDNA, energy pro- duction, and other functions will be affected, which may cause diseases. Here, we mainly analyzed the relationship between the heart and arterial-related CVDs, and mitochondrial dysfunction. Mitochondrial dysfunction in cardiomyocytes, vascular smooth muscle cells, and endothelial cells causes a wide variety of CVDs; and has attracted more and more scientists. With the deepening of CVDs pathogenesis related studies, we summarized the mitochondrial dysfunction causing CVDs into four important characteristics, including mtDNA mutations, impaired mitophagy, decreased OXPHOS, and mitochondrial-derived ROS increase. In multiple animal and human models, many relevant intervention experi- ments have been designed according to mitochondrial dysfunction, constantly exploring more effective CVDs related therapeutic strategies. According to the four important char- acteristics of mitochondrial dysfunction, the related treatment strategies of CVDs were sorted out. Exploring the significance, advantages, and current limitations of different mitochondrial targeted therapy strategies can provide more ideas and options for the treat- ment of different CVDs. Although each of these strategies for ameliorating mitochondrial dysfunction has its own characteristics, combination therapy may be more effective. It is well known that CVDs are quite complex, and their pathological mechanisms are even more complex and diverse. On the basis of continuously deepening the pathological mechanisms, mitochondrial targets can be found more accurately. In the case of harmless to human body, mitochondrial targeted therapy for CVDs may improve the efficiency and safety of treatment, and contribute to the development of human health. Author Contributions: Conceptualization, J.L. and Y.L. (Yongzhi Li); investigation, Y.L. (Yu Liu), Y.H., P.A. and Y.L. (Yongting Luo); writing—original draft preparation, Y.L. (Yu Liu) and Y.H.; writing— review and editing, P.A., Y.L. (Yongting Luo), J.L. and Y.L. (Yongzhi Li); visualization, C.X. and L.J.; supervision, J.L. and Y.L. (Yongzhi Li); project administration, J.L. and Y.L. (YonmtDNA replacement therapy (MRT) is to use enucleated donor embryos as healthy mtDNA to replace undesired defective/mutated mtDNA to prevent mitochondria from being maternally inherited. MRT is a form of in vitro fertilization (IVF) that includes spindle transfer (ST), prokaryotic transfer (PNT) and polar body transfer (PBT) [103]. In fact, embryos from human nuclear transfer can contain low levels of mutated mtDNA, which may be suitable for treating degenerative diseases caused by mtDNA mutations [104]. This opens up the possibility of MRT for CVDs, a chronic noncommunicable degenerative disease. Hyslop et al. developed a PNT protocol

that promotes efficient development at the blastocyst stage, keeping mtDNA residues as low as possible [105]. At present, there have been successful cases of applying MRT strategies [106,107], and offspring will not suffer from mtDNA mutation-related diseases. Therefore, hypertrophic cardiomyopathy, dilated cardiomyopathy, genetically related coronary heart disease and other CVDs can be considered using MRT, as an auxiliary means of human reproduction, to solve the problem from the embryo. However, the scientific knowledge related to MRT is still being explored, and the risks and ethical issues of this technology remain to be resolved [108]. 3.2. Mitophagy Therapy in CVDs Mitophagy clears dysfunctional mitochondria under normal physiological conditions, and in response to pathological stress [15]. Currently, there are three mechanisms of mitophagy, including mitochondrial outer membrane receptor-mediated, Pink1/Parkin pathway, and lipid receptor-mediated mechanisms (Figure 2) [109]. Notably, the mech- anism mediated by the Pink1/Parkin pathway is the most extensively studied. Under normal circumstances, the content of Pink1 is extremely low. When oxidative stress occurs and mitochondria damage is induced, Pink1 is activated and recruits Parkin to the mito- chondrial outer membrane for phosphorylation. The phosphorylated Parkin ubiquitinates the substrate protein on the mitochondrial membrane [110]. These ubiquitinated proteins subsequently recruit specific autophagy-related receptors to interact with LC3-II to form autophagosomes [111]. Mitophagy maintains cardiovascular homeostasis and performs significant functions in mitochondrial quality control. It has been shown that phosphorylation of Ser495 in Pink1 by AMPKα2 is necessary for effective mitotic inhibition of the progression of heart failure [15]. Ophiopogonin D' (OPD') is toxic to mitochondria, and OPD'-induced mitosis and mitochondrial damage in cardiomyocytes are partly mediated by the dysregulation of the Pink1/Parkin pathway, preventing excessive mitochondrial autophagy [112]. In a study on the improvement of cardiac function by berberine, it was found that the coordinated action of berberine and the Pink1/Parkin pathway enhances mitochondrial phagocytosis and protects patients with heart failure [16]. Ulk1/Rab9-dependent alternative mitophagy is activated during chronic high-fat diet depletion as an important mitochondrial quality control mechanism to protect the heart from the obesity effects of cardiomyopathy [81]. In conclusion, the control of mitophagy has an important role in the clearance of abnormal mitochondria and the protection of cardiomyocytes (Figure 2). In addition, when abnormal mitochondria undergo fission, they can trigger cardio- vascular dysfunction [113,114]. Cytoplasmic GTPase dynamics related protein 1 (Drp1) regulates mitochondrial fission by interacting with proteins located at fission sites such as mitochondrial fission 1 (Fis1), mitochondrial fission factor (Mff), and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51) [115]. A study identified mito- chondrial fission inhibitor (mdivi-1) as a cell-permeable quinazolinone derivative inhibitor of Drp1 [116]. In cardiomyocytes treated with mdivi-1, proteolytic cleavage of the OPA1 isoform and decreased expression of Mfn2, altered complex I and complex II protein expres- sion of OXPHOS, and increased superoxide production were observed, which resulted in mitochondrial respiration defects and macro- autophagy inhibition [117]. Taken together, it is speculated that targeting mitochondrial fission or Drp1 may be useful for CVDs therapy. Int. J. Mol. Sci. 2022, 23, 16053 8 of 16 Figure 2. Three mechanisms of mitophagy and the ways they intervene in treating CVDs. Three mechanisms of mitophagy include mitochondrial outer membrane receptor-mediated (such as Bnip3, Nix and Fundc1), Pink1/Parkin

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more safe and effective new antioxidants to the clinical treatment of CVDs is a long way to go and needs to be continuously explored. 4. Conclusions and Perspective As an important component of the cell, mitochondria contain genetic material, produce energy, and participate in a wide variety of metabolic activities in the cell. It can be seen that if the mitochondrial dysfunction occurs, the normal replication of mtDNA, energy pro- duction, and other functions will be affected, which may cause diseases. Here, we mainly analyzed the relationship between the heart and arterial-related CVDs, and mitochondrial dysfunction. Mitochondrial dysfunction in cardiomyocytes, vascular smooth muscle cells, and endothelial cells causes a wide variety of CVDs; and has attracted more and more scientists. With the deepening of CVDs pathogenesis related studies, we summarized the mitochondrial dysfunction causing CVDs into four important characteristics, including mtDNA mutations, impaired mitophagy, decreased OXPHOS, and mitochondrial-derived ROS increase. In multiple animal and human models, many relevant intervention experi- ments have been designed according to mitochondrial dysfunction, constantly exploring more effective CVDs related therapeutic strategies. According to the four important char- acteristics of mitochondrial dysfunction, the related treatment strategies of CVDs were sorted out. Exploring the significance, advantages, and current limitations of different mitochondrial targeted therapy strategies can provide more ideas and options for the treat- ment of different CVDs. Although each of these strategies for ameliorating mitochondrial dysfunction has its own characteristics, combination therapy may be more effective. It is well known that CVDs are quite complex, and their pathological mechanisms are even more complex and diverse. On the basis of continuously deepening the pathological mechanisms, mitochondrial targets can be found more accurately. In the case of harmless to human body, mitochondrial targeted therapy for CVDs may improve the efficiency and safety of treatment, and contribute to the development of human health. Author Contributions: Conceptualization, J.L. and Y.L. (Yongzhi Li); investigation, Y.L. (Yu Liu), Y.H., P.A. and Y.L. (Yongting Luo); writing—original draft preparation, Y.L. (Yu Liu) and Y.H.; writing— review and editing, P.A., Y.L. (Yongting Luo), J.L. and Y.L. (Yongzhi Li); visualization, C.X. and L.J.; supervision, J.L. and Y.L. (Yongzhi Li); project administration, J.L. and Y.L. (Yon