

Review

Unraveling the Cardiac Matrix: From Diabetes to Heart Failure, Exploring Pathways and Potential Medications

Bogdan-Sorin Tudurachi ^{1,2} , Larisa Anghel ^{1,2,*} , Andreea Tudurachi ² , Radu Andy Sascău ^{1,2},
Răzvan-Liviu Zanfirescu ^{2,3}  and Cristian Stătescu ^{1,2} 

- ¹ Internal Medicine Department, “Grigore T. Popa” University of Medicine and Pharmacy, 700503 Iasi, Romania; bogdan-sorin.tudurachi@d.umfiasi.ro (B.-S.T.); radu.sascau@umfiasi.ro (R.A.S.); cristian.statescu@umfiasi.ro (C.S.)
- ² Cardiology Department, Cardiovascular Diseases Institute “Prof. Dr. George I. M. Georgescu”, 700503 Iasi, Romania; leonteandreea32@gmail.com (A.T.); zanfirescu_razvan-liviu@d.umfiasi.ro (R.-L.Z.)
- ³ Physiology Department, “Grigore T. Popa” University of Medicine and Pharmacy, 700503 Iasi, Romania
- * Correspondence: larisa.anghel@umfiasi.ro; Tel.: +40-0232-211834

Abstract: Myocardial infarction (MI) often leads to heart failure (HF) through acute or chronic maladaptive remodeling processes. This establishes coronary artery disease (CAD) and HF as significant contributors to cardiovascular illness and death. Therefore, treatment strategies for patients with CAD primarily focus on preventing MI and lessening the impact of HF after an MI event. Myocardial fibrosis, characterized by abnormal extracellular matrix (ECM) deposition, is central to cardiac remodeling. Understanding these processes is key to identifying new treatment targets. Recent studies highlight SGLT2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP1-RAs) as favorable options in managing type 2 diabetes due to their low hypoglycemic risk and cardiovascular benefits. This review explores inflammation’s role in cardiac fibrosis and evaluates emerging anti-diabetic medications’ effectiveness, such as SGLT2i, GLP1-RAs, and dipeptidyl peptidase-4 inhibitors (DPP4i), in preventing fibrosis in patients with diabetes post-acute MI. Recent studies were analyzed to identify effective medications in reducing fibrosis risk in these patients. By addressing these areas, we can advance our understanding of the potential benefits of anti-diabetic medications in reducing cardiac fibrosis post-MI and improve patient outcomes in individuals with diabetes at risk of HF.

Keywords: diabetes; myocardial infarction; heart failure; myocardial fibrosis; SGLT2 inhibitors; GLP-1 agonist; dipeptidyl peptidase-4 inhibitors



Citation: Tudurachi, B.-S.; Anghel, L.; Tudurachi, A.; Sascău, R.A.; Zanfirescu, R.-L.; Stătescu, C.

Unraveling the Cardiac Matrix: From Diabetes to Heart Failure, Exploring Pathways and Potential Medications. *Biomedicines* **2024**, *12*, 1314. <https://doi.org/10.3390/biomedicines12061314>

Academic Editor: Serafino Fazio

Received: 9 April 2024

Revised: 8 May 2024

Accepted: 11 June 2024

Published: 13 June 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The cardiac muscle, comprising cardiomyocytes, capillaries, and ECM rich in collagen fibers, constitutes the fundamental elements crucial for efficient contraction. Left ventricular (LV) remodeling, an adaptive response to mechanical, neurohormonal, and genetic stimuli, orchestrates alterations in ventricular dimension, shape, and function. While physiological cardiomyocyte proliferation in scenarios like pregnancy signifies a reversible process facilitated by augmented microcirculatory perfusion, pathological remodeling after cardiac events such as MI poses a substantial risk for HF [1]. HF, a complex syndrome stemming from structural and functional aberrations within the heart, manifests pathologically through interstitial fibrosis, chamber remodeling, and diminished ventricular compliance [2]. Diabetes mellitus (DM) emerges as an independent risk factor for HF, with diabetic cardiomyopathy representing a significant complication fueled by metabolic perturbations including glucose and lipotoxicity, insulin resistance, endothelial dysfunction, and microvascular impairment, alongside ischemic heart disease sequelae, involving multifaceted pathophysiological pathways [3]. Type 2 diabetes mellitus (T2DM) assumes a pivotal role in cardiovascular (CV) pathology, directly intertwining with diabetic cardiomyopathy and exacerbating CV risk factors, thus amplifying susceptibility to CAD. CAD-induced MI and ischemia/reperfusion injuries frequently instigate HF via acute or

chronic maladaptive remodeling processes, establishing CAD and HF as principal contributors to CV morbidity and mortality. Consequently, therapeutic strategies for patients with CAD focus on averting MI occurrence and mitigating HF burden post-MI [4,5].

Traditionally, T2DM management commenced with insulin therapy; however, the evolution of oral anti-diabetic agents revolutionized glycemic control. Nonetheless, concerns regarding the CV safety profile of certain anti-diabetic drugs prompted extensive research aimed at elucidating their CV risk. Notably, studies unveiled two drug classes, SGLT2i and GLP1-RAs, which not only demonstrated CV safety but also exhibited remarkable reductions in major adverse CV events, including CV mortality, thereby positioning them as favorable options in T2DM management due to their low hypoglycemic risk and beneficial cardiovascular effects (CV benefits) [6]. Fibrosis, a chronic pathological process characterized by aberrant ECM deposition, serves as a hallmark feature across various cardiac pathologies, reflecting both reparative and maladaptive responses to injury. While initially pivotal for wound healing and tissue repair, persistent ECM accumulation engenders structural distortion and functional impairment within the heart. Myocardial fibrosis encompasses both interstitial and replacement forms, driven by diverse cellular and paracrine mechanisms involving inflammatory mediators, growth factors, and collagen-modulating enzymes such as matrix metalloproteinases (MMPs). Dysregulated collagen turnover precipitates myocardial fibrosis progression, further underscoring its pivotal role in cardiac remodeling [7].

Understanding key pathophysiological processes holds paramount importance for identifying novel therapeutic targets and leveraging diagnostic and prognostic modalities, including biomarkers and imaging techniques, to tailor medical interventions, thereby enhancing patient outcomes and clinical management strategies (Figure 1).

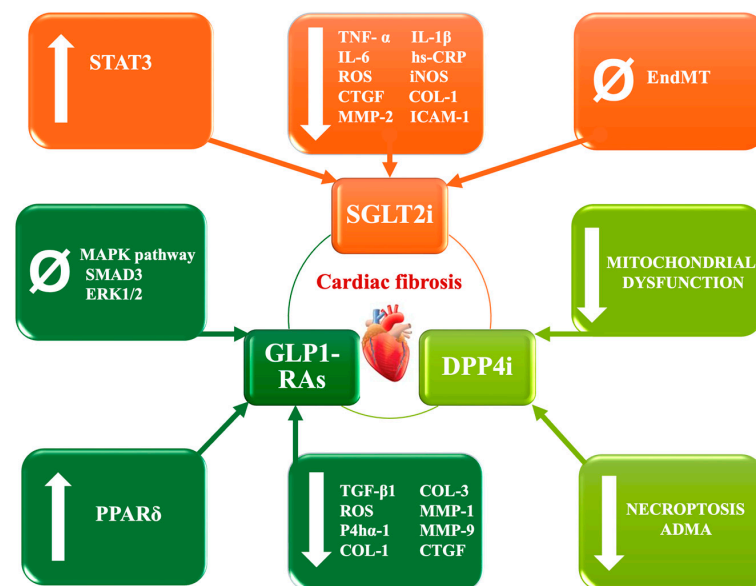


Figure 1. Pathways and potential medications related to cardiac fibrosis. ↑ = increase; ↓ = decrease; Ø = inhibit; STAT3 = signal transducer and activator of transcription 3; TNF-α = tumor necrosis factor-α; IL-1β = interleukin-1β; IL-6 = interleukin-6; hs-CRP = high sensitivity c-reactive protein; COL-1 = type 1 collagen; COL-3 = type 3 collagen; MMP-1 = matrix metalloproteinase 1; MMP-2 = matrix metalloproteinase 2; MMP-9 = matrix metalloproteinase 9; PPARα = peroxisome proliferator-activated receptor alpha; DPP4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = sodium-glucose cotransporter 2 inhibitors; GLP-1RAs = glucagon-like peptide-1 receptor agonists; CTGF = connective tissue growth factor; iNOS = inducible form of nitric oxide synthase; ROS = reactive oxygen species; ICAM-1 = intercellular adhesion molecule 1; MAPK = mitogen-activated protein kinase; ERK1/2 = extracellular signal-regulated kinase 1/2; EndMT = endothelial-to-mesenchymal transition; TGF-β1 = transforming growth factor-β; P4ha-1 = prolyl 4-hydroxylase subunit alpha 1; and ADMA = asymmetric dimethylarginine.

2. Materials and Methods

Myocardial fibrosis, often a leading cause of sudden cardiac death, occurs due to an accumulation of ECM, sometimes called interstitial myocardial enlargement. Myocardial ischemia/reperfusion (MI/R) injury damages cardiomyocytes, triggering fibroblast activation and fibrosis formation. In MI, “interstitial fibrosis” emerges as collagen-based scars that replace necrotic cardiac cells from ischemia. Another aspect, “perivascular fibrosis”, involves the thickening of microvascular adventitia. While dilated cardiomyopathy (DCM) does not typically result in immediate cardiomyocyte loss, abnormal metabolism can lead to their atypical demise, causing “replacement fibrosis” that worsens DCM. Although there is an established connection between cardiac fibrosis and acute myocardial infarction (AMI) as well as diabetes, the current research on the correlation between emerging anti-diabetic medications and this phenomenon is insufficient. Therefore, the present study aims to examine the inflammation role in cardiac fibrosis and the efficacy of drugs like SGLT2i, GLP-1RAs, or DPP4i in preventing fibrosis in patients with diabetes following acute MI [2,8,9]. We conducted a narrative review incorporating contemporary studies from the last five years, published in MEDLINE, PubMed, and EMBASE databases, with the goal to identify effective medications in reducing fibrosis risk in these patients.

3. Collagen Synthesis

3.1. C-Terminal Propeptide of Procollagen Type I

The C-Terminal Propeptide of Procollagen Type I (PICP) is released into the bloodstream when procollagen type I carboxy-terminal proteinase cleaves it from the protein to produce fibril-forming collagen type I. In individuals without liver cirrhosis, PICP serves as a marker of collagen type I production and is metabolized by the liver [10]. Elevated levels of PICP have been observed in the blood of patients with heart failure and hypertension, correlating with myocardial thickening and impaired heart relaxation in those with arterial hypertension [11]. Prior to receiving medication therapy, hypertensive individuals have notably higher levels of PICP in their bloodstreams [12]. Currently, there is no evidence indicating a relationship between PICP levels and the progression towards heart failure in individuals experiencing acute ischemic events who also have diabetes.

3.2. Procollagen Type I N-Terminal Propeptide

The Procollagen type I N-Terminal Propeptide (PINP), indicative of collagen type I production, is generated through the conversion of collagen type I. Unlike PICP, PINP is characterized by its delayed release. In a case-control study, it was revealed that patients with HF had significantly higher baseline serum PINP levels compared to controls. Furthermore, another study observed a notable increase in plasma PINP levels in the MI group compared to the normal control group in rats with ischemic cardiomyopathy [13,14].

3.3. Procollagen Type III Amino-Terminal Propeptide

Procollagen Type III Amino-Terminal Propeptide (PIIINP) is released into the bloodstream as a result of increased collagen type III production during cardiac fibrosis, and it plays a crucial role in myocardial elasticity. A study on DCM revealed that patients with idiopathic or ischemic DCM exhibited higher baseline blood PIIINP levels compared to healthy individuals. Additionally, in rats with a MI model, the reduction in fibrosis attributed to tanshinone IIA was associated with a decrease in serum PIIINP levels [7,15]. Osokina et al. demonstrated that the risk of cardiac fibrosis increases when PIIINP levels reach or exceed 381.4 ng/mL on the 12th day after ST-segment elevation myocardial infarction (STEMI) with maintained left ventricular ejection fraction (LVEF). Monitoring PIIINP levels during hospitalization may aid in identifying individuals at high risk of cardiac fibrosis one year after STEMI with normal LVEF [16].

4. Collagen Degradation

4.1. C-Terminal Telopeptide of Collagen Type I

As a marker of collagen turnover and a potential indicator for the early detection of adverse remodeling, C-terminal telopeptide, also referred to as beta-CTX, is a fragment of Type I collagen released into circulation following its breakdown. According to Zelniker et al., in individuals with non-ST-elevation acute coronary syndrome (NSTEMI), beta-CTX levels were associated with both HF and CV mortality [17]. Manhenke et al. suggested that, in patients experiencing AMI, plasma beta-CTX served as an independent predictor of CV death, with levels rising in those who died from any cause [18].

4.2. Matrix Metalloproteinases

The extracellular matrix is viewed as a dynamic and vital framework essential for cardiac healing processes. MMPs are zinc ion-dependent proteases responsible for collagen and proteoglycan breakdown, playing a critical role in atherosclerosis progression. MMPs also play a pivotal role in post-AMI cardiac remodeling and the development of associated complications, with the myocardium expressing numerous MMPs [19,20]. Research suggests that matrix metalloproteinase 28 (MMP-28) is associated with CV events and mortality both during hospitalization and within 30 days after discharge, serving as a potential predictor of short-term prognosis for individuals with MI [21]. Recent studies have shown that young patients experiencing STEMI exhibit significantly elevated levels of matrix metalloproteinase 3 (MMP-3), matrix metalloproteinase 9 (MMP-9), and tissue inhibitors of metalloproteinase (TIMP) compared to healthy individuals. Those experiencing Major Adverse Cardiovascular Events (MACEs), particularly HF hospitalizations, demonstrate markedly increased levels of MMP-9, suggesting its involvement in cardiac remodeling and its impact on LV function [22]. Furthermore, elevated MMP-9 levels have been associated with a notable increase in CV mortality over a two-year period, with patients with advanced HF being more prevalent in the high MMP-9 group during the monitoring period [23].

Watson et al. propose that the minor allele of genetic variation rs3918242 in the promoter region of the MMP-9 gene may be linked to hypertension and/or MI. Patients with diabetes carrying the minor T allele of rs3918242 showed a higher likelihood of experiencing MI, reduced ejection fraction (EF), and increased progression of LV systolic dysfunction over a 3.5-year follow-up period, indicating an elevated risk for developing HF [24].

4.3. Tissue Inhibitors of Metalloproteinases

TIMPs constitute a subgroup of small glycoproteins synthesized and released by fibroblasts, epithelial cells, and endothelial cells, prevalent in various tissues. They play a role in initiating the conversion of fibroblasts into myofibroblasts at sites of tissue damage and regulate the enzymatic activity of MMPs by inhibiting the activation of latent MMPs. Thus, maintaining an appropriate balance between MMPs and TIMP production is critical for the reconstruction of the extracellular matrix in cardiac tissues. Four types of TIMPs have been identified to be associated with myocardial fibrosis [7].

A retrospective cohort study has indicated that blood levels of tissue inhibitors of metalloproteinase 3 (TIMP-3), CA125, and NT-proBNP can predict ventricular remodeling in patients with HF following AMI. These three markers demonstrated excellent specificity and moderate sensitivity. Early detection of serum TIMP-3, CA125, and NT-proBNP levels may enhance the accuracy of predicting cardiac remodeling and facilitate early detection and management of HF post-AMI [25].

Clinical investigations have shown that MMP and TIMP levels during the acute phase may predict the development of HF or CV events within a 30-day follow-up period in patients with AMI who did not receive reperfusion treatment. Specifically, plasma levels of tissue inhibitors of metalloproteinase 1 (TIMP1) and the matrix metalloproteinase 2 (MMP2)/TIMP1 ratio can indicate the likelihood of HF and CV events. The matrix metalloproteinase 8 (MMP8)/TIMP1 ratio has shown predictive utility for the risk of CV-related events [26].

5. Collagen Metabolism

5.1. Transforming Growth Factor- β and SMADS

Transforming growth factor- β (TGF- β) is a crucial cytokine involved in promoting fibrosis within the heart muscle. It regulates the fibroblast growth, differentiation, migration, and synthesis of the ECM. The mammalian TGF- β subfamily comprises three isoforms (TGF- β 1, 2, and 3) that bind to identical receptors and target similar cellular substrates. However, they exhibit distinct regulatory patterns and different affinities for their receptors and co-receptors, suggesting unique functions in fibrotic disease development [2].

TGF- β induces fibrosis in cardiac fibroblasts by activating the Smad3, PI3K/Akt, and mitogen-activated protein kinase (MAPK) signaling pathways as a cytokine upstream of the oxidized low-density-lipoprotein receptor (LOX) [7]. Following MI, there is a significant increase in TGF- β 1 expression, which may interact with the renin–angiotensin system to promote heart remodeling. TGF- β 1 stimulates the activation of fetal genes in myocardial cells and induces fibroblasts in the heart to produce ECM proteins.

Research by Zhang et al. investigated the effects of TGF- β 1 therapy on myocardial cell death in rats with MI. AMI was induced in rats by occluding the left anterior descending coronary artery. Both the model and control groups were assessed for mRNA and protein expression levels of TGF- β 1 in myocardial cells. AMI rats exhibited significantly higher levels of TGF- β 1 mRNA and protein expression compared to the control group. The study suggested that the TGF- β 1/MAPK signaling pathway was activated in myocardial cells during AMI, and administration of TGF- β 1 was shown to attenuate myocardial cell death in AMI rats [27].

TGF- β transmits signals through intracellular effector proteins called Smads, as well as through Smad-independent pathways. In vivo research indicates that Smad3 signaling plays a crucial role in activating reparative fibroblasts after MI, leading to ECM protein synthesis and integrin transcription, which contribute to scar formation. Collagen levels decreased in the infarcted hearts of Smad3-deficient animals 7 days post-reperfusion, with reduced collagen deposition in the non-infarcted, remodeling myocardium. Smad3 signaling in myofibroblasts within the infarcted area inhibits cell proliferation, resulting in organized clusters of activated myofibroblasts and maintaining structural integrity through integrin and reactive oxygen species (ROS)-mediated pathways [2,7,28]. Disruption of the Smad gene appears to attenuate the remodeling process.

5.2. Corin

Corin, a transmembrane serine protease of type II, is predominantly found in atrial cardiomyocytes. It is a complex protein comprising a transmembrane domain near the N terminus, two frizzled-like domains, eight low-density lipoprotein (LDL) receptor repeats, a scavenger receptor-like domain, and a trypsin-like protease domain at the C terminus. Corin plays a crucial role in converting pro-atrial natriuretic peptide (pro-ANP) into its active form, ANP. Numerous studies have indicated that circulating corin levels have predictive value regarding various CV outcomes in individuals with AMI, chronic HF, and acute stroke [29–32]. However, preliminary findings from a small study suggest that serum levels of PCSK6 and corin are not independent predictors of CV outcomes in patients undergoing coronary angiography. Nonetheless, elevated blood PCSK6 levels in patients with non-chronic kidney disease (CKD) may indicate a higher risk of CV events [32]. To elucidate the critical genes and pathways involved in abnormal myocardial remodeling following prolonged ischemia, a study utilized a rhesus monkey model of MI. It revealed that cardiac remodeling may be aggravated by an imbalance in the expression of corin and natriuretic peptide A/natriuretic peptide B [33].

6. Inflammatory Factors

6.1. Galectin-3

The lectin family includes Galectin-3 (Gal-3), which has been associated with myocardial fibrosis, acute CV events, autoimmune diseases, and various inflammatory conditions. Animal models and a limited number of human samples have demonstrated its significant role in

tissue healing following AMI. Gal-3 is primarily produced by activated macrophages and injured cardiomyocytes, highlighting its critical involvement in myocardial fibrosis. Elevated Gal-3 expression has a strong correlation with the onset and progression of CV disorders, making it closely linked to the adverse remodeling of the heart and MACEs [34]. MACE remains the leading cause of morbidity and mortality in patients with AMI, and several studies suggest that Gal-3 plays a significant role in predicting adverse events post-AMI [34–39]. According to research by Grandin E. and colleagues, patients with elevated levels of both BNP and Gal-3 have the highest likelihood of developing HF, suggesting that Gal-3 may provide additional value in assessing HF risk after acute coronary syndrome (ACS) [40].

Increased levels of fibrosis and indicators of ECM remodeling, such as collagen, fibronectin, TGF- β , fibroblast proliferation, alpha smooth muscle actin (α SMA), and MMPs, have been associated with peak levels of Gal-3 in the ischemic region [41,42]. In addition to promoting ECM remodeling, Gal-3 may facilitate neutrophil adhesion and recruitment to the injured heart. While recent research suggests that neutrophils contribute to healing and the temporal progression of MI, their involvement is typically limited to the first week post-AMI. Neutrophils can alter their phenotype during the healing process, transitioning from a pro-inflammatory to an anti-inflammatory profile and contributing to scar formation [43–45].

In a rat model of MI, the inhibition of Gal-3 led to decreased collagen synthesis and reduced myocardial fibrosis [46]. Additionally, through its dual roles as a chemotactic factor for macrophage recruitment and a regulator of their polarization towards the reparative M2 phenotype, Gal-3 plays a multifaceted role in post-infarction wound healing. Gal-3's dual function is crucial for coordinating the immune response and tissue repair mechanisms after myocardial infarction, ultimately aiding in the recovery of heart tissue [41,47]. Animals with Gal-3 knockdown and pharmacologic suppression of Galectin exhibited decreased fibrosis, apoptosis, inflammation, and infarct size [48,49].

Gal-3 is intricately linked to inflammation, fibrosis, remodeling, and dysfunction in CV pathophysiology. Its significant involvement in cardiac remodeling underscores the importance of understanding its role in cardiac function. Understanding how Gal-3 operates in the heart holds promise for therapeutic interventions aimed at reducing HF.

6.2. Tumor Necrosis Factor- α and Interleukins

Macrophages and monocytes can generate and release numerous pro-inflammatory mediators, including interleukin-1 β (IL-1 β), interleukin-4 (IL-4), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). These inflammatory factors collectively form a complex regulatory network that promotes fibrotic degenerative processes and the activation of myofibroblasts [50]. Kang et al. demonstrated elevated concentrations of TNF- α , IL-6, and IL-1 β , as well as increased expression of collagen I and III mRNAs compared to normal controls, suggesting a correlation between fibrosis and inflammation [51]. Fang et al. conducted a cross-sectional study on hypertrophic cardiomyopathy (HCM) and observed a positive correlation between plasma levels of IL-4, IL-6, and interleukin-10 (IL-10) with both diffuse and localized myocardial fibrosis [52].

TGF- β plays a critical role in transitioning from inflammation to fibrosis by inhibiting inflammation and promoting ECM deposition. Studies have shown that mice lacking TGF- β in their heart muscle exhibit reduced cardiac fibrosis and increased survival rates [53–55]. The IL-6 trans-signaling cascade has been implicated in cardiac fibrosis induced by aldosterone. Conversely, blocking IL-6 has shown beneficial effects by reducing inflammation and fibrosis in mice subjected to high salt intake after nephrectomy [56,57]. Interleukin-33 (IL-33) has been associated with pro-fibrotic signaling in rats with MI and in individuals diagnosed with HF. IL-4 has been identified as a contributor to heart fibrosis, as it stimulates pro-fibrotic activity in macrophages [58–60].

6.3. MicroRNA

The development of fibrosis in patients with diabetes or post-AMI may be attributed to pathophysiological processes, which may include the dysfunction of microRNA (miRNA),

miR). These are tiny, single-stranded, non-coding RNAs that control gene expression after the transcription process. miRNAs have widespread expression in both the nucleus and cytoplasm. Nevertheless, miRNAs may still be detected in the bloodstream. They have a significant impact on several biological processes such as cell growth, specialization, programmed cell death, and metabolism by either inhibiting or promoting the expression of genes. Due to their stable expression in blood, miRNAs have the potential to serve as biomarkers for diagnosing, predicting outcomes, and developing new treatment approaches for cardiovascular disease [61–63].

In individuals with diabetes, there is an abnormal regulation of miRNA expression in the serum or plasma. Each miRNA has one or many targets that play a role in the development of diabetic fibrosis in the heart. Each gene might potentially be associated with one or many miRNAs, which can then inhibit its expression. Cardiac fibroblasts, endothelial cells, and cardiomyocytes have a role in the development of cardiac fibrosis. Every microRNA has a distinct target in certain cells, but many microRNAs have several targets in diverse cells. Mimicking of microRNAs inhibits the production of molecules of interest. Research indicates that cardiac fibrosis may include the activation of many crucial signaling pathways to enhance the production of pro-fibrotic molecules or hinder the production of anti-fibrotic molecules at the levels of gene expression and protein synthesis. miRNAs selectively target these molecules to exert an influence on the development of cardiac fibrosis in the diabetic heart or after a MI [64]. Several miRNAs have a function in reducing fibrosis in the diabetic heart affected by cardiac fibrosis. Those are represented by miR-15a/b, miR-18a-5p, miR-20a-5p, miR-26b-5p, miR-29, miR-133a, miR-141, miR-146a, miR-200b, miR-203, miR-222, and miR-551b-5p. Increased production of these miRNAs with anti-fibrotic properties inhibits the development of cardiac fibrosis in vivo and decreases the levels of molecules that promote fibrosis [65–76].

In addition, some miRNAs are increased in expression in the presence of high blood sugar levels. Typically, their specific objectives are genes or proteins that are suppressed in the heart of individuals with diabetes or in cells that are exposed to high levels of glucose. Myocardial fibrosis and heightened production of pro-fibrotic molecules are a consequence of overproduction of these miRNAs (miR-21-5p, miR-21-3p, miR-150-5p, miR-155, miR-221-3p, miR-223, miR-451). Antagomirs of these molecules, which are modified antisense oligonucleotides designed to target certain mature miRNA sequences, have been shown to provide cardiac protection and decrease cardiac fibrosis [77–87].

Following a MI, it has been proposed that miRNAs target many important fibrogenic pathways, including TGF- β /Smad, PTEN/Akt, angiotensin II/MAPK, or PIGF/VEGF-A. A full understanding of the function of miRNAs in fibrotic circumstances is hindered by the intricate nature of their activities in many cell types, as well as the extensive array of their molecular targets. Research findings indicate that certain miRNAs, such as miR-1, miR-19b, and miR-590-3p, could have a role in suppressing cardiac fibrosis by inhibiting the pathways triggered by fibrogenic growth factors or extracellular proteins [88–90]. The suppression of miR-34a and miR-1955 inhibits the pro-fibrogenic effects of TGF- β 1 or those caused by angiotensin II in cardiac fibroblasts [91,92]. On the other hand, it has been proposed that miR-21, miR-92a, miR-195, miR-200a-3p, miR-125b, miR-34a, miR-146b-5p and miR-144-3p have fibrogenic effects [91,93–101].

The primary goal of miRNA-based therapeutics post-MI is to reinstate miRNA expression levels. According to the findings, administering a miR-21 mimic to mice with cardiac macrophages changed their condition from one that promotes inflammation to one that reduces inflammatory processes. This alteration led to an increase in angiogenesis, a decrease in apoptosis, and abnormal restructuring in the infarct-affected region [102]. Cardiomyocyte apoptosis is closely associated with the suppression of a particular gene known as protein phosphatase 1 regulatory subunit 10 or PNU10. A microRNA known as miR-34a controls the expression of this gene. In mice, PNU10 improves function recovery following a heart attack [103]. Other therapeutic targets for miRNAs and exosomal miRNAs in MI are represented by miR-210, miR-15, exosomal miR-4943p, and miR-132 [104–107].

Future research should focus on identifying miRNAs as biomarkers and therapeutic targets that are common to various components of the metabolic illness group or ischemic disease.

7. Insulin Resistance and Hyperinsulinemia

Diabetic cardiomyopathy (DC) is a critical complication of DM marked by structural and functional impairments in the heart muscle, occurring without typical cardiovascular issues like coronary artery disease or valve disorders. It primarily develops due to prolonged high levels of hemoglobin A1c (HbA1c), a long duration of diabetes, and older age [108,109].

The etiology of DC is complex, involving multiple cellular and molecular factors that contribute to heart dysfunction. These include the overproduction of advanced glycation end-products (AGEs), activation of the hexosamine biosynthetic pathway, lipotoxicity, mitochondrial dysfunction, increased oxidative stress, and activation of the renin–angiotensin system and calcium homeostasis. These processes compound the effects of hyperglycemia, hyperinsulinemia, and insulin resistance, exacerbating the structural and functional decline of the heart in individuals with diabetes [110].

Prolonged high blood sugar levels in individuals with diabetes lead to increased insulin resistance and higher insulin levels, causing the death of heart muscle cells and the formation of scar tissue in the heart. This condition also impairs glucose processing, reduces glucose clearance, and increases gluconeogenesis. In diabetic cardiomyopathy, the diminished functionality of glucose transporters GLUT1 and GLUT4 in cardiac cells further disrupts glucose absorption and metabolism, which normally meets only 30% to 40% of the energy requirements for heart functions through glycolysis [111,112]. There is also an intense proliferation of cardiac fibroblasts, key players in initiating cardiac fibrosis, and an increase in ECM synthesis. AGEs, formed from prolonged glucose exposure, bind to receptors on heart cells, triggering collagen production and other ECM proteins through pathways like TGF β , ultimately exacerbating cardiac dysfunction through fibrosis. Furthermore, the AGEs-RAGE signaling pathway activates inflammatory responses and promotes interstitial fibrosis, while lipid-related metabolic changes further impair cardiac function by promoting cardiomyocyte death and reducing myocardial energy efficiency [113–115].

Oxidative stress plays a pivotal role in the development and progression of DC, primarily through the increased production of ROS and a reduction in antioxidant defenses such as glutathione peroxidase and superoxide dismutase, leading to heart fibrosis and mitochondrial damage. These oxidative changes impair mitochondrial function and calcium handling within cells, further reducing cardiac efficiency. Additionally, persistent ROS activity activates the TGF β 1/Smad3 signaling pathway, which enhances fibrotic changes in the heart by upregulating fibrotic markers and promoting the growth of cardiac fibroblasts, contributing significantly to the structural and functional decline observed in DC [116,117].

In individuals with diabetes, the chronic activation of the renin–angiotensin–aldosterone (RAS) pathway leads to the increased levels of angiotensin II (AT-II), which promotes left ventricular hypertrophy, vasoconstriction, cardiac dysfunction through fibrosis, oxidative stress, and cardiomyocyte death. This activation, further enhanced by elevated glucose, AGEs, and ROS, results in increased collagen production and decreased breakdown, contributing to the progression of cardiac fibrosis in DC [110,118].

In DM, identified as an inflammatory condition, the activation of pro-inflammatory genes and proteins, particularly through nuclear factor-KB (NF-kB), plays a crucial role in cardiac damage. NF-kB promotes the expression of pro-inflammatory cytokines and the NLRP3 inflammasome in the heart, leading to a self-perpetuating cycle of inflammation exacerbated by elevated ROS and the pro-inflammatory activation of monocytes/macrophages [119–121].

Inflammation, oxidative stress, activated RAS, compromised mitochondrial function, and disrupted calcium handling drive the structural and functional deterioration observed in DC.

8. Novel Drugs and Their Anti-Fibrotic Role

8.1. SGLT2 Inhibitors

SGLT2i works by enhancing glucose excretion in urine, primarily through inhibiting SGLT2, thereby reducing the renal threshold value of glucose and decreasing the reabsorption of filtered glucose. However, the benefits observed in HF associated with SGLT2i are unlikely to be solely attributed to glucose lowering. Rather, the advantages for CV and renal health have been linked to various mechanisms including hemodynamic effects, anti-inflammatory properties, anti-fibrotic effects, antioxidant actions, reno-protective effects, attenuation of glucotoxicity, reduction in uric acid levels, modification of the neurohumoral system, and cardiac metabolism [6,122–124]. While the CV benefits of SGLT2i are evident, the precise mechanisms underlying these effects are not fully understood.

SGLT2i plays a significant role in managing blood glucose levels by specifically targeting the SGLT2 transporter in the proximal renal tubules, leading to decreased glucose reabsorption and increased glucose excretion in the urine. This mechanism effectively reduces blood glucose concentrations independent of insulin pathways, thereby not triggering insulin release or causing hypoglycemia. Consequently, this reduction in circulating glucose helps to improve insulin sensitivity in muscle tissues and enhances β -cell function, contributing to the management of insulin resistance in patients with diabetes [125–129].

ACS is characterized by coronary artery obstruction, leading to myocardial ischemic damage, which can have life-threatening consequences. Immediate treatment is provided to restore oxygenation to the affected tissue, and patients are often prescribed secondary preventive medications to reduce the risk of future ACS events. Despite consistent prescription practices over the years, there is potential to include SGLT2i in this regimen due to their demonstrated CV benefits. Clinical research on the impact of SGLT2i on CV health in patients after MI has yielded conflicting results, with most trials focusing on MACEs rather than the underlying cellular processes including inflammation, cardiac metabolism, or cardiac fibrosis.

Inflammation plays a central role in myocardial fibrosis development, involving various inflammatory factors. However, it remains uncertain whether SGLT2i influences the inflammatory response and whether they can impede myocardial fibrosis progression by targeting inflammation. Wang et al. found that dapagliflozin effectively reduced levels of TNF- α , IL-1 β , IL-6, and hs-CRP in patients with diabetes and HF, leading to a gradual decline in inflammation and alleviation of myocardial fibrosis [130]. Dapagliflozin also reduced cardiac fibrosis in T2DM rats by inhibiting endothelial-to-mesenchymal transition (EndMT) and fibroblast activation via AMPK α activation, which suppressed the TGF- β /Smad signaling pathway [131]. Dapagliflozin decreased oxidative stress in the heart and prevented the production of inflammatory substances, thereby inhibiting myocardial enlargement and scar tissue formation [132–134]. Additionally, via raising AMPK phosphorylation, it inhibits high glucose-induced endothelial cell dysfunction [135]. A recent clinical trial has shown the efficacy of dapagliflozin in improving glycemic fluctuations and reducing oxidative stress in individuals with T2DM [136]. Recent investigations have shown that dapagliflozin provides protection against myocardial ischemia/reperfusion injury (IRI) via restricting the activation of the NLRP3 inflammasome [137].

In mouse models, empagliflozin was found to reduce myocardial infarct size and preserve myocardial function after ischemia/reperfusion injury by regulating inflammatory responses and redox signaling in the ischemic myocardium [138,139]. Empagliflozin also reduced cardiomyocyte hypertrophy, interstitial fibrosis, and oxidative stress in non-diabetic rat models of HF [140,141]. However, long-term empagliflozin administration did not significantly improve LV function, shape, adiposity, or diffuse fibrosis in individuals with T2DM [142]. Similarly, no significant difference in mortality was observed between patients with diabetes receiving low-dose empagliflozin after percutaneous coronary intervention (PCI) for ACS and the placebo group [143]. Nonetheless, empagliflozin treatment improved heart function in mice with diabetes after infarction, particularly diastolic function, suggesting potential benefits in diabetic cardiomyopathy [144]. Nrf2 has a crucial role as a transcription factor in regulating the expression of genes that are involved in antioxidant

and cytoprotective functions. Empagliflozin enhances Nrf2 expression and facilitates its nuclear translocation, therefore mitigating heart dysfunction in db/db mice with diabetes via the amelioration of oxidative stress and mitochondrial dysfunction [145,146].

Furthermore, SGLT2i such as dapagliflozin, canagliflozin, and empagliflozin have been shown to have anti-inflammatory effects by reducing the production of the NLRP3 inflammatory, IL-1 β , IL-6, TNF- α , and LV ECM remodeling in diabetes animal models [137,147–151]. In the same line, Hodrea, J. et al. demonstrated that dapagliflozin effectively decreased the levels of IL-1 β , IL-6, and TNF- α in the LV of rats with type 1 diabetes mellitus (T1DM), indicating its potential as an anti-inflammatory agent [149]. Empagliflozin attenuates TGF- β 1-induced fibroblast activation and decreases pro-fibrotic markers such as type I collagen (COL-1), connective tissue growth factor (CTGF), and MMP-2 [152]. Additionally, it has been shown to alleviate cardiac fibrosis by downregulating the TGF- β /Smad pathway, triggering Nrf2/ARE signaling, and lowering the concentrations of Smad1, Smad2, and Smad3 in the heart tissue of mice with diabetes [146].

According to recent research, SGLT2i may have a role in LV remodeling in individuals with diabetes. Following this therapy, individuals with T2DM with or without CAD showed a decrease in LV mass measured by cardiac MRI, as stated by two randomized trials [153,154]. Recent results indicate that the treatment of SGLT2i to individuals with diabetes resulted in a decrease in blood hs-CRP levels and an improvement in endothelial function. In contrast, the EMBLEM study found that a 24-week therapy with empagliflozin did not lead to any improvement in endothelial dysfunction in patients with preexisting cardiovascular disease and T2DM [155–158]. Collectively, these findings suggest that SGLT2i may have potential therapeutic effects beyond glucose lowering, particularly in mitigating inflammation and fibrosis in CV diseases.

8.2. Glucagon-like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) is a hormone naturally produced and released by endocrine L-cells in the small intestine upon food ingestion. It binds to specific GLP-1 receptors in the pancreas, stimulating insulin release in a glucose dependent manner. Despite its widespread presence in various organs, natural GLP-1 has a short half-life due to rapid breakdown by dipeptidyl peptidase-4 (DPP-4) [159–161].

Incretin hormones significantly influence insulin production post-meal, accounting for 50–70% of total insulin release, but their effect is reduced in patients with T2DM due to various factors. These hormones, particularly GLP-1, enhance insulin secretion, delay stomach emptying, and suppress glucagon release, helping regulate postprandial blood glucose levels. To augment the actions of GLP-1, two therapeutic strategies are employed and are as follows: GLP-1RAs, which resist the degradation by DPP-4 enzyme and thus prolong receptor activation, and DPP-4 inhibitors, which extend the life of endogenous incretin hormones. GLP-1RAs improve glucose-dependent insulin release, reduce glucagon secretion, enhance insulin sensitivity, and have additional benefits on appetite suppression, cardiovascular protection, renal sodium excretion, and metabolic functions in adipose and muscle tissues. The efficacy of GLP-1RAs varies with their duration of action; long-acting forms are particularly effective in controlling both postprandial and fasting glucose levels, demonstrating significant improvements in glycemic control in patients with T2DM [162–165].

Studies have shown that GLP-1RAs can modulate ECM homeostasis by inhibiting the mitogen-activated protein kinase (MAPK) pathway and BATF/JUN heterodimer formation. They also downregulate the pro-fibrotic factor TGF- β 1, suppressing SMAD3 and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling while enhancing WNT/ β -catenin signaling and other pathways, thus reducing extracellular matrix protein deposition and delaying fibrosis [166–168].

GLP-1RAs ameliorate diabetes-related cardiac fibrosis by stimulating PPAR δ expression. Additionally, GLP-1 attenuates high glucose-induced ROS production in cardiomyocytes through an AMPK/mTORC1/p70S6K-dependent mechanism [169,170]. In vitro, semaglutide suppressed cardiomyocyte apoptosis produced by ischemia/reperfusion (I/R)

via activating the PKG/PKC ϵ /ERK1/2 pathway [171]. It also might potentially be a beneficial treatment target for preventing diabetic cardiomyopathy by modifying integrin-linked kinase (ILK)-associated TGF- β /SMAD signaling pathways [172].

Research has shown that GLP-1 analogs, such as liraglutide, may prevent myocardial damage by activating the Sirt1/AMPK signaling pathways to suppress cellular pyroptosis in diabetic cardiac tissues and by lowering the expression of fibrotic markers [173,174]. Moreover, treatment with liraglutide limits infarct size, expansion, and cardiac rupture in the normal and diabetic heart by activating prosurvival kinases and cytoprotective genes in the heart in a preclinical murine model of experimental ischemia following coronary artery obstruction. In mouse cardiomyocytes cultivated in vitro, it also raises cAMP and lowers apoptosis [175].

GLP-1 analog exendin-4 has been found to suppress fibrosis and PPAR α -mediated lipid accumulation via the protein kinase A/Rho-associated protein kinase (PKA/ROCK) pathway [176]. Recent studies in vitro have shown that exendin-4 effectively reduces the formation of intracellular and mitochondrial ROS, prevents apoptosis, and improves mitochondrial membrane potential impairment. Additionally, it activates genes associated with mitochondrial functions and dynamics via the cAMP/Epac/PI3K/Akt pathway. By encouraging the nuclear translocation of TFEB, it restores autophagic flux. It also protects endothelial function by upregulating the expression of HDL scavenger receptor class BI via the AMPK/FoxO1 pathway and eNOS activation. Lastly, it decreases the size of infarcts and maintains cardiac function by having anti-apoptotic and antioxidative properties [177–179]. Research have demonstrated the cardioprotective benefits of exendin-4 in rats with diabetes. This is due to its capacity to enhance mitochondrial activities by targeting inflammatory and autophagy processes and suppressing cardiomyocyte pyroptosis via the AMPK-TXNIP pathway [180,181]. In mice models, after MI, the positive impacts of exendin-4 on cardiac remodeling may be achieved via activating the eNOS/cGMP/PKG pathway, β -arrestin-2, and protein phosphatase 2A and suppressing β -catenin, collagen I, collagen III, transforming growth factor- β 1, and PI3K/AKT signaling pathway [181–184].

Modified mesenchymal stem cells engineered to secrete a fusion protein have demonstrated positive effects on cardiac recovery post-infarction by reducing TGF- β expression and influencing extracellular matrix protein deposition. GLP-1RAs inhibit cardiac remodeling in rats after AMI by modulating various signaling pathways [182,185]. In murine models, liraglutide reduces cardiac fibrosis and enhances capillary density, potentially improving heart function [186,187].

Clinical studies have also shown the anti-fibrotic effects of GLP-1RAs. Reduced GLP-1 levels in plasma have been associated with atheroma instability and cardiac fibrosis in non-diabetic patients with ACS [188]. Initiating GLP-1RAs therapy shortly after a first AMI in patients with diabetes has been linked to a reduced risk of significant CV events [189]. Long-term treatment with GLP-1RAs and/or SGLT-2i positively impacts the clinical prognosis of patients with diabetes that are hospitalized with AMI [190,191].

However, conflicting results exist in clinical trials regarding the impact of GLP-1RAs on myocardial remodeling. While some studies show potential benefits, others reveal no significant effects on cardiac function or fibrosis parameters [192,193]. Nonetheless, retrospective studies suggest a reduced risk of CV events and mortality in patients with diabetes treated with GLP-1RAs [194].

In summary, the potential anti-fibrotic effects of GLP-1RAs offer promising avenues for clinical treatment by inhibiting epithelial–endothelial transformation, suppressing inflammatory responses, and reducing oxidative stress damage while controlling blood glucose levels.

8.3. Dipeptidyl Peptidase-4 Inhibitors

DPP4i are small, orally administered compounds that specifically interact with the catalytic site of DPP4 without affecting its other known activities, such as its immunomodulatory effects. DPP-4 is a serine protease primarily responsible for deactivating the GLP-1 and GIP generated in the intestines. The efficacy of DPP4i as anti-diabetic agents is closely tied to their

ability to inhibit DPP4 enzyme activity, thus leading to a prolongation of the lifespan of incretin hormones and an improvement in insulin production, which is reliant on glucose levels. By prolonging the half-life of GLP-1, increasing insulin levels, and lowering blood glucose levels, DPP4i offer therapeutic benefits [195,196]. Contrary to the anti-diabetic medications stated above, DPP-4 inhibitors do not impact insulin sensitivity or secretion [197–200].

A meta-analysis has shown that DPP-4 inhibitors may effectively reduce low-grade inflammation in individuals with T2DM by decreasing levels of C-reactive protein (CRP), TNF- α , IL-6, and IL-1 β [201]. Recent studies on diabetic animal models, such as db/db mice, have demonstrated the cardioprotective effects of DPP4 inhibitors like evogliptin. These inhibitors mitigate the primary drivers of diabetic cardiomyopathy, including cardiac hypertrophy, fibrosis, and systolic and diastolic dysfunction. Evogliptin has been shown to reduce mitochondrial dysfunction and lipotoxicity by reducing myocardial fat formation or modulating transcription factors [202]. Additionally, gemigliptin was also shown to reduce cardiomyocyte cross-sectional areas and interstitial and perivascular fibrosis [203]. In rats with HF, monotherapy with DPP4i like valsartan and vildagliptin has been found to decrease LV hypertrophy, alleviate cardiac interstitial fibrosis, and improve systolic and diastolic performance [204].

Studies by Wójcicka et al. investigated whether incretin drugs like exenatide and sitagliptin exert heart-protective and anti-fibrotic effects through their influence on asymmetric dimethylarginine (ADMA) metabolism. Both drugs reduced cardiac fibrosis and immune response around blood vessels. In metabolic syndrome, sitagliptin and exenatide positively impacted cardiac fibrotic remodeling and circulating levels of endogenous NOS inhibitors, such as ADMA, which inhibit NO production, essential for maintaining healthy blood vessels [205]. Additionally, DPP4i have been found to have antifibrotic effects by blocking the interaction between membrane-bound DPP-4, integrin, and the caveolin complex [206].

Linagliptin improved systolic and diastolic blood pressure and cardiac function while reducing cardiac fibrosis in animal models. It also ameliorated structural disruptions in the heart induced by diabetic conditions [207]. In db/db mice with MI, it targeted the NLRP3/ASC inflammasome, increasing EF and lowering IL-1 β and IL-6 levels [208].

Sitagliptin treatment effectively hindered cardiac fibrosis development and alleviated cardiac hypertrophy [209]. It also mitigates heart dysfunction and unfavorable remodeling after AMI in diabetic animal models [210]. Additionally, it reduced the severity of diabetic cardiomyopathy by suppressing the JAK/STAT signaling pathway and decreasing TGF- β 1 protein levels, therefore avoiding myocardial remodeling [211,212].

Alogliptin reduced interstitial fibrosis and decreased mitochondrial ROS generation, preventing the mitochondrial depolarization of membranes and swelling in rabbits with diabetes [213,214]. Interestingly, adding saxagliptin to dapagliflozin may have reduced the degree of activation of the NLRP3/ASC inflammasome. Higher myocardial lipid deposits, oxidative stress, and apoptosis were all reduced by saxagliptin [150,176].

Despite several CV outcome trials evaluating the efficacy and safety of new glucose-lowering drugs for CV outcomes, there is limited research on their correlation with the reduction in cardiac fibrosis risk in patients with diabetes and ACS.

8.4. Neprilysin Inhibitor

Neutral endopeptidase, also known as neprilysin (NEP), breaks down natriuretic peptides (NPs) by hydrolysis. Neprilysin inhibitors (NEPis) have been discovered to elevate the concentration of defensive natriuretic peptides (NPs), hence enhancing their ability to defend against diabetic consequences. Nevertheless, NEPi alone proved inadequate in addressing cardiovascular disorders as mandated by conventional pharmacology, prompting the development of dual-acting inhibitors that target both neprilysin and the pressor arm (Ang II/ACE/AT1R) of the RAS. Recent human trials have shown that the dual angiotensin receptor–neprilysin inhibitor (ARNi) has been effective in enhancing glycemic control and insulin sensitivity in persons with T2DM and/or obesity. Additionally, preclinical

research has also shown that inhibiting neprilysin, either on its own or in conjunction with renin–angiotensin system blockers, has positive effects on glucose regulation [215–217].

Studies have shown that ARNIs enhance glucose homeostasis, glucose management, and insulin sensitivity in individuals with T2DM [215]. Evidence from human research substantiates the efficacy of neprilysin inhibitors for both preventing and treating type 2 diabetes. The PARADIGM-HF study shown that administering the ARNi over a duration of 3 years led to a more significant decrease in HbA1c levels and a reduced number of patients needing to start oral glucose-lowering medicines or insulin therapy, in comparison to using just an ACE inhibitor. In an additional investigation, switching the therapy from either an ACE inhibitor or ARB to ARNi for a duration of 3 months led to a drop in serum neprilysin activity. This decrease was shown to be linked to lower levels of fructosamine, a marker used to measure protein glycation. The results of this study, along with a previous publication, indicated that ARNi may have positive effects on glycemic management by partially raising the levels of GLP-1 in the bloodstream [218,219].

In streptozotocin (STZ)-induced mice with diabetes and HF and a decreased EF, LCZ696, the initial member of ARNi, has been shown to enhance cardiac functions and mitigate fibrosis by inhibiting TGF- β [220]. According to research by Qing et al., mice with diabetes treated with LCZ696 had better cardiac function and ventricular remodeling than mice with diabetes that were left untreated. Additionally, LCZ696 reduced oxidative stress in vitro and in vivo. Finally, via lowering oxidative stress, apoptosis, and cardiac inflammation, LCZ696 ameliorated diabetic cardiomyopathy [221].

Researchers have created and tested omapatrilat, the most researched vasopeptidase inhibitor, against heart diseases associated with diabetes. Compared to ACEi, this medication had greater cardioprotective potential in spontaneously diabetic rats because it controlled systolic blood pressure, improved diastolic function, and decreased heart hypertrophy [222]. By restoring RAS and NPS activities, raising cGMP, and suppressing inflammatory, profibrotic, and apoptotic signaling, a recent study demonstrated the cardioprotective efficacy of NEPi and ACE2 activator combination treatment, which was successful in preventing DC [223].

In conclusion, not many studies have been conducted to determine how neprilysin inhibitors affect DC. Additional research is required to investigate the possible processes that underlie its effects, since this might serve as the foundation for a novel treatment approach for it.

8.5. Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase

The pathological and molecular processes that underlie diabetes include irregularities in the control of calcium homeostasis within cardiomyocytes, which subsequently modifies the ventricular excitation–contraction coupling. A dysregulation of Ca²⁺ cycling in the diabetic heart involves a decrease in sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) activity, which may also be accompanied by a drop in SERCA protein expression. Multiple preclinical and clinical experiments have shown that maintaining proper management of blood sugar levels is ineffective in slowing the course of diabetic cardiomyopathy, particularly in the intermediate and advanced phases. Thus, individuals with diabetic cardiomyopathy may continue to experience hyperglycemic stress despite the careful management of blood glucose levels. The etiology of DC is mostly investigated utilizing tiny molecular probes that have strong effectiveness against it. As a result, SERCA could be a target molecule for pharmacological intervention targeted at improving the mechanical performance and energy efficiency of the diabetic heart, which is characterized by a malfunctioning SR Ca²⁺ loading [224].

Recent research has shown that SJ-12, a new curcumin derivative, has therapeutic efficacy in STZ-induced diabetic cardiomyopathy. Furthermore, SJ-12 administration may reduce the fibrotic response. SJ-12 functions as an anti-fibrosis agent by specifically targeting the OGT-regulated O-GlcNAc-Sp1/SERCA2a/calcium signaling pathway [225].

A significant buildup of collagen and ECM proteins, linked to higher death rates, defines cardiac fibrosis. Recent findings suggest that the deregulation of SERCA2a and

inappropriate handling of Ca²⁺ cause cardiac fibrosis. An imbalance in Ca²⁺ levels, on the other hand, can cause problems with energy metabolism, which in turn speeds up the development of cardiac fibrosis by making more matrix proteins. Conventional autophagy is responsible for breaking down and reusing cellular components, which helps to sustain cellular energy production. Excessive or inadequate autophagy may have a detrimental effect on the viability of cardiomyocytes, leading to a deterioration in both the structure and function of the heart. Latest research has shown that inhibiting the expression of SERCA might serve as a trigger for endoplasmic reticulum (ER) stress, which in turn leads to excessive autophagy and eventually results in cardiac fibrosis [226–228].

Most of the studies have mostly focused on the function of SERCA as the calcium pump responsible for transporting calcium from the cytosol to the SR lumen, working against the concentration gradient. However, there is little information about its involvement in cardiac fibrosis in patients with diabetes.

In Table 1, the main studies evaluating the antifibrotic effects of hypoglycemic medication are depicted.

Table 1. The main antifibrotic effect of novel medication.

Novel Medication	Antifibrotic Effect
SGLT2i	- Reduces the levels of TNF-α, IL-1β, IL-6, and hs-CRP in patients with HF and diabetes [130]. - Reduces cardiac fibrosis in rats with T2DM by inhibiting EndMT and fibroblast activation [131]. - Decreases oxidative stress and prevents the production of TNF-α, IL-1β, IL-6, and MCP-1 [132–134]. - Increases the phosphorylation and expression of STAT3 while reducing the expression of myocardial IL-6 and iNOS [138]. - Increases the activation of M2 macrophages, leading to a reduction in cardiac fibrosis at a molecular level [139]. - Decreases the production of the NLRP3 inflammasome, IL-1β, IL-6, and TNF-α [137,147,148]. - Attenuates TGF-β1-induced fibroblast activation and decreases COL-1, connective tissue growth factor, and MMP-2 [152]. - Alleviates cardiac fibrosis by downregulating the TGF-β/Smad pathway, triggering Nrf2/ARE signaling, and lowering the concentrations of Smad1, Smad2, and Smad3 in the heart tissue of mice with diabetes [146]. - Effectively decreases the levels of IL-1β, IL-6, and TNF-α in the LV of rats with T1DM [149]. - Enhances Nrf2 expression and facilitates its nuclear translocation, ameliorating oxidative stress and mitochondrial dysfunction [145].
GLP-1RAs	- By stimulating the expression of PPARδ, GLP-1RAs ameliorate diabetes-related cardiac fibrosis in a diabetic cardiomyopathy model [169]. - Decrease high glucose-induced ROS production in cardiomyocytes via a mechanism that is reliant on AMPK/mTORC1/p70S6K [170]. - Lower the expressions of P4hα-1, COL-1, COL-3, MMP-1, and MMP-9 [173]. - Suppress fibrosis and PPARα-mediated lipid accumulation and toxicity controlled by the PKA/ROCK pathway [176]. - Reduce cardiac remodeling in rats after AMI by inhibiting the activation of β-arrestin-2, PP2A, and GSK3β [182,185]. - Suppress the production of CTGF in both the infarcted and non-infarcted regions of mice after a heart attack by stimulating cAMP and decreasing the migration of collagen fibers from the infarcted region to the non-infarcted region [186,187]. - Suppress cardiomyocyte apoptosis produced by ischemia/reperfusion (I/R) via activating the PKG/PKCϵ/ERK1/2 pathway [171]. - Prevent myocardial damage by activating the Sirt1/AMPK signaling pathways to suppress cellular pyroptosis in diabetic cardiac tissues [173,174]. - Effectively reduce the formation of intracellular and mitochondrial ROS, prevent apoptosis, and improve mitochondrial membrane potential impairment [177–179]. - Activate genes associated with mitochondrial functions and dynamics via the cAMP/Epac/PI3K/Akt pathway [177–179]. - Enhance mitochondrial activities by targeting inflammatory and autophagy processes and suppressing cardiomyocyte pyroptosis via the AMPK-TXNIP pathway [180,181].
DPP4i	- Decreases LV hypertrophy, relieves cardiac interstitial fibrosis, and enhances systolic and diastolic performance [204]. - Decreases the amount of fibrosis around blood vessels and has positive impact on cardiac fibrotic remodeling and the circulating level of endogenous NOS inhibitors [205]. - Exhibits antifibrotic effects by blocking the interaction between membrane-bound DPP-4, integrin, and the caveolin complex [206]. - Linagliptin exhibits improvements by reducing disruptions in myocardial fiber, mitochondria, and sarcomere, along with the necroptosis [207]. - Sitagliptin treatment effectively hinders the development of cardiac fibrosis and alleviates cardiac hypertrophy [209]. - Reduces the severity of diabetic cardiomyopathy by suppressing the JAK/STAT signaling pathway and decreasing TGF-β1 protein levels, therefore avoiding myocardial remodeling [211,212].
ARNi	Enhances cardiac functions and mitigates fibrosis by inhibiting TGF-β [220]

HF = heart failure; LV = left ventricle; TNF- α = tumor necrosis factor- α ; IL-1 β = interleukin-1 β ; IL-6 = interleukin-6; hs-CRP = high sensitivity c-reactive protein; COL-1 = type 1 collagen; COL-3 = type 3 collagen; MMP-1 = matrix metalloproteinase 1; MMP-2 = matrix metalloproteinase 2; MMP-9 = matrix metalloproteinase 9; PPAR α = peroxisome proliferator-activated receptor alpha; PKA/ROCK = protein kinase A/Rho-associated protein kinase; PP2A = protein phosphatase 2; DPP4 = dipeptidyl peptidase-4; DPP4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = sodium-glucose cotransporter 2 inhibitors; GLP-1RAs = glucagon-like peptide-1 receptor agonists; CTGF = connective tissue growth factor; cAMP = cyclic adenosine monophosphate; GSK3 β = glycogen synthase kinase 3 beta; STAT3 = signal transducer and activator of transcription 3; iNOS = inducible form of nitric oxide synthase; P4h α -1 = prolyl 4-hydroxylase subunit alpha 1; EndMT = endothelial-to-mesenchymal transition; ARNi = angiotensin receptor-neprilysin inhibitor; and T1DM = type 1 diabetes mellitus.

9. Limitations and Future Directions

While this research offers valuable insights, it is important to acknowledge certain limitations that may affect the interpretation and generalization of findings. Firstly, many

studies assessing the effectiveness of anti-diabetic medications in reducing fibrosis risk post-MI have relatively short follow-up periods, limiting our understanding of their long-term effects. Secondly, variability in patient characteristics, such as age, comorbidities, and medication history, across different studies may affect the generalizability of findings. Finally, while some studies demonstrate the efficacy of anti-diabetic medications in reducing fibrosis, the exact mechanisms underlying these effects remain incompletely understood.

Thus, we recognize the need for future research to focus on addressing these limitations, exploring new directions, and contributing to advancing our knowledge in the field. Further research is needed to elucidate the precise mechanisms through which anti-diabetic medications exert their anti-fibrotic effects post-MI, potentially uncovering novel therapeutic targets. Longitudinal studies with extended follow-up periods are necessary to assess the sustained efficacy and safety of anti-diabetic medications in reducing fibrosis and improving CV outcomes. Investigating the potential synergistic effects of combining anti-diabetic medications with other therapeutic agents targeting different pathways involved in fibrosis could lead to enhanced treatment efficacy. In conclusion, future research should focus on elucidating the underlying mechanisms of action of these medications, conducting longitudinal studies with extended follow-up periods, and exploring personalized medicine approaches and combination therapies.

10. Conclusions

In conclusion, myocardial fibrosis is a critical contributor to adverse cardiac remodeling following AMI, particularly in patients with DM. Emerging evidence suggests that anti-diabetic medications, such as SGLT2i, GLP-1RAs, and DPP4i, may hold promise in attenuating fibrosis and improving CV outcomes in this patient population. Overall, the identification of effective anti-fibrotic strategies in patients with diabetes post-MI holds significant clinical implications for improving CV outcomes and reducing the burden of heart failure. Continued research efforts in this area are essential for advancing our understanding and refining treatment strategies to optimize patient care.

Author Contributions: Conceptualization, L.A. and A.T.; methodology, L.A.; software, A.T. and B.-S.T.; validation, L.A., R.A.S. and C.S.; formal analysis, L.A., C.S., R.-L.Z. and B.-S.T.; investigation, A.T. and B.-S.T.; data curation, L.A., A.T. and B.-S.T.; writing—original draft preparation, L.A., A.T., R.-L.Z. and B.-S.T.; writing—review and editing, L.A., A.T. and B.-S.T.; supervision, R.A.S. and C.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Frantz, S.; Hundertmark, M.J.; Schulz-Menger, J.; Bengel, F.M.; Bauersachs, J. Left ventricular remodelling post-myocardial infarction: Pathophysiology, imaging, and novel therapies. *Eur. Heart J.* **2022**, *43*, 2549–2561. [[CrossRef](#)] [[PubMed](#)]
2. Frangogiannis, N.G. Cardiac fibrosis. *Cardiovasc. Res.* **2021**, *117*, 1450–1488. [[CrossRef](#)] [[PubMed](#)]
3. Nakamura, K.; Miyoshi, T.; Yoshida, M.; Akagi, S.; Saito, Y.; Ejiri, K.; Matsuo, N.; Ichikawa, K.; Iwasaki, K.; Naito, T.; et al. Pathophysiology and Treatment of Diabetic Cardiomyopathy and Heart Failure in Patients with Diabetes Mellitus. *Int. J. Mol. Sci.* **2022**, *23*, 3587. [[CrossRef](#)] [[PubMed](#)]
4. Preis, S.R.; Pencina, M.J.; Hwang, S.J.; D'Agostino, R.B., Sr.; Savage, P.J.; Levy, D.; Fox, C.S. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. *Circulation* **2009**, *120*, 212–220. [[CrossRef](#)] [[PubMed](#)]
5. Matheus, A.S.; Tannus, L.R.; Cobas, R.A.; Palma, C.C.; Negrato, C.A.; Gomes, M.B. Impact of diabetes on cardiovascular disease: An update. *Int. J. Hypertens.* **2013**, *2013*, 653789. [[CrossRef](#)] [[PubMed](#)]
6. Davies, M.J.; Aroda, V.R.; Collins, B.S.; Gabbay, R.A.; Green, J.; Maruthur, N.M.; Rosas, S.E.; Del Prato, S.; Mathieu, C.; Mingrone, G.; et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **2022**, *45*, 2753–2786. [[CrossRef](#)] [[PubMed](#)]

7. Ding, Y.; Wang, Y.; Zhang, W.; Jia, Q.; Wang, X.; Li, Y.; Lv, S.; Zhang, J. Roles of Biomarkers in Myocardial Fibrosis. *Aging Dis.* **2020**, *11*, 1157–1174. [[CrossRef](#)] [[PubMed](#)]
8. Frangogiannis, N.G. Cardiac fibrosis: Cell biological mechanisms, molecular pathways and therapeutic opportunities. *Mol. Aspects Med.* **2019**, *65*, 70–99. [[CrossRef](#)]
9. Ma, T.; Huang, X.; Zheng, H.; Huang, G.; Li, W.; Liu, X.; Liang, J.; Cao, Y.; Hu, Y.; Huang, Y. SFRP2 Improves Mitochondrial Dynamics and Mitochondrial Biogenesis, Oxidative Stress, and Apoptosis in Diabetic Cardiomyopathy. *Oxidative Med. Cell Longev.* **2021**, *2021*, 9265016. [[CrossRef](#)]
10. Salib, M.; Girerd, N.; Simon, A.; Kearney-Schwartz, A.; Duarte, K.; Leroy, C.; Rossignol, P.; Benetos, A.; Frimat, L.; Girerd, S. Levels of Procollagen Type I C-Terminal Pro-Peptide and Galectin-3, Arterial Stiffness Measured By Pulse Wave Velocity, and Cardiovascular Morbidity and Mortality in 44 Patients 2 Years After Kidney Transplantation. *Ann. Transplant.* **2023**, *28*, e938137. [[CrossRef](#)]
11. Ponikowska, B.; Iwanek, G.; Zdanowicz, A.; Urban, S.; Zymlinski, R.; Ponikowski, P.; Biegus, J. Biomarkers of Myocardial Injury and Remodeling in Heart Failure. *J. Pers. Med.* **2022**, *12*, 799. [[CrossRef](#)] [[PubMed](#)]
12. Ferreira, J.P.; Rossignol, P.; Pizard, A.; Machu, J.L.; Collier, T.; Girerd, N.; Huby, A.C.; Gonzalez, A.; Diez, J.; Lopez, B.; et al. Potential spironolactone effects on collagen metabolism biomarkers in patients with uncontrolled blood pressure. *Heart* **2019**, *105*, 307–314. [[CrossRef](#)] [[PubMed](#)]
13. Zile, M.R.; O'Meara, E.; Claggett, B.; Prescott, M.F.; Solomon, S.D.; Swedberg, K.; Packer, M.; McMurray, J.J.V.; Shi, V.; Lefkowitz, M.; et al. Effects of Sacubitril/Valsartan on Biomarkers of Extracellular Matrix Regulation in Patients With HFrEF. *J. Am. Coll. Cardiol.* **2019**, *73*, 795–806. [[CrossRef](#)] [[PubMed](#)]
14. Zhang, B.; Li, X.; Chen, C.; Jiang, W.; Lu, D.; Liu, Q.; Wang, K.; Yan, Y.; Jiang, Z.; Geng, J.; et al. Renal Denervation Effects on Myocardial Fibrosis and Ventricular Arrhythmias in Rats with Ischemic Cardiomyopathy. *Cell Physiol. Biochem.* **2018**, *46*, 2471–2479. [[CrossRef](#)] [[PubMed](#)]
15. Santanasto, A.J.; Cvejkus, R.K.; Wojczynski, M.K.; Marron, M.M.; Schupf, N.; Christensen, K.; Thyagarajan, B.; Zmuda, J.M. Circulating Procollagen Type III N-Terminal Peptide and Physical Function in Adults from the Long Life Family Study. *J. Gerontol. A Biol. Sci. Med. Sci.* **2021**, *76*, 1273–1279. [[CrossRef](#)] [[PubMed](#)]
16. Osokina, A.; Karetnikova, V.; Polikutina, O.; Ivanova, A.; Gruzdeva, O.; Dyleva, Y.; Kokov, A.; Brel, N.; Pecherina, T.; Barbarash, O. Prognostic potential of cardiac structural and functional parameters and N-terminal propeptide of type III procollagen in predicting cardiac fibrosis one year after myocardial infarction with preserved left ventricular ejection fraction. *Aging* **2021**, *13*, 194–203. [[CrossRef](#)] [[PubMed](#)]
17. Zelniker, T.A.; Jarolim, P.; Scirica, B.M.; Braunwald, E.; Park, J.G.; Das, S.; Sabatine, M.S.; Morrow, D.A. Biomarker of Collagen Turnover (C-Terminal Telopeptide) and Prognosis in Patients With Non-ST-Elevation Acute Coronary Syndromes. *J. Am. Heart Assoc.* **2019**, *8*, e011444. [[CrossRef](#)] [[PubMed](#)]
18. Manhenke, C.; Orn, S.; Squire, I.; Radauceanu, A.; Alla, F.; Zannad, F.; Dickstein, K. The prognostic value of circulating markers of collagen turnover after acute myocardial infarction. *Int. J. Cardiol.* **2011**, *150*, 277–282. [[CrossRef](#)] [[PubMed](#)]
19. Owolabi, U.S.; Amraotkar, A.R.; Coulter, A.R.; Singam, N.S.V.; Aladili, B.N.; Singh, A.; Trainor, P.J.; Mitra, R.; DeFilippis, A.P. Change in matrix metalloproteinase 2, 3, and 9 levels at the time of and after acute atherothrombotic myocardial infarction. *J. Thromb. Thrombolysis* **2020**, *49*, 235–244. [[CrossRef](#)]
20. Myasoedova, V.A.; Chistiakov, D.A.; Grechko, A.V.; Orekhov, A.N. Matrix metalloproteinases in pro-atherosclerotic arterial remodeling. *J. Mol. Cell Cardiol.* **2018**, *123*, 159–167. [[CrossRef](#)]
21. Zhou, K.; Li, Y.; Xu, Y.; Guo, R. Circulating Matrix Metalloproteinase-28 Levels Are Related to GRACE Scores and Short-Term Outcomes in Patients with Acute Myocardial Infarction. *Biomed. Res. Int.* **2020**, *2020*, 9206703. [[CrossRef](#)] [[PubMed](#)]
22. Basia, D.; Gupta, M.D.; Kunal, S.; Muheeb, G.; Girish, M.P.; Bansal, A.; Batra, V.; Yusuf, J.; Mukhopadhyay, S.; Tyagi, S.; et al. Matrix metalloproteinases and their gene polymorphism in young ST-segment elevation myocardial infarction. *Indian Heart J.* **2022**, *74*, 519–523. [[CrossRef](#)] [[PubMed](#)]
23. Somuncu, M.U.; Pusuroglu, H.; Karakurt, H.; Bolat, I.; Karakurt, S.T.; Demir, A.R.; Isiksacan, N.; Akgul, O.; Surgit, O. The prognostic value of elevated matrix metalloproteinase-9 in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: A two-year prospective study. *Rev. Port. Cardiol.* **2020**, *39*, 267–276. [[CrossRef](#)] [[PubMed](#)]
24. Watson, C.; Spiers, J.P.; Waterstone, M.; Russell-Hallinan, A.; Gallagher, J.; McDonald, K.; Ryan, C.; Gilmer, J.; Ledwidge, M. Investigation of association of genetic variant rs3918242 of matrix metalloproteinase-9 with hypertension, myocardial infarction and progression of ventricular dysfunction in Irish Caucasian patients with diabetes: A report from the STOP-HF follow-up programme. *BMC Cardiovasc. Disord.* **2021**, *21*, 87. [[CrossRef](#)] [[PubMed](#)]
25. Xie, Y.T.; Dang, Y.; Zhang, F.F.; Zhang, Q.H.; Wu, H.B.; Liu, G. Combination of serum TIMP-3, CA125, and NT-proBNP in predicting ventricular remodeling in patients with heart failure following acute myocardial infarction. *Cardiovasc. Diagn. Ther.* **2020**, *10*, 1184–1191. [[CrossRef](#)] [[PubMed](#)]
26. Pang, H.F.; Gao, Y.; Liu, J.M.; Lu, J.P.; Wang, Y.P.; Wang, S.M.; Hou, L.B.; Tian, A.X.; Gao, Y. Prognostic value of tissue inhibitor of metalloproteinase-matrix metalloproteinase biomarkers at 30 days in patients with acute myocardial infarction without reperfusion therapy. *Chin. Med. J.* **2020**, *134*, 481–483. [[CrossRef](#)] [[PubMed](#)]
27. Zhang, X.G.; Wei, Y.; Jiang, J.; Wang, L.; Liang, H.Y.; Lei, C.B. Effect of TGF-beta1 on myocardial cell apoptosis in rats with acute myocardial infarction via MAPK signaling pathway. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 1350–1356. [[CrossRef](#)] [[PubMed](#)]

28. Kong, P.; Shinde, A.V.; Su, Y.; Russo, I.; Chen, B.; Saxena, A.; Conway, S.J.; Graff, J.M.; Frangogiannis, N.G. Opposing Actions of Fibroblast and Cardiomyocyte Smad3 Signaling in the Infarcted Myocardium. *Circulation* **2018**, *137*, 707–724. [[CrossRef](#)] [[PubMed](#)]
29. Zhou, X.; Chen, J.; Zhang, Q.; Shao, J.; Du, K.; Xu, X.; Kong, Y. Prognostic Value of Plasma Soluble Corin in Patients With Acute Myocardial Infarction. *J. Am. Coll. Cardiol.* **2016**, *67*, 2008–2014. [[CrossRef](#)]
30. Zhou, X.; Chen, J.C.; Liu, Y.; Yang, H.; Du, K.; Kong, Y.; Xu, X.H. Plasma Corin as a Predictor of Cardiovascular Events in Patients With Chronic Heart Failure. *JACC Heart Fail.* **2016**, *4*, 664–669. [[CrossRef](#)]
31. Hu, W.; Chen, S.; Song, Y.; Zhu, F.; Shi, J.; Han, X.; Zhou, D.; Zhi, Z.; Zhang, F.; Shen, Y.; et al. Serum Soluble Corin Deficiency Predicts Major Disability within 3 Months after Acute Stroke. *PLoS ONE* **2016**, *11*, e0163731. [[CrossRef](#)] [[PubMed](#)]
32. Yang, S.F.; Chou, R.H.; Lin, S.J.; Li, S.Y.; Huang, P.H. Serum PCSK6 and corin levels are not associated with cardiovascular outcomes in patients undergoing coronary angiography. *PLoS ONE* **2019**, *14*, e0226129. [[CrossRef](#)] [[PubMed](#)]
33. Liu, X.; Zhang, J.; Li, P.; Han, P.; Kang, Y.J.; Zhang, W. Gene expression patterns and related pathways in the hearts of rhesus monkeys subjected to prolonged myocardial ischemia. *Exp. Biol. Med.* **2023**, *248*, 350–360. [[CrossRef](#)] [[PubMed](#)]
34. Vucic, R.M.; Andrejic, O.M.; Stokanovic, D.; Stoimenov, T.J.; McClements, L.; Nikolic, V.N.; Sreckovic, M.; Veselinovic, M.; Aleksandric, S.; Popadic, V.; et al. Galectin-3 as a Prognostic Biomarker in Patients with First Acute Myocardial Infarction without Heart Failure. *Diagnostics* **2023**, *13*, 3348. [[CrossRef](#)] [[PubMed](#)]
35. Li, M.; Guo, K.; Huang, X.; Feng, L.; Yuan, Y.; Li, J.; Lao, Y.; Guo, Z. Association Between Serum Galectin-3 Levels and Coronary Stenosis Severity in Patients With Coronary Artery Disease. *Front. Cardiovasc. Med.* **2022**, *9*, 818162. [[CrossRef](#)] [[PubMed](#)]
36. Kokturk, U.; Pusuroglu, H.; Somuncu, M.U.; Akgul, O.; Uygur, B.; Ozyilmaz, S.; Isiksacan, N.; Surgit, O.; Yildirim, A. Short and Long-Term Prognostic Significance of Galectin-3 in Patients with ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Angiology* **2023**, *74*, 889–896. [[CrossRef](#)] [[PubMed](#)]
37. Wang, Q.; Huai, W.; Ye, X.; Pan, Y.; Yang, X.; Chen, M.; Ma, Q.B.; Gao, Y.; Zhang, Y. Circulating plasma galectin-3 predicts new-onset atrial fibrillation in patients after acute myocardial infarction during hospitalization. *BMC Cardiovasc. Disord.* **2022**, *22*, 392. [[CrossRef](#)] [[PubMed](#)]
38. Erdogan, O.; Karaayvaz, E.; Erdogan, T.; Panc, C.; Sarikaya, R.; Oncul, A.; Bilge, A.K. A new biomarker that predicts ventricular arrhythmia in patients with ischemic dilated cardiomyopathy: Galectin-3. *Rev. Port. Cardiol.* **2021**, *40*, 829–835. [[CrossRef](#)] [[PubMed](#)]
39. Obeid, S.; Yousif, N.; Davies, A.; Loretz, R.; Saleh, L.; Niederseer, D.; Noor, H.A.; Amin, H.; Mach, F.; Gencer, B.; et al. Prognostic role of plasma galectin-3 levels in acute coronary syndrome. *Eur. Heart J. Acute Cardiovasc. Care* **2020**, *9*, 869–878. [[CrossRef](#)]
40. Grandin, E.W.; Jarolim, P.; Murphy, S.A.; Ritterova, L.; Cannon, C.P.; Braunwald, E.; Morrow, D.A. Galectin-3 and the development of heart failure after acute coronary syndrome: Pilot experience from PROVE IT-TIMI 22. *Clin. Chem.* **2012**, *58*, 267–273. [[CrossRef](#)]
41. Cassaglia, P.; Penas, F.; Betazza, C.; Fontana Estevez, F.; Miksztowicz, V.; Martinez Naya, N.; Llamosas, M.C.; Noli Truant, S.; Wilensky, L.; Volberg, V.; et al. Genetic Deletion of Galectin-3 Alters the Temporal Evolution of Macrophage Infiltration and Healing Affecting the Cardiac Remodeling and Function after Myocardial Infarction in Mice. *Am. J. Pathol.* **2020**, *190*, 1789–1800. [[CrossRef](#)] [[PubMed](#)]
42. Frangogiannis, N.G. Targeting galectin-3 in myocardial infarction: A unique opportunity for biomarker-guided therapy. *Cardiovasc. Res.* **2023**, *119*, 2495–2496. [[CrossRef](#)] [[PubMed](#)]
43. Daseke, M.J., 2nd; Valerio, F.M.; Kalusche, W.J.; Ma, Y.; DeLeon-Pennell, K.Y.; Lindsey, M.L. Neutrophil proteome shifts over the myocardial infarction time continuum. *Basic Res. Cardiol.* **2019**, *114*, 37. [[CrossRef](#)] [[PubMed](#)]
44. Daseke, M.J., 2nd; Chalise, U.; Becirovic-Agic, M.; Salomon, J.D.; Cook, L.M.; Case, A.J.; Lindsey, M.L. Neutrophil signaling during myocardial infarction wound repair. *Cell Signal* **2021**, *77*, 109816. [[CrossRef](#)] [[PubMed](#)]
45. Ma, Y. Role of Neutrophils in Cardiac Injury and Repair Following Myocardial Infarction. *Cells* **2021**, *10*, 1676. [[CrossRef](#)] [[PubMed](#)]
46. Li, W.; Jin, Q.; Zhang, L.; He, S.; Song, Y.; Xu, L.; Deng, C.; Wang, L.; Qin, X.; Xie, M. Ultrasonic Microbubble Cavitation Deliver Gal-3 shRNA to Inhibit Myocardial Fibrosis after Myocardial Infarction. *Pharmaceutics* **2023**, *15*, 729. [[CrossRef](#)] [[PubMed](#)]
47. Kubota, A.; Frangogiannis, N.G. Macrophages in myocardial infarction. *Am. J. Physiol. Cell Physiol.* **2022**, *323*, C1304–C1324. [[CrossRef](#)] [[PubMed](#)]
48. Mo, D.; Tian, W.; Zhang, H.N.; Feng, Y.D.; Sun, Y.; Quan, W.; Hao, X.W.; Wang, X.Y.; Liu, X.X.; Li, C.; et al. Cardioprotective effects of galectin-3 inhibition against ischemia/reperfusion injury. *Eur. J. Pharmacol.* **2019**, *863*, 172701. [[CrossRef](#)] [[PubMed](#)]
49. Zhang, M.; Cheng, K.; Chen, H.; Tu, J.; Shen, Y.; Pang, L.; Wu, W. Galectin-3 knock down inhibits cardiac ischemia-reperfusion injury through interacting with bcl-2 and modulating cell apoptosis. *Arch. Biochem. Biophys.* **2020**, *694*, 108602. [[CrossRef](#)]
50. Kong, P.; Christia, P.; Frangogiannis, N.G. The pathogenesis of cardiac fibrosis. *Cell Mol. Life Sci.* **2014**, *71*, 549–574. [[CrossRef](#)]
51. Kang, P.; Wang, J.; Fang, D.; Fang, T.; Yu, Y.; Zhang, W.; Shen, L.; Li, Z.; Wang, H.; Ye, H.; et al. Activation of ALDH2 attenuates high glucose induced rat cardiomyocyte fibrosis and necroptosis. *Free Radic. Biol. Med.* **2020**, *146*, 198–210. [[CrossRef](#)]
52. Fang, L.; Ellims, A.H.; Beale, A.L.; Taylor, A.J.; Murphy, A.; Dart, A.M. Systemic inflammation is associated with myocardial fibrosis, diastolic dysfunction, and cardiac hypertrophy in patients with hypertrophic cardiomyopathy. *Am. J. Transl. Res.* **2017**, *9*, 5063–5073.

53. Bhandary, B.; Meng, Q.; James, J.; Osinska, H.; Gulick, J.; Valiente-Alandi, I.; Sargent, M.A.; Bhuiyan, M.S.; Blaxall, B.C.; Molkenin, J.D.; et al. Cardiac Fibrosis in Proteotoxic Cardiac Disease is Dependent Upon Myofibroblast TGF- β Signaling. *J. Am. Heart Assoc.* **2018**, *7*, e010013. [[CrossRef](#)]
54. Yao, Y.; Hu, C.; Song, Q.; Li, Y.; Da, X.; Yu, Y.; Li, H.; Clark, I.M.; Chen, Q.; Wang, Q.K. ADAMTS16 activates latent TGF- β , accentuating fibrosis and dysfunction of the pressure-overloaded heart. *Cardiovasc. Res.* **2020**, *116*, 956–969. [[CrossRef](#)] [[PubMed](#)]
55. Dzialo, E.; Czepiel, M.; Tkacz, K.; Siedlar, M.; Kania, G.; Blyszczuk, P. WNT/ β -Catenin Signaling Promotes TGF- β -Mediated Activation of Human Cardiac Fibroblasts by Enhancing IL-11 Production. *Int. J. Mol. Sci.* **2021**, *22*, 10072. [[CrossRef](#)] [[PubMed](#)]
56. Chou, C.H.; Hung, C.S.; Liao, C.W.; Wei, L.H.; Chen, C.W.; Shun, C.T.; Wen, W.F.; Wan, C.H.; Wu, X.M.; Chang, Y.Y.; et al. IL-6 trans-signalling contributes to aldosterone-induced cardiac fibrosis. *Cardiovasc. Res.* **2018**, *114*, 690–702. [[CrossRef](#)]
57. Tanaka, H.; Sun, T.; Kinashi, H.; Kamiya, K.; Yamaguchi, M.; Nobata, H.; Sakata, F.; Kim, H.; Mizuno, M.; Kunoki, S.; et al. Interleukin-6 blockade reduces salt-induced cardiac inflammation and fibrosis in subtotal nephrectomized mice. *Am. J. Physiol. Renal Physiol.* **2022**, *323*, F654–F665. [[CrossRef](#)] [[PubMed](#)]
58. Tseng, C.C.S.; Huibers, M.M.H.; van Kuik, J.; de Weger, R.A.; Vink, A.; de Jonge, N. The Interleukin-33/ST2 Pathway Is Expressed in the Failing Human Heart and Associated with Pro-fibrotic Remodeling of the Myocardium. *J. Cardiovasc. Transl. Res.* **2018**, *11*, 15–21. [[CrossRef](#)]
59. Zhong, C.; Min, K.; Zhao, Z.; Zhang, C.; Gao, E.; Huang, Y.; Zhang, X.; Baldini, M.; Roy, R.; Yang, X.; et al. MAP Kinase Phosphatase-5 Deficiency Protects Against Pressure Overload-Induced Cardiac Fibrosis. *Front. Immunol.* **2021**, *12*, 790511. [[CrossRef](#)]
60. Mia, M.M.; Cibi, D.M.; Ghani, S.; Singh, A.; Tee, N.; Sivakumar, V.; Bogireddi, H.; Cook, S.A.; Mao, J.; Singh, M.K. Loss of Yap/Taz in cardiac fibroblasts attenuates adverse remodelling and improves cardiac function. *Cardiovasc. Res.* **2022**, *118*, 1785–1804. [[CrossRef](#)]
61. Pordzik, J.; Jakubik, D.; Jarosz-Popek, J.; Wicik, Z.; Eyileten, C.; De Rosa, S.; Indolfi, C.; Siller-Matula, J.M.; Czajka, P.; Postula, M. Significance of circulating microRNAs in diabetes mellitus type 2 and platelet reactivity: Bioinformatic analysis and review. *Cardiovasc. Diabetol.* **2019**, *18*, 113. [[CrossRef](#)]
62. Zhao, Y.; Du, D.; Chen, S.; Chen, Z.; Zhao, J. New Insights into the Functions of MicroRNAs in Cardiac Fibrosis: From Mechanisms to Therapeutic Strategies. *Genes* **2022**, *13*, 1390. [[CrossRef](#)]
63. Guo, R.; Nair, S. Role of microRNA in diabetic cardiomyopathy: From mechanism to intervention. *Biochim. Biophys. Acta Mol. Basis Dis.* **2017**, *1863*, 2070–2077. [[CrossRef](#)]
64. Jin, Z.Q. MicroRNA targets and biomarker validation for diabetes-associated cardiac fibrosis. *Pharmacol. Res.* **2021**, *174*, 105941. [[CrossRef](#)]
65. Rawal, S.; Munasinghe, P.E.; Nagesh, P.T.; Lew, J.K.S.; Jones, G.T.; Williams, M.J.A.; Davis, P.; Bunton, D.; Galvin, I.F.; Manning, P.; et al. Down-regulation of miR-15a/b accelerates fibrotic remodelling in the Type 2 diabetic human and mouse heart. *Clin. Sci.* **2017**, *131*, 847–863. [[CrossRef](#)]
66. Geng, H.; Guan, J. MiR-18a-5p inhibits endothelial-mesenchymal transition and cardiac fibrosis through the Notch2 pathway. *Biochem. Biophys. Res. Commun.* **2017**, *491*, 329–336. [[CrossRef](#)]
67. Liu, X.; Guo, B.; Zhang, W.; Ma, B.; Li, Y. MiR-20a-5p overexpression prevented diabetic cardiomyopathy via inhibition of cardiomyocyte apoptosis, hypertrophy, fibrosis and JNK/NF- κ B signalling pathway. *J. Biochem.* **2021**, *170*, 349–362. [[CrossRef](#)]
68. Tang, C.M.; Zhang, M.; Huang, L.; Hu, Z.Q.; Zhu, J.N.; Xiao, Z.; Zhang, Z.; Lin, Q.X.; Zheng, X.L.; Yang, M.; et al. CircRNA_000203 enhances the expression of fibrosis-associated genes by derepressing targets of miR-26b-5p, Col1a2 and CTGF, in cardiac fibroblasts. *Sci. Rep.* **2017**, *7*, 40342. [[CrossRef](#)]
69. Zhang, Y.; Wang, J.H.; Zhang, Y.Y.; Wang, Y.Z.; Wang, J.; Zhao, Y.; Jin, X.X.; Xue, G.L.; Li, P.H.; Sun, Y.L.; et al. Deletion of interleukin-6 alleviated interstitial fibrosis in streptozotocin-induced diabetic cardiomyopathy of mice through affecting TGF β 1 and miR-29 pathways. *Sci. Rep.* **2016**, *6*, 23010. [[CrossRef](#)] [[PubMed](#)]
70. Chen, S.; Puthanveetil, P.; Feng, B.; Matkovich, S.J.; Dorn, G.W., 2nd; Chakrabarti, S. Cardiac miR-133a overexpression prevents early cardiac fibrosis in diabetes. *J. Cell Mol. Med.* **2014**, *18*, 415–421. [[CrossRef](#)] [[PubMed](#)]
71. Che, H.; Wang, Y.; Li, H.; Li, Y.; Sahil, A.; Lv, J.; Liu, Y.; Yang, Z.; Dong, R.; Xue, H.; et al. Melatonin alleviates cardiac fibrosis via inhibiting lncRNA MALAT1/miR-141-mediated NLRP3 inflammasome and TGF- β 1/Smads signaling in diabetic cardiomyopathy. *FASEB J.* **2020**, *34*, 5282–5298. [[CrossRef](#)] [[PubMed](#)]
72. Feng, B.; Chen, S.; Gordon, A.D.; Chakrabarti, S. miR-146a mediates inflammatory changes and fibrosis in the heart in diabetes. *J. Mol. Cell Cardiol.* **2017**, *105*, 70–76. [[CrossRef](#)] [[PubMed](#)]
73. Feng, B.; Cao, Y.; Chen, S.; Chu, X.; Chu, Y.; Chakrabarti, S. miR-200b Mediates Endothelial-to-Mesenchymal Transition in Diabetic Cardiomyopathy. *Diabetes* **2016**, *65*, 768–779. [[CrossRef](#)] [[PubMed](#)]
74. Yang, X.; Li, X.; Lin, Q.; Xu, Q. Up-regulation of microRNA-203 inhibits myocardial fibrosis and oxidative stress in mice with diabetic cardiomyopathy through the inhibition of PI3K/Akt signaling pathway via PIK3CA. *Gene* **2019**, *715*, 143995. [[CrossRef](#)] [[PubMed](#)]
75. Wang, Z.; Wang, Z.; Gao, L.; Xiao, L.; Yao, R.; Du, B.; Li, Y.; Wu, L.; Liang, C.; Huang, Z.; et al. miR-222 inhibits cardiac fibrosis in diabetic mice heart via regulating Wnt/ β -catenin-mediated endothelium to mesenchymal transition. *J. Cell Physiol.* **2020**, *235*, 2149–2160. [[CrossRef](#)] [[PubMed](#)]

76. Feng, Y.; Xu, W.; Zhang, W.; Wang, W.; Liu, T.; Zhou, X. LncRNA DCRF regulates cardiomyocyte autophagy by targeting miR-551b-5p in diabetic cardiomyopathy. *Theranostics* **2019**, *9*, 4558–4566. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Li, Q.; Yao, Y.; Shi, S.; Zhou, M.; Zhou, Y.; Wang, M.; Chiu, J.J.; Huang, Z.; Zhang, W.; Liu, M.; et al. Inhibition of miR-21 alleviated cardiac perivascular fibrosis via repressing EndMT in T1DM. *J. Cell Mol. Med.* **2020**, *24*, 910–920. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Liu, S.; Li, W.; Xu, M.; Huang, H.; Wang, J.; Chen, X. Micro-RNA 21Targets dual specific phosphatase 8 to promote collagen synthesis in high glucose-treated primary cardiac fibroblasts. *Can. J. Cardiol.* **2014**, *30*, 1689–1699. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Li, X.; Meng, C.; Han, F.; Yang, J.; Wang, J.; Zhu, Y.; Cui, X.; Zuo, M.; Xu, J.; Chang, B. Vildagliptin Attenuates Myocardial Dysfunction and Restores Autophagy via miR-21/SPRY1/ERK in Diabetic Mice Heart. *Front. Pharmacol.* **2021**, *12*, 634365. [\[CrossRef\]](#)
80. Shi, P.; Zhao, X.D.; Shi, K.H.; Ding, X.S.; Tao, H. MiR-21-3p triggers cardiac fibroblasts pyroptosis in diabetic cardiac fibrosis via inhibiting androgen receptor. *Exp. Cell Res.* **2021**, *399*, 112464. [\[CrossRef\]](#)
81. Che, H.; Wang, Y.; Li, Y.; Lv, J.; Li, H.; Liu, Y.; Dong, R.; Sun, Y.; Xu, X.; Zhao, J.; et al. Inhibition of microRNA-150-5p alleviates cardiac inflammation and fibrosis via targeting Smad7 in high glucose-treated cardiac fibroblasts. *J. Cell Physiol.* **2020**, *235*, 7769–7779. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Wang, J.; He, W.; Xu, X.; Guo, L.; Zhang, Y.; Han, S.; Shen, D. The mechanism of TGF-beta/miR-155/c-Ski regulates endothelial-mesenchymal transition in human coronary artery endothelial cells. *Biosci. Rep.* **2017**, *37*, BSR20160603. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Zhang, D.; Cui, Y.; Li, B.; Luo, X.; Li, B.; Tang, Y. miR-155 regulates high glucose-induced cardiac fibrosis via the TGF-beta signaling pathway. *Mol. Biosyst.* **2016**, *13*, 215–224. [\[CrossRef\]](#)
84. Chen, D.; Zhang, M. GAS5 regulates diabetic cardiomyopathy via miR-221-3p/p27 axis-associated autophagy. *Mol. Med. Rep.* **2021**, *23*, 135. [\[CrossRef\]](#)
85. Xu, D.; Zhang, X.; Chen, X.; Yang, S.; Chen, H. Inhibition of miR-223 attenuates the NLRP3 inflammasome activation, fibrosis, and apoptosis in diabetic cardiomyopathy. *Life Sci.* **2020**, *256*, 117980. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Liu, X.; Xu, Y.; Deng, Y.; Li, H. MicroRNA-223 Regulates Cardiac Fibrosis After Myocardial Infarction by Targeting RASA1. *Cell Physiol. Biochem.* **2018**, *46*, 1439–1454. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Liang, C.; Gao, L.; Liu, Y.; Liu, Y.; Yao, R.; Li, Y.; Xiao, L.; Wu, L.; Du, B.; Huang, Z.; et al. MiR-451 antagonist protects against cardiac fibrosis in streptozotocin-induced diabetic mouse heart. *Life Sci.* **2019**, *224*, 12–22. [\[CrossRef\]](#)
88. Valkov, N.; King, M.E.; Moeller, J.; Liu, H.; Li, X.; Zhang, P. MicroRNA-1-Mediated Inhibition of Cardiac Fibroblast Proliferation Through Targeting Cyclin D2 and CDK6. *Front. Cardiovasc. Med.* **2019**, *6*, 65. [\[CrossRef\]](#)
89. Zhong, C.; Wang, K.; Liu, Y.; Lv, D.; Zheng, B.; Zhou, Q.; Sun, Q.; Chen, P.; Ding, S.; Xu, Y.; et al. miR-19b controls cardiac fibroblast proliferation and migration. *J. Cell Mol. Med.* **2016**, *20*, 1191–1197. [\[CrossRef\]](#)
90. Yuan, X.; Pan, J.; Wen, L.; Gong, B.; Li, J.; Gao, H.; Tan, W.; Liang, S.; Zhang, H.; Wang, X. MiR-590-3p regulates proliferation, migration and collagen synthesis of cardiac fibroblast by targeting ZEB1. *J. Cell Mol. Med.* **2020**, *24*, 227–237. [\[CrossRef\]](#)
91. Huang, Y.; Qi, Y.; Du, J.Q.; Zhang, D.F. MicroRNA-34a regulates cardiac fibrosis after myocardial infarction by targeting Smad4. *Expert. Opin. Ther. Targets* **2014**, *18*, 1355–1365. [\[CrossRef\]](#)
92. Wei, Y.; Yan, X.; Yan, L.; Hu, F.; Ma, W.; Wang, Y.; Lu, S.; Zeng, Q.; Wang, Z. Inhibition of microRNA-155 ameliorates cardiac fibrosis in the process of angiotensin II-induced cardiac remodeling. *Mol. Med. Rep.* **2017**, *16*, 7287–7296. [\[CrossRef\]](#)
93. Yuan, X.; Pan, J.; Wen, L.; Gong, B.; Li, J.; Gao, H.; Tan, W.; Liang, S.; Zhang, H.; Wang, X. MiR-144-3p Enhances Cardiac Fibrosis After Myocardial Infarction by Targeting PTEN. *Front. Cell Dev. Biol.* **2019**, *7*, 249. [\[CrossRef\]](#)
94. Zhou, X.L.; Xu, H.; Liu, Z.B.; Wu, Q.C.; Zhu, R.R.; Liu, J.C. miR-21 promotes cardiac fibroblast-to-myofibroblast transformation and myocardial fibrosis by targeting Jagged1. *J. Cell Mol. Med.* **2018**, *22*, 3816–3824. [\[CrossRef\]](#)
95. Surina, S.; Fontanella, R.A.; Scisciola, L.; Marfella, R.; Paolisso, G.; Barbieri, M. miR-21 in Human Cardiomyopathies. *Front. Cardiovasc. Med.* **2021**, *8*, 767064. [\[CrossRef\]](#)
96. Wang, X.; Morelli, M.B.; Matarese, A.; Sardu, C.; Santulli, G. Cardiomyocyte-derived exosomal microRNA-92a mediates post-ischemic myofibroblast activation both in vitro and ex vivo. *ESC Heart Fail.* **2020**, *7*, 284–288. [\[CrossRef\]](#)
97. Morelli, M.B.; Shu, J.; Sardu, C.; Matarese, A.; Santulli, G. Cardiosomal microRNAs Are Essential in Post-Infarction Myofibroblast Phenocconversion. *Int. J. Mol. Sci.* **2019**, *21*, 201. [\[CrossRef\]](#)
98. Ranjan, P.; Kumari, R.; Goswami, S.K.; Li, J.; Pal, H.; Suleiman, Z.; Cheng, Z.; Krishnamurthy, P.; Kishore, R.; Verma, S.K. Myofibroblast-Derived Exosome Induce Cardiac Endothelial Cell Dysfunction. *Front. Cardiovasc. Med.* **2021**, *8*, 676267. [\[CrossRef\]](#)
99. Jazbutyte, V.; Fiedler, J.; Kneitz, S.; Galuppo, P.; Just, A.; Holzmann, A.; Bauersachs, J.; Thum, T. MicroRNA-22 increases senescence and activates cardiac fibroblasts in the aging heart. *Age* **2013**, *35*, 747–762. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Nagpal, V.; Rai, R.; Place, A.T.; Murphy, S.B.; Verma, S.K.; Ghosh, A.K.; Vaughan, D.E. MiR-125b Is Critical for Fibroblast-to-Myofibroblast Transition and Cardiac Fibrosis. *Circulation* **2016**, *133*, 291–301. [\[CrossRef\]](#) [\[PubMed\]](#)
101. Liao, Y.; Li, H.; Cao, H.; Dong, Y.; Gao, L.; Liu, Z.; Ge, J.; Zhu, H. Therapeutic silencing miR-146b-5p improves cardiac remodeling in a porcine model of myocardial infarction by modulating the wound reparative phenotype. *Protein Cell* **2021**, *12*, 194–212. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Mohammed, O.A.; Alghamdi, M.; Alfaifi, J.; Alamri, M.M.S.; Al-Shahrani, A.M.; Alharthi, M.H.; Alshahrani, A.M.; Alhalafi, A.H.; Adam, M.I.E.; Bahashwan, E.; et al. The emerging role of miRNAs in myocardial infarction: From molecular signatures to therapeutic targets. *Pathol. Res. Pract.* **2024**, *253*, 155087. [\[CrossRef\]](#) [\[PubMed\]](#)

103. Boon, R.A.; Iekushi, K.; Lechner, S.; Seeger, T.; Fischer, A.; Heydt, S.; Kaluza, D.; Treguer, K.; Carmona, G.; Bonauer, A.; et al. MicroRNA-34a regulates cardiac ageing and function. *Nature* **2013**, *495*, 107–110. [[CrossRef](#)] [[PubMed](#)]
104. Song, R.; Dasgupta, C.; Mulder, C.; Zhang, L. MicroRNA-210 Controls Mitochondrial Metabolism and Protects Heart Function in Myocardial Infarction. *Circulation* **2022**, *145*, 1140–1153. [[CrossRef](#)] [[PubMed](#)]
105. Yang, Y.; Ding, S.; Xu, G.; Chen, F.; Ding, F. MicroRNA-15a inhibition protects against hypoxia/reoxygenation-induced apoptosis of cardiomyocytes by targeting mothers against decapentaplegic homolog 7. *Mol. Med. Rep.* **2017**, *15*, 3699–3705. [[CrossRef](#)] [[PubMed](#)]
106. Taubel, J.; Hauke, W.; Rump, S.; Viereck, J.; Batkai, S.; Poetzsch, J.; Rode, L.; Weigt, H.; Genschel, C.; Lorch, U.; et al. Novel antisense therapy targeting microRNA-132 in patients with heart failure: Results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study. *Eur. Heart J.* **2021**, *42*, 178–188. [[CrossRef](#)] [[PubMed](#)]
107. Liu, H.; Zhang, Y.; Yuan, J.; Gao, W.; Zhong, X.; Yao, K.; Lin, L.; Ge, J. Dendritic cell-derived exosomal miR-494-3p promotes angiogenesis following myocardial infarction. *Int. J. Mol. Med.* **2021**, *47*, 315–325. [[CrossRef](#)] [[PubMed](#)]
108. Seferovic, P.M.; Petrie, M.C.; Filippatos, G.S.; Anker, S.D.; Rosano, G.; Bauersachs, J.; Paulus, W.J.; Komajda, M.; Cosentino, F.; de Boer, R.A.; et al. Type 2 diabetes mellitus and heart failure: A position statement from the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2018**, *20*, 853–872. [[CrossRef](#)]
109. Lee, M.M.Y.; McMurray, J.J.V.; Lorenzo-Almoros, A.; Kristensen, S.L.; Sattar, N.; Jhund, P.S.; Petrie, M.C. Diabetic cardiomyopathy. *Heart* **2019**, *105*, 337–345. [[CrossRef](#)]
110. Zamora, M.; Villena, J.A. Contribution of Impaired Insulin Signaling to the Pathogenesis of Diabetic Cardiomyopathy. *Int. J. Mol. Sci.* **2019**, *20*, 2833. [[CrossRef](#)]
111. Fazakerley, D.J.; Lawrence, S.P.; Lizunov, V.A.; Cushman, S.W.; Holman, G.D. A common trafficking route for GLUT4 in cardiomyocytes in response to insulin, contraction and energy-status signalling. *J. Cell Sci.* **2009**, *122*, 727–734. [[CrossRef](#)] [[PubMed](#)]
112. Huo, J.L.; Feng, Q.; Pan, S.; Fu, W.J.; Liu, Z.; Liu, Z. Diabetic cardiomyopathy: Early diagnostic biomarkers, pathogenetic mechanisms, and therapeutic interventions. *Cell Death Discov.* **2023**, *9*, 256. [[CrossRef](#)] [[PubMed](#)]
113. Xiong, J.; Dong, X.; Li, S.; Jiang, F.; Chen, J.; Yu, S.; Dong, B.; Su, Q. Effects of (Pro)renin Receptor on Diabetic Cardiomyopathy Pathological Processes in Rats via the PRR-AMPK-YAP Pathway. *Front. Physiol.* **2021**, *12*, 657378. [[CrossRef](#)] [[PubMed](#)]
114. Bodiga, V.L.; Eda, S.R.; Bodiga, S. Advanced glycation end products: Role in pathology of diabetic cardiomyopathy. *Heart Fail. Rev.* **2014**, *19*, 49–63. [[CrossRef](#)] [[PubMed](#)]
115. Jia, G.; DeMarco, V.G.; Sowers, J.R. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nat. Rev. Endocrinol.* **2016**, *12*, 144–153. [[CrossRef](#)] [[PubMed](#)]
116. Biernacka, A.; Cavallera, M.; Wang, J.; Russo, I.; Shinde, A.; Kong, P.; Gonzalez-Quesada, C.; Rai, V.; Dobaczewski, M.; Lee, D.W.; et al. Smad3 Signaling Promotes Fibrosis While Preserving Cardiac and Aortic Geometry in Obese Diabetic Mice. *Circ. Heart Fail.* **2015**, *8*, 788–798. [[CrossRef](#)] [[PubMed](#)]
117. Wilson, A.J.; Gill, E.K.; Abudalo, R.A.; Edgar, K.S.; Watson, C.J.; Grieve, D.J. Reactive oxygen species signalling in the diabetic heart: Emerging prospect for therapeutic targeting. *Heart* **2018**, *104*, 293–299. [[CrossRef](#)] [[PubMed](#)]
118. Zhang, Y.C.; Mou, Y.L.; Xie, Y.Y. Research progress in relations between renin angiotensin system and diabetic cardiomyopathy. *Sheng Li Ke Xue Jin Zhan* **2011**, *42*, 269–275. [[PubMed](#)]
119. Fuentes-Antras, J.; Ioan, A.M.; Tunon, J.; Egidio, J.; Lorenzo, O. Activation of toll-like receptors and inflammasome complexes in the diabetic cardiomyopathy-associated inflammation. *Int. J. Endocrinol.* **2014**, *2014*, 847827. [[CrossRef](#)] [[PubMed](#)]
120. Giacco, F.; Brownlee, M. Oxidative stress and diabetic complications. *Circ. Res.* **2010**, *107*, 1058–1070. [[CrossRef](#)]
121. Pal, P.B.; Sonowal, H.; Shukla, K.; Srivastava, S.K.; Ramana, K.V. Aldose Reductase Mediates NLRP3 Inflammasome-Initiated Innate Immune Response in Hyperglycemia-Induced Thp1 Monocytes and Male Mice. *Endocrinology* **2017**, *158*, 3661–3675. [[CrossRef](#)]
122. Grubic Rotkvic, P.; Cigrovski Berkovic, M.; Bulj, N.; Rotkvic, L.; Celap, I. Sodium-glucose cotransporter 2 inhibitors' mechanisms of action in heart failure. *World J. Diabetes* **2020**, *11*, 269–279. [[CrossRef](#)] [[PubMed](#)]
123. Verma, S.; McMurray, J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. *Diabetologia* **2018**, *61*, 2108–2117. [[CrossRef](#)] [[PubMed](#)]
124. Garla, V.V.; Butler, J.; Lien, L.F. SGLT-2 Inhibitors in Heart Failure: Guide for Prescribing and Future Perspectives. *Curr. Cardiol. Rep.* **2021**, *23*, 59. [[CrossRef](#)] [[PubMed](#)]
125. Navale, A.M.; Paranjape, A.N. Glucose transporters: Physiological and pathological roles. *Biophys. Rev.* **2016**, *8*, 5–9. [[CrossRef](#)]
126. Ghezzi, C.; Hirayama, B.A.; Gorraitz, E.; Loo, D.D.; Liang, Y.; Wright, E.M. SGLT2 inhibitors act from the extracellular surface of the cell membrane. *Physiol. Rep.* **2014**, *2*, e12058. [[CrossRef](#)] [[PubMed](#)]
127. Al Jobori, H.; Daniele, G.; Adams, J.; Cersosimo, E.; Solis-Herrera, C.; Triplitt, C.; DeFronzo, R.A.; Abdul-Ghani, M. Empagliflozin Treatment Is Associated With Improved beta-Cell Function in Type 2 Diabetes Mellitus. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 1402–1407. [[CrossRef](#)] [[PubMed](#)]
128. Merovci, A.; Mari, A.; Solis-Herrera, C.; Xiong, J.; Daniele, G.; Chavez-Velazquez, A.; Tripathy, D.; Urban McCarthy, S.; Abdul-Ghani, M.; DeFronzo, R.A. Dapagliflozin lowers plasma glucose concentration and improves beta-cell function. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 1927–1932. [[CrossRef](#)] [[PubMed](#)]

129. Luna-Marco, C.; Iannantuoni, F.; Hermo-Argibay, A.; Devos, D.; Salazar, J.D.; Victor, V.M.; Rovira-Llopis, S. Cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists through effects on mitochondrial function and oxidative stress. *Free Radic. Biol. Med.* **2024**, *213*, 19–35. [\[CrossRef\]](#)
130. Wang, C.; Qin, Y.; Zhang, X.; Yang, Y.; Wu, X.; Liu, J.; Qin, S.; Chen, K.; Xiao, W. Effect of Dapagliflozin on Indicators of Myocardial Fibrosis and Levels of Inflammatory Factors in Heart Failure Patients. *Dis. Markers* **2022**, *2022*, 5834218. [\[CrossRef\]](#)
131. Tian, J.; Zhang, M.; Suo, M.; Liu, D.; Wang, X.; Liu, M.; Pan, J.; Jin, T.; An, F. Dapagliflozin alleviates cardiac fibrosis through suppressing EndMT and fibroblast activation via AMPK α /TGF- β /Smad signalling in type 2 diabetic rats. *J. Cell Mol. Med.* **2021**, *25*, 7642–7659. [\[CrossRef\]](#) [\[PubMed\]](#)
132. Katsurada, K.; Nandi, S.S.; Sharma, N.M.; Patel, K.P. Enhanced Expression and Function of Renal SGLT2 (Sodium-Glucose Cotransporter 2) in Heart Failure: Role of Renal Nerves. *Circ. Heart Fail.* **2021**, *14*, e008365. [\[CrossRef\]](#) [\[PubMed\]](#)
133. McMurray, J.J.V.; DeMets, D.L.; Inzucchi, S.E.; Kober, L.; Kosiborod, M.N.; Langkilde, A.M.; Martinez, F.A.; Bengtsson, O.; Ponikowski, P.; Sabatine, M.S.; et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur. J. Heart Fail.* **2019**, *21*, 665–675. [\[CrossRef\]](#)
134. Gager, G.M.; von Lewinski, D.; Sourij, H.; Jilma, B.; Eyileten, C.; Filipiak, K.; Hulsmann, M.; Kubica, J.; Postula, M.; Siller-Matula, J.M. Effects of SGLT2 Inhibitors on Ion Homeostasis and Oxidative Stress associated Mechanisms in Heart Failure. *Biomed. Pharmacother.* **2021**, *143*, 112169. [\[CrossRef\]](#) [\[PubMed\]](#)
135. Faridvand, Y.; Kazemzadeh, H.; Vahedian, V.; Mirzajanzadeh, P.; Nejabati, H.R.; Safaie, N.; Maroufi, N.F.; Pezeshkian, M.; Nouri, M.; Jodati, A. Dapagliflozin attenuates high glucose-induced endothelial cell apoptosis and inflammation through AMPK/SIRT1 activation. *Clin. Exp. Pharmacol. Physiol.* **2022**, *49*, 643–651. [\[CrossRef\]](#) [\[PubMed\]](#)
136. Li, F.F.; Gao, G.; Li, Q.; Zhu, H.H.; Su, X.F.; Wu, J.D.; Ye, L.; Ma, J.H. Influence of Dapagliflozin on Glycemic Variations in Patients with Newly Diagnosed Type 2 Diabetes Mellitus. *J. Diabetes Res.* **2016**, *2016*, 5347262. [\[CrossRef\]](#) [\[PubMed\]](#)
137. Yu, Y.W.; Que, J.Q.; Liu, S.; Huang, K.Y.; Qian, L.; Weng, Y.B.; Rong, F.N.; Wang, L.; Zhou, Y.Y.; Xue, Y.J.; et al. Sodium-Glucose Co-transporter-2 Inhibitor of Dapagliflozin Attenuates Myocardial Ischemia/Reperfusion Injury by Limiting NLRP3 Inflammasome Activation and Modulating Autophagy. *Front. Cardiovasc. Med.* **2021**, *8*, 768214. [\[CrossRef\]](#) [\[PubMed\]](#)
138. Andreadou, I.; Efentakis, P.; Balafas, E.; Togliatto, G.; Davos, C.H.; Varela, A.; Dimitriou, C.A.; Nikolaou, P.E.; Maratou, E.; Lambadiari, V.; et al. Empagliflozin Limits Myocardial Infarction in Vivo and Cell Death in Vitro: Role of STAT3, Mitochondria, and Redox Aspects. *Front. Physiol.* **2017**, *8*, 1077. [\[CrossRef\]](#) [\[PubMed\]](#)
139. Lee, T.M.; Chang, N.C.; Lin, S.Z. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic. Biol. Med.* **2017**, *104*, 298–310. [\[CrossRef\]](#)
140. Yurista, S.R.; Sillje, H.H.W.; Oberdorf-Maass, S.U.; Schouten, E.M.; Pavez Giani, M.G.; Hillebrands, J.L.; van Goor, H.; van Veldhuisen, D.J.; de Boer, R.A.; Westenbrink, B.D. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. *Eur. J. Heart Fail.* **2019**, *21*, 862–873. [\[CrossRef\]](#)
141. Daud, E.; Ertracht, O.; Bandel, N.; Moady, G.; Shehadeh, M.; Reuveni, T.; Atar, S. The impact of empagliflozin on cardiac physiology and fibrosis early after myocardial infarction in non-diabetic rats. *Cardiovasc. Diabetol.* **2021**, *20*, 132. [\[CrossRef\]](#) [\[PubMed\]](#)
142. Hsu, J.C.; Wang, C.Y.; Su, M.M.; Lin, L.Y.; Yang, W.S. Effect of Empagliflozin on Cardiac Function, Adiposity, and Diffuse Fibrosis in Patients with Type 2 Diabetes Mellitus. *Sci. Rep.* **2019**, *9*, 15348. [\[CrossRef\]](#) [\[PubMed\]](#)
143. Adel, S.M.H.; Jorfi, F.; Mombeini, H.; Rashidi, H.; Fazeli, S. Effect of a low dose of empagliflozin on short-term outcomes in type 2 diabetics with acute coronary syndrome after percutaneous coronary intervention. *Saudi Med. J.* **2022**, *43*, 458–464. [\[CrossRef\]](#) [\[PubMed\]](#)
144. Connelly, K.A.; Zhang, Y.; Desjardins, J.F.; Nghiem, L.; Visram, A.; Batchu, S.N.; Yerra, V.G.; Kabir, G.; Thai, K.; Advani, A.; et al. Load-independent effects of empagliflozin contribute to improved cardiac function in experimental heart failure with reduced ejection fraction. *Cardiovasc. Diabetol.* **2020**, *19*, 13. [\[CrossRef\]](#) [\[PubMed\]](#)
145. Wang, J.; Huang, X.; Liu, H.; Chen, Y.; Li, P.; Liu, L.; Li, J.; Ren, Y.; Huang, J.; Xiong, E.; et al. Empagliflozin Ameliorates Diabetic Cardiomyopathy via Attenuating Oxidative Stress and Improving Mitochondrial Function. *Oxidative Med. Cell Longev.* **2022**, *2022*, 1122494. [\[CrossRef\]](#)
146. Li, C.; Zhang, J.; Xue, M.; Li, X.; Han, F.; Liu, X.; Xu, L.; Lu, Y.; Cheng, Y.; Li, T.; et al. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. *Cardiovasc. Diabetol.* **2019**, *18*, 15. [\[CrossRef\]](#)
147. Kim, S.R.; Lee, S.G.; Kim, S.H.; Kim, J.H.; Choi, E.; Cho, W.; Rim, J.H.; Hwang, I.; Lee, C.J.; Lee, M.; et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nat. Commun.* **2020**, *11*, 2127. [\[CrossRef\]](#)
148. Dekkers, C.C.J.; Petrykiv, S.; Laverman, G.D.; Cherney, D.Z.; Gansevoort, R.T.; Heerspink, H.J.L. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. *Diabetes Obes. Metab.* **2018**, *20*, 1988–1993. [\[CrossRef\]](#) [\[PubMed\]](#)
149. Hodrea, J.; Saeed, A.; Molnar, A.; Fintha, A.; Barcsi, A.; Wagner, L.J.; Szabo, A.J.; Fekete, A.; Balogh, D.B. SGLT2 inhibitor dapagliflozin prevents atherosclerotic and cardiac complications in experimental type 1 diabetes. *PLoS ONE* **2022**, *17*, e0263285. [\[CrossRef\]](#)

150. Ye, Y.; Bajaj, M.; Yang, H.C.; Perez-Polo, J.R.; Birnbaum, Y. SGLT-2 Inhibition with Dapagliflozin Reduces the Activation of the Nlrp3/ASC Inflammasome and Attenuates the Development of Diabetic Cardiomyopathy in Mice with Type 2 Diabetes. Further Augmentation of the Effects with Saxagliptin, a DPP4 Inhibitor. *Cardiovasc. Drugs Ther.* **2017**, *31*, 119–132. [\[CrossRef\]](#)
151. Li, X.; Kerindongo, R.P.; Preckel, B.; Kalina, J.O.; Hollmann, M.W.; Zuurbier, C.J.; Weber, N.C. Canagliflozin inhibits inflammasome activation in diabetic endothelial cells—Revealing a novel calcium-dependent anti-inflammatory effect of canagliflozin on human diabetic endothelial cells. *Biomed. Pharmacother.* **2023**, *159*, 114228. [\[CrossRef\]](#) [\[PubMed\]](#)
152. Kang, S.; Verma, S.; Hassanabad, A.F.; Teng, G.; Belke, D.D.; Dundas, J.A.; Guzzardi, D.G.; Svystonyuk, D.A.; Pattar, S.S.; Park, D.S.J.; et al. Direct Effects of Empagliflozin on Extracellular Matrix Remodelling in Human Cardiac Myofibroblasts: Novel Translational Clues to Explain EMPA-REG OUTCOME Results. *Can. J. Cardiol.* **2020**, *36*, 543–553. [\[CrossRef\]](#) [\[PubMed\]](#)
153. Verma, S.; Mazer, C.D.; Yan, A.T.; Mason, T.; Garg, V.; Teoh, H.; Zuo, F.; Quan, A.; Farkouh, M.E.; Fitchett, D.H.; et al. Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. *Circulation* **2019**, *140*, 1693–1702. [\[CrossRef\]](#) [\[PubMed\]](#)
154. Brown, A.J.M.; Gandy, S.; McCrimmon, R.; Houston, J.G.; Struthers, A.D.; Lang, C.C. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: The DAPA-LVH trial. *Eur. Heart J.* **2020**, *41*, 3421–3432. [\[CrossRef\]](#) [\[PubMed\]](#)
155. Hattori, S. Anti-inflammatory effects of empagliflozin in patients with type 2 diabetes and insulin resistance. *Diabetol. Metab. Syndr.* **2018**, *10*, 93. [\[CrossRef\]](#) [\[PubMed\]](#)
156. Sezai, A.; Sekino, H.; Unosawa, S.; Taoka, M.; Osaka, S.; Tanaka, M. Canagliflozin for Japanese patients with chronic heart failure and type II diabetes. *Cardiovasc. Diabetol.* **2019**, *18*, 76. [\[CrossRef\]](#) [\[PubMed\]](#)
157. Shigiyama, F.; Kumashiro, N.; Miyagi, M.; Ikehara, K.; Kanda, E.; Uchino, H.; Hirose, T. Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. *Cardiovasc. Diabetol.* **2017**, *16*, 84. [\[CrossRef\]](#)
158. Tanaka, A.; Shimabukuro, M.; Machii, N.; Teragawa, H.; Okada, Y.; Shima, K.R.; Takamura, T.; Taguchi, I.; Hisauchi, I.; Toyoda, S.; et al. Effect of Empagliflozin on Endothelial Function in Patients With Type 2 Diabetes and Cardiovascular Disease: Results from the Multicenter, Randomized, Placebo-Controlled, Double-Blind EMBLEM Trial. *Diabetes Care* **2019**, *42*, e159–e161. [\[CrossRef\]](#)
159. Lee, Y.S.; Jun, H.S. Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. *Metabolism* **2014**, *63*, 9–19. [\[CrossRef\]](#)
160. Pyke, C.; Heller, R.S.; Kirk, R.K.; Orskov, C.; Reedtz-Runge, S.; Kastrup, P.; Hvelplund, A.; Bardram, L.; Calatayud, D.; Knudsen, L.B. GLP-1 receptor localization in monkey and human tissue: Novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology* **2014**, *155*, 1280–1290. [\[CrossRef\]](#)
161. Sharma, D.; Verma, S.; Vaidya, S.; Kalia, K.; Tiwari, V. Recent updates on GLP-1 agonists: Current advancements & challenges. *Biomed. Pharmacother.* **2018**, *108*, 952–962. [\[CrossRef\]](#)
162. Ussher, J.R.; Drucker, D.J. Glucagon-like peptide 1 receptor agonists: Cardiovascular benefits and mechanisms of action. *Nat. Rev. Cardiol.* **2023**, *20*, 463–474. [\[CrossRef\]](#)
163. Tan, Q.; Akindehin, S.E.; Orsso, C.E.; Waldner, R.C.; DiMarchi, R.D.; Muller, T.D.; Haqq, A.M. Recent Advances in Incretin-Based Pharmacotherapies for the Treatment of Obesity and Diabetes. *Front. Endocrinol.* **2022**, *13*, 838410. [\[CrossRef\]](#) [\[PubMed\]](#)
164. Gilbert, M.P.; Pratley, R.E. GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. *Front. Endocrinol.* **2020**, *11*, 178. [\[CrossRef\]](#)
165. Uccellatore, A.; Genovese, S.; Dicembrini, I.; Mannucci, E.; Ceriello, A. Comparison Review of Short-Acting and Long-Acting Glucagon-like Peptide-1 Receptor Agonists. *Diabetes Ther.* **2015**, *6*, 239–256. [\[CrossRef\]](#) [\[PubMed\]](#)
166. Peng, Y.; Lin, H.; Tian, S.; Liu, S.; Li, J.; Lv, X.; Chen, S.; Zhao, L.; Pu, F.; Chen, X.; et al. Glucagon-like peptide-1 receptor activation maintains extracellular matrix integrity by inhibiting the activity of mitogen-activated protein kinases and activator protein-1. *Free Radic. Biol. Med.* **2021**, *177*, 247–259. [\[CrossRef\]](#) [\[PubMed\]](#)
167. Li, Y.K.; Ma, D.X.; Wang, Z.M.; Hu, X.F.; Li, S.L.; Tian, H.Z.; Wang, M.J.; Shu, Y.W.; Yang, J. The glucagon-like peptide-1 (GLP-1) analog liraglutide attenuates renal fibrosis. *Pharmacol. Res.* **2018**, *131*, 102–111. [\[CrossRef\]](#) [\[PubMed\]](#)
168. Huang, L.; Lin, T.; Shi, M.; Chen, X.; Wu, P. Liraglutide suppresses production of extracellular matrix proteins and ameliorates renal injury of diabetic nephropathy by enhancing Wnt/beta-catenin signaling. *Am. J. Physiol. Renal Physiol.* **2020**, *319*, F458–F468. [\[CrossRef\]](#)
169. Wang, D.; Jiang, L.; Feng, B.; He, N.; Zhang, Y.; Ye, H. Protective effects of glucagon-like peptide-1 on cardiac remodeling by inhibiting oxidative stress through mammalian target of rapamycin complex 1/p70 ribosomal protein S6 kinase pathway in diabetes mellitus. *J. Diabetes Investig.* **2020**, *11*, 39–51. [\[CrossRef\]](#)
170. Picatoste, B.; Ramirez, E.; Caro-Vadillo, A.; Iborra, C.; Ares-Carrasco, S.; Egido, J.; Tunon, J.; Lorenzo, O. Sitagliptin reduces cardiac apoptosis, hypertrophy and fibrosis primarily by insulin-dependent mechanisms in experimental type-II diabetes. Potential roles of GLP-1 isoforms. *PLoS ONE* **2013**, *8*, e78330. [\[CrossRef\]](#)
171. Zhu, Q.; Luo, Y.; Wen, Y.; Wang, D.; Li, J.; Fan, Z. Semaglutide inhibits ischemia/reperfusion-induced cardiomyocyte apoptosis through activating PKG/PKCepsilon/ERK1/2 pathway. *Biochem. Biophys. Res. Commun.* **2023**, *647*, 1–8. [\[CrossRef\]](#) [\[PubMed\]](#)
172. Bin Dayel, A.F.; Alonazi, A.S.; Alrasheed, N.M.; Alamin, M.A.; Sarawi, W.S.; Alharbi, A.O.; Alabbad, N.A.; Albuaian, D.A.; Alassiri, D.N.; Aljarbua, A.F.; et al. Role of the integrin-linked kinase/TGF-beta/SMAD pathway in sitagliptin-mediated cardioprotective effects in a rat model of diabetic cardiomyopathy. *J. Pharm. Pharmacol.* **2024**, *76*, 64–73. [\[CrossRef\]](#) [\[PubMed\]](#)

173. Zhao, T.; Chen, H.; Xu, F.; Wang, J.; Liu, Y.; Xing, X.; Guo, L.; Zhang, M.; Lu, Q. Liraglutide alleviates cardiac fibrosis through inhibiting P4halpha-1 expression in STZ-induced diabetic cardiomyopathy. *Acta Biochim. Biophys. Sin.* **2019**, *51*, 293–300. [[CrossRef](#)] [[PubMed](#)]
174. Zhang, Z.; Wang, X.; Yang, L.; Yang, L.; Ma, H. Liraglutide ameliorates myocardial damage in experimental diabetic rats by inhibiting pyroptosis via Sirt1/AMPK signaling. *Iran. J. Basic Med. Sci.* **2021**, *24*, 1358–1365. [[CrossRef](#)] [[PubMed](#)]
175. Noyan-Ashraf, M.H.; Momen, M.A.; Ban, K.; Sadi, A.M.; Zhou, Y.Q.; Riazi, A.M.; Baggio, L.L.; Henkelman, R.M.; Husain, M.; Drucker, D.J. GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes* **2009**, *58*, 975–983. [[CrossRef](#)]
176. Wu, L.; Wang, K.; Wang, W.; Wen, Z.; Wang, P.; Liu, L.; Wang, D.W. Glucagon-like peptide-1 ameliorates cardiac lipotoxicity in diabetic cardiomyopathy via the PPARalpha pathway. *Aging Cell* **2018**, *17*, e12763. [[CrossRef](#)] [[PubMed](#)]
177. Lyu, J.; Imachi, H.; Fukunaga, K.; Sato, S.; Kobayashi, T.; Saheki, T.; Japar, S.; Iwama, H.; Matsumura, Y.; Ozaki, M.; et al. Exendin-4 Increases Scavenger Receptor Class BI Expression via Activation of AMPK/FoxO1 in Human Vascular Endothelial Cells. *Curr. Issues Mol. Biol.* **2022**, *44*, 5474–5484. [[CrossRef](#)] [[PubMed](#)]
178. He, W.; Tong, G.; Fan, H.; Zhen, C.; Zeng, L.; Xue, L.; Chen, J.; Sun, Z.; He, P. Exendin-4 alleviates myocardial ischemia reperfusion injury by enhancing autophagy through promoting nuclear translocation of TFEB. *Exp. Cell Res.* **2023**, *423*, 113469. [[CrossRef](#)] [[PubMed](#)]
179. Nuamnaichati, N.; Mangmool, S.; Chattipakorn, N.; Parichatikanond, W. Stimulation of GLP-1 Receptor Inhibits Methylglyoxal-Induced Mitochondrial Dysfunctions in H9c2 Cardiomyoblasts: Potential Role of Epac/PI3K/Akt Pathway. *Front. Pharmacol.* **2020**, *11*, 805. [[CrossRef](#)]
180. Wei, H.; Bu, R.; Yang, Q.; Jia, J.; Li, T.; Wang, Q.; Chen, Y. Exendin-4 Protects against Hyperglycemia-Induced Cardiomyocyte Pyroptosis via the AMPK-TXNIP Pathway. *J. Diabetes Res.* **2019**, *2019*, 8905917. [[CrossRef](#)]
181. Wassef, M.A.E.; Tork, O.M.; Rashed, L.A.; Ibrahim, W.; Morsi, H.; Rabie, D.M.M. Mitochondrial Dysfunction in Diabetic Cardiomyopathy: Effect of Mesenchymal Stem Cell with PPAR-gamma Agonist or Exendin-4. *Exp. Clin. Endocrinol. Diabetes* **2018**, *126*, 27–38. [[CrossRef](#)] [[PubMed](#)]
182. Eid, R.A.; Khalil, M.A.; Alkhateeb, M.A.; Eleawa, S.M.; Zaki, M.S.A.; El-Kott, A.F.; Al-Shraim, M.; El-Sayed, F.; Eldeen, M.A.; Bin-Meferij, M.M.; et al. Exendin-4 Attenuates Remodeling in the Remote Myocardium of Rats After an Acute Myocardial Infarction by Activating beta-Arrestin-2, Protein Phosphatase 2A, and Glycogen Synthase Kinase-3 and Inhibiting beta-Catenin. *Cardiovasc. Drugs Ther.* **2021**, *35*, 1095–1110. [[CrossRef](#)] [[PubMed](#)]
183. Chen, J.; Xu, S.; Wang, L.; Zhou, W.; Li, P.; Deng, N.; Tang, Q.; Li, Y.; Wu, L.; Chen, J.; et al. Exendin-4 inhibits atrial arrhythmogenesis in a model of myocardial infarction-induced heart failure via the GLP-1 receptor signaling pathway. *Exp. Ther. Med.* **2020**, *20*, 3669–3678. [[CrossRef](#)] [[PubMed](#)]
184. Chen, J.; Wang, D.; Wang, F.; Shi, S.; Chen, Y.; Yang, B.; Tang, Y.; Huang, C. Exendin-4 inhibits structural remodeling and improves Ca(2+) homeostasis in rats with heart failure via the GLP-1 receptor through the eNOS/cGMP/PKG pathway. *Peptides* **2017**, *90*, 69–77. [[CrossRef](#)] [[PubMed](#)]
185. Wright, E.J.; Hodson, N.W.; Sherratt, M.J.; Kassem, M.; Lewis, A.L.; Wallrapp, C.; Malik, N.; Holt, C.M. Combined MSC and GLP-1 Therapy Modulates Collagen Remodeling and Apoptosis following Myocardial Infarction. *Stem Cells Int.* **2016**, *2016*, 7357096. [[CrossRef](#)] [[PubMed](#)]
186. Withaar, C.; Meems, L.M.G.; Markousis-Mavrogenis, G.; Boogerd, C.J.; Sillje, H.H.W.; Schouten, E.M.; Dokter, M.M.; Voors, A.A.; Westenbrink, B.D.; Lam, C.S.P.; et al. The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit mouse model of heart failure with preserved ejection fraction. *Cardiovasc. Res.* **2021**, *117*, 2108–2124. [[CrossRef](#)] [[PubMed](#)]
187. Huang, D.D.; Huang, H.F.; Yang, Q.; Chen, X.Q. Liraglutide improves myocardial fibrosis after myocardial infarction through inhibition of CTGF by activating cAMP in mice. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 4648–4656. [[CrossRef](#)] [[PubMed](#)]
188. Mitsuhashi, T.; Hibi, K.; Konishi, M.; Maejima, N.; Iwahashi, N.; Tsukahara, K.; Kosuge, M.; Ebina, T.; Umemura, S.; Kimura, K. Plasma Glucagon-Like Peptide-1 and Tissue Characteristics of Coronary Plaque in Non-Diabetic Acute Coronary Syndrome Patients. *Circ. J.* **2016**, *80*, 469–476. [[CrossRef](#)] [[PubMed](#)]
189. Trevisan, M.; Fu, E.L.; Szummer, K.; Norhammar, A.; Lundman, P.; Wanner, C.; Sjolander, A.; Jernberg, T.; Carrero, J.J. Glucagon-like peptide-1 receptor agonists and the risk of cardiovascular events in diabetes patients surviving an acute myocardial infarction. *Eur. Heart J. Cardiovasc. Pharmacother.* **2021**, *7*, 104–111. [[CrossRef](#)]
190. Trombara, F.; Cosentino, N.; Bonomi, A.; Ludergrani, M.; Poggio, P.; Gionti, L.; Baviera, M.; Colacioppo, P.; Roncaglioni, M.C.; Leoni, O.; et al. Impact of chronic GLP-1 RA and SGLT-2I therapy on in-hospital outcome of diabetic patients with acute myocardial infarction. *Cardiovasc. Diabetol.* **2023**, *22*, 26. [[CrossRef](#)]
191. Marfella, R.; Prattichizzo, F.; Sardu, C.; Rambaldi, P.F.; Fumagalli, C.; Marfella, L.V.; La Grotta, R.; Frige, C.; Pellegrini, V.; D'Andrea, D.; et al. GLP-1 receptor agonists-SGLT-2 inhibitors combination therapy and cardiovascular events after acute myocardial infarction: An observational study in patients with type 2 diabetes. *Cardiovasc. Diabetol.* **2024**, *23*, 10. [[CrossRef](#)] [[PubMed](#)]
192. Marso, S.P.; Daniels, G.H.; Brown-Frandsen, K.; Kristensen, P.; Mann, J.F.; Nauck, M.A.; Nissen, S.E.; Pocock, S.; Poulter, N.R.; Ravn, L.S.; et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **2016**, *375*, 311–322. [[CrossRef](#)] [[PubMed](#)]

193. Paiman, E.H.M.; van Eyk, H.J.; van Aalst, M.M.A.; Bizino, M.B.; van der Geest, R.J.; Westenberg, J.J.M.; Geelhoed-Duijvestijn, P.H.; Kharagitsingh, A.V.; Rensen, P.C.N.; Smit, J.W.A.; et al. Effect of Liraglutide on Cardiovascular Function and Myocardial Tissue Characteristics in Type 2 Diabetes Patients of South Asian Descent Living in the Netherlands: A Double-Blind, Randomized, Placebo-Controlled Trial. *J. Magn. Reson. Imaging* **2020**, *51*, 1679–1688. [\[CrossRef\]](#) [\[PubMed\]](#)
194. Zimmerman, R.S.; Hobbs, T.M.; Wells, B.J.; Kong, S.X.; Kattan, M.W.; Bouchard, J.; Chagin, K.M.; Yu, C.; Sakurada, B.; Milinovich, A.; et al. Association of glucagon-like peptide-1 receptor agonist use and rates of acute myocardial infarction, stroke and overall mortality in patients with type 2 diabetes mellitus in a large integrated health system. *Diabetes Obes. Metab.* **2017**, *19*, 1555–1561. [\[CrossRef\]](#) [\[PubMed\]](#)
195. Deacon, C.F. Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **2020**, *16*, 642–653. [\[CrossRef\]](#) [\[PubMed\]](#)
196. Fu, W.J.; Huo, J.L.; Mao, Z.H.; Pan, S.K.; Liu, D.W.; Liu, Z.S.; Wu, P.; Gao, Z.X. Emerging role of antidiabetic drugs in cardiorenal protection. *Front. Pharmacol.* **2024**, *15*, 1349069. [\[CrossRef\]](#) [\[PubMed\]](#)
197. Ishii, H.; Hayashino, Y.; Akai, Y.; Yabuta, M.; Tsujii, S. Dipeptidyl peptidase-4 inhibitors as preferable oral hypoglycemic agents in terms of treatment satisfaction: Results from a multicenter, 12-week, open label, randomized controlled study in Japan (PREFERENCE 4 study). *J. Diabetes Investig.* **2018**, *9*, 137–145. [\[CrossRef\]](#) [\[PubMed\]](#)
198. Nauck, M.A.; Meininger, G.; Sheng, D.; Terranella, L.; Stein, P.P.; Sitagliptin Study, G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial. *Diabetes Obes. Metab.* **2007**, *9*, 194–205. [\[CrossRef\]](#) [\[PubMed\]](#)
199. Jermendy, G. Incretin-based antidiabetic treatment and diseases of the pancreas (pancreatitis, pancreas carcinoma). *Orv. Hetil.* **2016**, *157*, 523–528. [\[CrossRef\]](#)
200. Nicholson, G.; Hall, G.M. Diabetes mellitus: New drugs for a new epidemic. *Br. J. Anaesth.* **2011**, *107*, 65–73. [\[CrossRef\]](#)
201. Xie, D.; Wang, Q.; Huang, W.; Zhao, L. Dipeptidyl-peptidase-4 inhibitors have anti-inflammatory effects in patients with type 2 diabetes. *Eur. J. Clin. Pharmacol.* **2023**, *79*, 1291–1301. [\[CrossRef\]](#)
202. Pham, T.K.; Nguyen, T.H.T.; Yi, J.M.; Kim, G.S.; Yun, H.R.; Kim, H.K.; Won, J.C. Evogliptin, a DPP-4 inhibitor, prevents diabetic cardiomyopathy by alleviating cardiac lipotoxicity in db/db mice. *Exp. Mol. Med.* **2023**, *55*, 767–778. [\[CrossRef\]](#)
203. Moon, J.Y.; Woo, J.S.; Seo, J.W.; Lee, A.; Kim, D.J.; Kim, Y.G.; Kim, S.Y.; Lee, K.H.; Lim, S.J.; Cheng, X.W.; et al. The Dose-Dependent Organ-Specific Effects of a Dipeptidyl Peptidase-4 Inhibitor on Cardiovascular Complications in a Model of Type 2 Diabetes. *PLoS ONE* **2016**, *11*, e0150745. [\[CrossRef\]](#)
204. Arruda-Junior, D.F.; Salles, T.A.; Martins, F.L.; Antonio, E.L.; Tucci, P.J.F.; Gowdak, L.H.W.; Tavares, C.A.M.; Girardi, A.C. Unraveling the interplay between dipeptidyl peptidase 4 and the renin-angiotensin system in heart failure. *Life Sci.* **2022**, *305*, 120757. [\[CrossRef\]](#)
205. Wojcicka, G.; Pradiuch, A.; Fornal, E.; Stachniuk, A.; Korolczuk, A.; Marzec-Kotarska, B.; Nikolaichuk, H.; Czechowska, G.; Kozub, A.; Trzpił, A.; et al. The effect of exenatide (a GLP-1 analogue) and sitagliptin (a DPP-4 inhibitor) on asymmetric dimethylarginine (ADMA) metabolism and selected biomarkers of cardiac fibrosis in rats with fructose-induced metabolic syndrome. *Biochem. Pharmacol.* **2023**, *214*, 115637. [\[CrossRef\]](#)
206. Shao, S.; Xu, Q.; Yu, X.; Pan, R.; Chen, Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. *Pharmacol. Ther.* **2020**, *209*, 107503. [\[CrossRef\]](#)
207. Adhikari, J.; Hirai, T.; Kawakita, E.; Iwai, K.; Koya, D.; Kanasaki, K. Linagliptin ameliorated cardiac fibrosis and restored cardiomyocyte structure in diabetic mice associated with the suppression of necroptosis. *J. Diabetes Investig.* **2023**, *14*, 844–855. [\[CrossRef\]](#)
208. Birnbaum, Y.; Tran, D.; Bajaj, M.; Ye, Y. DPP-4 inhibition by linagliptin prevents cardiac dysfunction and inflammation by targeting the Nlrp3/ASC inflammasome. *Basic Res. Cardiol.* **2019**, *114*, 35. [\[CrossRef\]](#)
209. Beraldo, J.I.; Benetti, A.; Borges-Junior, F.A.; Arruda-Junior, D.F.; Martins, F.L.; Jensen, L.; Dariolli, R.; Shimizu, M.H.; Seguro, A.C.; Luchi, W.M.; et al. Cardioprotection Conferred by Sitagliptin Is Associated with Reduced Cardiac Angiotensin II/Angiotensin-(1-7) Balance in Experimental Chronic Kidney Disease. *Int. J. Mol. Sci.* **2019**, *20*, 1940. [\[CrossRef\]](#)
210. Hong, S.K.; Choo, E.H.; Ihm, S.H.; Chang, K.; Seung, K.B. Dipeptidyl peptidase 4 inhibitor attenuates obesity-induced myocardial fibrosis by inhibiting transforming growth factor-beta1 and Smad2/3 pathways in high-fat diet-induced obesity rat model. *Metabolism* **2017**, *76*, 42–55. [\[CrossRef\]](#)
211. Chen, Y.F.; Zhang, L.J.; Liu, Q.H.; Li, X.W. Effects of Sitagliptin on myocardial remodeling and autophagy in diabetic mice and its mechanism. *Zhongguo Ying Yong Sheng Li Xue Za Zhi* **2021**, *37*, 534–537. [\[CrossRef\]](#)
212. Al-Rasheed, N.M.; Al-Rasheed, N.M.; Hasan, I.H.; Al-Amin, M.A.; Al-Ajmi, H.N.; Mahmoud, A.M. Sitagliptin attenuates cardiomyopathy by modulating the JAK/STAT signaling pathway in experimental diabetic rats. *Drug Des. Dev. Ther.* **2016**, *10*, 2095–2107. [\[CrossRef\]](#)
213. Zhang, X.; Zhang, Z.; Yang, Y.; Suo, Y.; Liu, R.; Qiu, J.; Zhao, Y.; Jiang, N.; Liu, C.; Tse, G.; et al. Alogliptin prevents diastolic dysfunction and preserves left ventricular mitochondrial function in diabetic rabbits. *Cardiovasc. Diabetol.* **2018**, *17*, 160. [\[CrossRef\]](#)
214. Zhang, X.; Zhang, Z.; Zhao, Y.; Jiang, N.; Qiu, J.; Yang, Y.; Li, J.; Liang, X.; Wang, X.; Tse, G.; et al. Alogliptin, a Dipeptidyl Peptidase-4 Inhibitor, Alleviates Atrial Remodeling and Improves Mitochondrial Function and Biogenesis in Diabetic Rabbits. *J. Am. Heart Assoc.* **2017**, *6*, e005945. [\[CrossRef\]](#)

215. Esser, N.; Zraika, S. Neprilysin inhibition: A new therapeutic option for type 2 diabetes? *Diabetologia* **2019**, *62*, 1113–1122. [\[CrossRef\]](#)
216. Potter, L.R. Natriuretic peptide metabolism, clearance and degradation. *FEBS J.* **2011**, *278*, 1808–1817. [\[CrossRef\]](#)
217. McMurray, J.J. Neprilysin inhibition to treat heart failure: A tale of science, serendipity, and second chances. *Eur. J. Heart Fail.* **2015**, *17*, 242–247. [\[CrossRef\]](#)
218. Jordan, J.; Stinkens, R.; Jax, T.; Engeli, S.; Blaak, E.E.; May, M.; Havekes, B.; Schindler, C.; Albrecht, D.; Pal, P.; et al. Improved Insulin Sensitivity With Angiotensin Receptor Neprilysin Inhibition in Individuals With Obesity and Hypertension. *Clin. Pharmacol. Ther.* **2017**, *101*, 254–263. [\[CrossRef\]](#)
219. Nougue, H.; Pezel, T.; Picard, F.; Sadoune, M.; Arrigo, M.; Beauvais, F.; Launay, J.M.; Cohen-Solal, A.; Vodovar, N.; Logeart, D. Effects of sacubitril/valsartan on neprilysin targets and the metabolism of natriuretic peptides in chronic heart failure: A mechanistic clinical study. *Eur. J. Heart Fail.* **2019**, *21*, 598–605. [\[CrossRef\]](#)
220. Suematsu, Y.; Miura, S.; Goto, M.; Matsuo, Y.; Arimura, T.; Kuwano, T.; Imaizumi, S.; Iwata, A.; Yahiro, E.; Saku, K. LCZ696, an angiotensin receptor-neprilysin inhibitor, improves cardiac function with the attenuation of fibrosis in heart failure with reduced ejection fraction in streptozotocin-induced diabetic mice. *Eur. J. Heart Fail.* **2016**, *18*, 386–393. [\[CrossRef\]](#)
221. Ge, Q.; Zhao, L.; Ren, X.M.; Ye, P.; Hu, Z.Y. LCZ696, an angiotensin receptor-neprilysin inhibitor, ameliorates diabetic cardiomyopathy by inhibiting inflammation, oxidative stress and apoptosis. *Exp. Biol. Med.* **2019**, *244*, 1028–1039. [\[CrossRef\]](#)
222. Gronholm, T.; Cheng, Z.J.; Palojoiki, E.; Eriksson, A.; Backlund, T.; Vuolteenaho, O.; Finckenberg, P.; Laine, M.; Mervaala, E.; Tikkanen, I. Vasopeptidase inhibition has beneficial cardiac effects in spontaneously diabetic Goto-Kakizaki rats. *Eur. J. Pharmacol.* **2005**, *519*, 267–276. [\[CrossRef\]](#)
223. Malek, V.; Sharma, N.; Gaikwad, A.B. Simultaneous inhibition of neprilysin and activation of ACE2 prevented diabetic cardiomyopathy. *Pharmacol. Rep.* **2019**, *71*, 958–967. [\[CrossRef\]](#)
224. Torre, E.; Arici, M.; Lodrini, A.M.; Ferrandi, M.; Barassi, P.; Hsu, S.C.; Chang, G.J.; Boz, E.; Sala, E.; Vagni, S.; et al. SERCA2a stimulation by istaroxime improves intracellular Ca²⁺ handling and diastolic dysfunction in a model of diabetic cardiomyopathy. *Cardiovasc. Res.* **2022**, *118*, 1020–1032. [\[CrossRef\]](#)
225. Lou, S.; Zhu, W.; Yu, T.; Zhang, Q.; Wang, M.; Jin, L.; Xiong, Y.; Xu, J.; Wang, Q.; Chen, G.; et al. Compound SJ-12 attenuates streptozotocin-induced diabetic cardiomyopathy by stabilizing SERCA2a. *Biochim. Biophys. Acta Mol. Basis Dis.* **2024**, *1870*, 167140. [\[CrossRef\]](#)
226. Xiong, X.; Zhang, X.; Zhang, Y.; Xie, J.; Bian, Y.; Yin, Q.; Tong, R.; Yu, D.; Pan, L. Sarco/endoplasmic reticulum Ca(2+) ATPase (SERCA)-mediated ER stress crosstalk with autophagy is involved in tris(2-chloroethyl) phosphate stress-induced cardiac fibrosis. *J. Inorg. Biochem.* **2022**, *236*, 111972. [\[CrossRef\]](#)
227. Katz, M.G.; Brandon-Warner, E.; Fagnoli, A.S.; Williams, R.D.; Kendle, A.P.; Hajjar, R.J.; Schrum, L.W.; Bridges, C.R. Mitigation of myocardial fibrosis by molecular cardiac surgery-mediated gene overexpression. *J. Thorac. Cardiovasc. Surg.* **2016**, *151*, 1191–1200.e3. [\[CrossRef\]](#)
228. Banks, T.E.; Rajapaksha, M.; Zhang, L.H.; Bai, F.; Wang, N.P.; Zhao, Z.Q. Suppression of angiotensin II-activated NOX4/NADPH oxidase and mitochondrial dysfunction by preserving glucagon-like peptide-1 attenuates myocardial fibrosis and hypertension. *Eur. J. Pharmacol.* **2022**, *927*, 175048. [\[CrossRef\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.