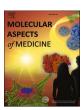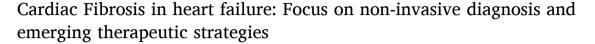Contents lists available at ScienceDirect

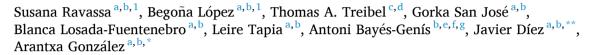# Molecular Aspects of Medicine

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Review

Cardiac Fibrosis in heart failure: Focus on non-invasive diagnosis and emerging therapeutic strategies

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ABSTRACT

Heart failure is a leading cause of mortality and hospitalization worldwide. Cardiac fibrosis, resulting from the excessive deposition of collagen fibers, is a common feature across the spectrum of conditions converging in heart failure. Eventually, either reparative or reactive in nature, in the long-term cardiac fibrosis contributes to heart failure development and progression and is associated with poor clinical outcomes. Despite this, specific cardiac antifibrotic therapies are lacking, making cardiac fibrosis an urgent unmet medical need. In this context, a better patient phenotyping is needed to characterize the heterogenous features of cardiac fibrosis to advance toward its personalized management. In this review, we will describe the different phenotypes associated with cardiac fibrosis in heart failure and we will focus on the potential usefulness of imaging techniques and circulating biomarkers for the non-invasive characterization and phenotyping of this condition and for tracking its clinical impact. We will also recapitulate the cardiac antifibrotic effects of existing heart failure and non-heart failure drugs and we will discuss potential strategies under preclinical development targeting the activation of cardiac fibroblasts at different levels, as well as targeting additional extracardiac processes.

1. Introduction

Heart failure (HF) is a major healthcare problem and is associated with a high use of resources and healthcare costs (reviewed in (Savarese et al., 2023)). Despite significant improvements in HF therapies, morbidity and mortality still remain high. In this conceptual framework, pathological structural remodeling of the myocardium plays a detrimental role in the pathophysiology and clinical course of HF. In particular, cardiac fibrosis is considered a major driver associated with the growing burden of HF. In fact, it is a key contributor to HF and its progression and to adverse outcomes, both in coronary artery disease (CAD) (Frangogiannis and Kovacic, 2020) and non-ischemic cardiac

diseases (Díez et al., 2020). Cardiac fibrosis is a heterogenous and dynamic process dependent on the etiopathogenic cause of HF and on the stage of evolution of the disease. Accordingly, it has been proposed that integrating cardiac fibrosis in HF management is a medical need that requires appropriate diagnostic and therapeutic strategies (Díez and de Boer, 2022). This review article, after considering the general aspects of cardiac fibrosis, focuses on analyzing its accurate and precise non-invasive diagnosis, as well as on evaluating options for its personalized treatment and prevention.
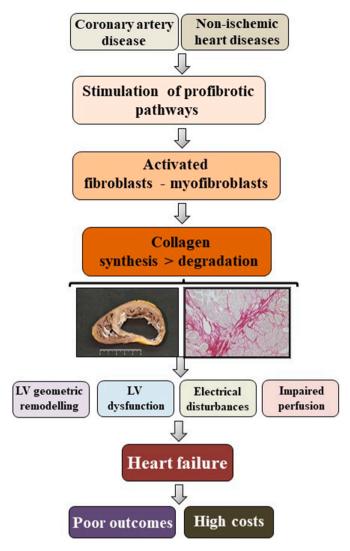
Fig. 1. General overview of cardiac fibrosis from its triggering factors, the cellular and molecular aspects involved in the excessive collagen deposition and the functional impact on the heart. The photographs in the figure correspond to a macroscopic view of a post-myocardial infarction scar (courtesy of Dra. María Dolores Lozano, Department of Pathology, Clínica Universidad de Navarra, Pamplona, Spain), and a microscopic view of interstitial fibrosis in a picrosirius red-stained tissue section corresponding to a patient with hypertensive heart disease.

2. General considerations on cardiac fibrosis

Cardiac fibrosis is defined as an excessive deposition of collagen fibers within the myocardium that occurs in the damaged heart (reviewed in (de Boer et al., 2019)) (Fig. 1). The characterization of cardiac fibrosis is not only a matter of collagen quantity, but also of collagen quality. In fact, different fibrillary collagen types are present in the heart that have different biophysical and physicochemical properties. Type I collagen represents approximately 85% of the total collagen proteins and builds thick fibers that are important for strength, whereas type III collagen forms flexible, thin fibers that are important for elasticity. An abnormal increase in the ratio of type I to type III collagen has been reported in endomyocardial biopsies (EMBs) from patients with severe aortic stenosis (AS) and with HF with preserved left ventricular (LV) ejection fraction (HFpEF) (Echegaray et al., 2017). In contrast, a predominance of collagen type III over type I has been described in EMBs from patients with end-stage HF with reduced LV ejection fraction (HFrEF) due to either CAD or idiopathic dilated cardiomyopathy (DCM) (Herpel et al.,

2006). Another factor that critically determines the stiffness or elasticity of collagen fibers is the degree of covalent bonds between constituent microfibrils (i.e. cross-linking). The degree of myocardial collagen cross-linking in EMBs is associated with LV stiffness and filling pressures in hypertensive patients with either HFpEF or HFrEF (López et al., 2012).

2.1. Types of collagen deposits

Based on the characteristics of the deposits there are two major types of cardiac fibrosis (reviewed in (de Boer et al., 2019)): reparative (or replacement) fibrosis and reactive fibrosis. The former is visible as focal macroscopic or microscopic collagen fiber-based scars that are formed during a healing process and replace dying cardiomyocytes after ischemic and non-ischemic insults. The latter manifests as diffuse strands and bands of collagen fibers deposited in interstitial and perivascular areas and develops as a reaction to chronic exposure of the heart to biomechanical stress present in several cardiac conditions and extracardiac diseases. Both patterns of fibrous deposits may coexist. For instance, in explanted hearts from patients with advanced CAD and myocardial infarction (MI), besides a macroscopic reparative scar reflecting the loss of a large number of cardiomyocytes, reactive interstitial fibrosis in myocardial areas remote to the scar is present (Beltrami et al., 1994). On the other hand, in patients with severe AS, reactive diffuse interstitial and perivascular fibrosis is associated with reparative microscars reflecting the loss of small foci of cardiomyocytes (Treibel et al., 2018b).

2.2. Critical role of fibroblasts

Cardiac fibrosis is characterized by the presence of activated cardiac fibroblasts and myofibroblasts whose secretome leads to alterations in the extracellular processing of fibrillary collagen facilitating the excessive accumulation of collagen fibers (Ivey and Tallquist, 2016; Kurose, 2021). The activation of cardiac fibroblasts encompasses a broad number of changes, including proliferation and increased periostin expression, with an extensive formation of endoplasmic reticulum (a feature of synthetically active fibroblasts) and differentiation into myofibroblasts, which have ultrastructural and phenotypic characteristics of smooth muscle cells acquired through the formation of contractile polymerized stress fibers that incorporate *de novo* synthesized α-smooth muscle actin (α-SMA). Although resident cardiac fibroblasts are the major source of activated fibroblasts (Humeres and Frangogiannis, 2019), they exhibit a remarkable heterogeneity during development, in the adult heart, and in disease states (Tallquist, 2020). For instance, single-cell transcriptional profiling of the mouse heart has revealed different clusters among resident fibroblasts identified by the expression of canonical markers such as *Col1a1*, *Pdgfra* and *Tcf21* (Skelly et al., 2018).

Several pathways can activate cardiac fibroblasts (reviewed in (López et al., 2021)). A diversity of mechanisms participate in the activation of cardiac fibroblasts in response to local cardiac injury resulting in damaged or dying cardiomyocytes (that release damage-associated molecular patterns molecules or alarmins), increased biomechanical stress (due to pressure or volume overload, genetic alterations, infectious agents and cardiotoxic pharmacological drugs), and systemic extra-cardiac alterations that are profibrotic for the heart (e.g. diabetes mellitus, chronic kidney disease and dysbiosis of gut microbiota, among others). These mechanisms include neurohumoral pathways (such as the renin-angiotensin-aldosterone system), inflammatory signaling cascades (triggered by cytokines and chemokines), mechano-sensitive pathways (e.g. mediated by integrins and ion channels), metabolic intracellular dysregulation (with increased glycolysis and lactic acid accumulation), and several growth factors (including transforming growth factor-β [TGF-β] and many others). A large body of evidence supports the central role of TGF-β signaling pathways in fibroblast activation through canonical small mothers against

decapentaplegic (Smad)-dependent pathways and through other non-canonical signaling cascades (reviewed in (Frangogiannis, 2022)). Finally, cardiac fibroblasts are also activated by changes in the mechanical properties of the heart, including increased myocardial tissue stiffness (Herum et al., 2017). As alterations in this property are mainly determined by fibrillar collagen type I and by the degree of collagen cross-linking, the possibility exists for positive feedback between increased deposition of cross-linked collagen fibers and activation of cardiac fibroblasts.

Considering the heterogeneity of cardiac fibroblasts subpopulations, the activation process might not be the same for all cell subsets and might also lead to different fibroblast phenotypes and even to dynamic phenotypic transitions. This can be the case in conditions of reparative fibrosis (Venugopal et al., 2022). During the inflammatory phase of infarct healing, the release of alarmins by necrotic cardiomyocytes promotes a proinflammatory fibroblast phenotype (via secretion of cytokines and chemokines) that may contribute to leukocyte recruitment to the injury site. The clearance of dead cardiomyocytes and matrix debris from the infarct leads to the anti-inflammatory and proliferative phase of infarct healing in which resident cardiac fibroblasts proliferate, migrate and undergo myofibroblast conversion. Myofibroblasts facilitate the formation of a collagen-based scar that protects the infarcted ventricle from rupture and adverse dilative remodeling. During scar maturation, fibroblasts disassemble α-SMA stress fibers and convert to matrifibrocytes, specialized cells expressing matrix metalloproteinases (MMPs) and bone-cartilage proteins, that may play a role in scar maintenance and promotion of angiogenesis.

The secretome of myofibroblasts contains several profibrogenic proteins including procollagen type I and type III precursors, enzymes involved in the synthesis of mature fibril-forming collagen molecules from the precursors (i.e. procollagen proteinases), enzymes involved in fibril cross-linking (i.e. lysyl oxidases [LOX]) to form the final collagen fiber that is deposited in the extracellular matrix (ECM), and enzymes involved in the degradation of deposited fibers (i.e. MMPs) (reviewed in (Weber et al., 2013)). In fibrotic conditions, the fibrogenic procollagen proteinases-LOX mediated-axis predominates over the fibrolytic MMP-mediated axis (Fig. 1). Besides molecules involved in the extracellular processing of fibrillar collagen, myofibroblasts may also secrete a number of cytokines, thus contributing to the interplay between inflammation and fibrosis in the injured heart (Thomas and Grisanti, 2020). Interestingly, different mediators of cardiac fibroblasts activation have distinct effects on the myofibroblast cytokine secretome (Bräuninger et al., 2021; Ceccato et al., 2020). Different causes of fibrosis may have a differential myofibroblast secretory signature. Overall, TGF-β is the principal profibrotic growth factor secreted by myofibroblasts (reviewed in (Frangogiannis, 2022)). Data obtained in human myofibroblasts showed that upregulation of interleukin-11 (IL-11) was the dominant transcriptional response of these cells to TGF-β exposure and was required for fibrogenic protein synthesis (Schafer et al., 2017).

2.3. Role of other cells

Studies using cell lineage markers in mouse models indicate that, after MI or in response to pressure overload (caused by aortic constriction or by hypertension), the activation of resident fibroblasts into myofibroblasts is predominantly observed, with little contribution from other cellular sources (Kanisicak et al., 2016; Moore-Morris et al., 2014).

As previously mentioned, damaged or dying cardiomyocytes can release alarmins that are sensed by the cardiac fibroblast to initiate the process of activation (Turner, 2016). On the other hand, in response to hypoxia, cardiomyocytes release TGF-β, which can directly activate fibroblasts (Kuhn et al., 2020).

As shown experimentally, vascular endothelial cells participate in cardiac fibrosis through indirect mechanisms, including the enhanced recruitment of leukocytes through increased expression of adhesion molecules (e.g. intercellular adhesion molecule-1) (Salvador et al., 2016), and through secretion of profibrotic factors such as TGF-β (Chua et al., 1994) and endothelin-1 (Adiarto et al., 2012) in response to Ang II.

As demonstrated in experimental and clinical studies, cardiac fibrosis is associated with the infiltration of a diversity of leukocytes in both CAD and non-ischemic heart disease (reviewed in (Baci et al., 2020; Okyere and Tilley, 2020)). Either through the release of TGF-β induced by IL-6 (Ma et al., 2012) or through direct cell-cell interactions (Nevers et al., 2017), immunoinflammatory cells contribute to the activation of cardiac fibroblasts. Interestingly, cardiac myofibroblasts can also stimulate leukocyte recruitment by secreting granulocyte-macrophage colony-stimulating factor (GM-CSF) (Anzai et al., 2017) and several chemokines, cytokines and growth factors that modulate inflammatory cells (Lindner et al., 2014).

2.4. Contribution of the non-fibrillary component of the extracellular matrix

Although the role of fibrillary collagens in cardiac fibrosis is well studied, the contribution of the non-fibrillary ECM components has remained less explored and much more remains to be unraveled about the specific and collective fibrotic roles of its constituents. There are, however, some aspects that deserve to be considered.

For instance, in an experimental model of MI, the matrikine endostatin, derived from the basement membrane-anchored collagen type XVIII, stimulated the proliferation and migration of myofibroblasts into the infarcted area (Sugiyama et al., 2018). Recent experimental data demonstrate that ablating the gene of the non-structural glycoprotein fibronectin specifically in cardiac fibroblast populations limits their activation, and that suppressing fibronectin deposition with a peptide to attenuate its polymerization reduces collagen deposition in HF (Valiente-Alandi et al., 2018). The myocardial matricellular protein osteopontin, which up-regulates LOX expression in human cardiac fibroblasts, is associated with increased LOX, insoluble collagen, collagen type I deposition, and LV stiffness and filling pressures in patients with HF attributable to hypertensive heart disease (López et al., 2013). Finally, in adults with non-ischemic DCM, glycosaminoglycans exhibited a significantly lower affinity for TGF-β and this alteration was associated with enhanced activation of the Smad2/3 signaling pathway and more pronounced interstitial fibrosis (Jana et al., 2018).

3. Clinical relevance of cardiac fibrosis

Either initially reparative or reactive in nature, it seems that the fibrotic response to the initial cardiac insult cannot be switched off, and that accumulation of fibrotic tissue remains persistent, leading to the progressive impairment of myocardial properties and LV function that facilitate HF (de Boer et al., 2019). Additionally, myofibroblasts can influence cardiac function through direct and indirect effects on cardiomyocytes (Hall et al., 2021). Therefore, the clinical relevance of pathological cardiac fibrosis is strongly supported by clinical and experimental data and deserves consideration both in HF of ischemic and non-ischemic origin (Díez et al., 2020; Frangogiannis and Kovacic, 2020) (Fig. 1).

Several sudies have shown that both the quantity and the quality of cardiac fibrosis are associated with the severity of clinical symptoms, the hormonal profile, LV systolic and/or diastolic function and even with a higher risk of cardiovascular events, irrespective of the aetiology and type of HF (reviewed in (López et al., 2021)). In addition, as discussed in subsequent sections, some HF drugs have shown anti-fibrotic effects associated with clinical improvement. Although these clinical associations do not prove causality, cumulative evidence obtained in preclinical models of cardiac fibrosis has revealed that this lesion plays a key role in HF onset and progression. Addressing the experimental evidence supporting the causative role of fibrosis in cardiac dysfunction and HF is

beyond the scope of this review and has been elegantly reviewed elsewhere (Frangogiannis, 2019; Wang et al., 2022). Overall, available clinical and experimental data strongly indicate that cardiac fibrosis, either primarily reactive or secondary to cardiomyocyte death, plays a pivotal role in cardiac remodeling, dysfunction and HF progression (de Boer et al., 2019). In this section we will discuss some of the potential mechanisms related to the clinical impact of cardiac fibrosis.

3.1. Contribution to morphological alterations

Although the pathophysiology of LV adverse morphological remodeling is complex, changes in tissue composition, especially cardiac fibrosis, may play a major role. This is suggested by findings from studies using cardiac magnetic resonance (CMR) imaging biomarkers which capture focal scar by late gadolinium enhancement (LGE) and diffuse fibrosis by extracellular volume fraction (ECV); both discussed in more detail later. For instance, in patients with MI the percentage of LGE of the total LV mass was reported as a major determinant of LV adverse eccentric remodeling (Pezel et al., 2020) and the higher ECV values in the remote myocardium were significantly associated with adverse LV eccentric remodeling (Bulluck et al., 2016). On the other hand, abnormally increased ECV values have been reported in patients with LV hypertrophy secondary to hypertension and AS, where patients with higher ECV also have greater LV adverse concentric remodeling (Kuruvilla et al., 2015; Treibel et al., 2018b).

3.2. Impairment of cardiac function

Cardiac fibrosis is involved in the development of both HFrEF and HFpEF (reviewed in (Pilz et al., 2022; Sweeney et al., 2020)). Indeed, clinical evidence supports that cardiac fibrosis may impair both diastolic and systolic function in HF patients in whom significant CAD had been excluded by angiography. The severity of diffuse interstitial fibrosis (as assessed by the amount of collagen deposition and/or the degree of fiber cross-linking) is related to diastolic dysfunction in patients with HF (Kasner et al., 2011; Zile et al., 2015). On the other hand, the severity of diffuse interstitial fibrosis is inversely associated with the LV ejection fraction in hypertensive HF patients (López et al., 2012; Querejeta et al., 2004).

Mechanistically cardiac fibrosis increases LV stiffness, thus hampering passive inflow and causing a backward diastolic flow that further impairs early filling. Consequently, a large portion of the filling depends on the final atrial contraction and the total diastolic phase becomes less efficient (Burlew and Weber, 2002). On the other hand, the loss of LV helical (spiral) orientation of cardiomyocytes, that results from an excess of collagen tissue, impairs the transmission of force generated by these cells to the ventricular chamber, compromising contractility (Triposkiadis et al., 2018).

3.3. Disturbances of cardiac electrical activity

Cardiac fibrosis (assessed in EMBs) is associated with ventricular arrhythmias in patients with either CAD or non-ischemic heart disease without (McLenachan and Dargie, 1990) and with (Kawara et al., 2001) HF. Furthermore, cardiac fibrosis (detected by CMR) predicts ventricular arrhythmias and sudden death in patients with CAD and a wide range of LV ejection fraction (Zegard et al., 2021). Cardiac fibrosis generates an arrhythmogenic substrate through the distortion of the electrophysiological harmony of the myocardium (i.e. slowing the action potential propagation and initiating re-entry) (Nguyen et al., 2017). In addition, myofibroblasts contribute to the arrhythmogenic substrate by directly interacting with cardiomyocytes, reducing their action potential duration and hyperpolarizing their resting membrane potential (Nagaraju et al., 2019).

Of interest, atrial fibrosis occurs in conditions of severe chronic pressure overload (e.g. hypertension and AS) or HF that are associated with LV fibrosis, resulting in class II or III atrial cardiomyopathy with increased risk of atrial fibrillation (Goette et al., 2016). These observations suggest that the profibrotic cardiac microenvironment is not limited to the ventricles.

3.4. Compromise of myocardial perfusion and oxygenation

Cardiac fibrosis may also compromise myocardial perfusion and oxygenation. Indeed, perivascular fibrosis evaluated in EMBs is inversely correlated to coronary flow reserve in patients with non-ischemic HF (Dai et al., 2012). In addition, a strong association was found between CMR-determined ECV and CMR-determined blood oxygen level in the same cardiac segments in patients with hypertrophic cardiomyopathy (HCM), suggesting that cardiac fibrosis is related to myocardial hypoxia in this setting (Ando et al., 2020). Furthermore, the histological severity of diffuse interstitial fibrosis is associated with both structural and functional alterations in the vascular wall of coronary arterioles and with capillary rarefaction in patients with HF, independently of the presence or absence of CAD (Galati et al., 2016; Mohammed et al., 2015). Therefore, cardiac fibrosis and coronary microvascular disease probably act synergistically to facilitate ischemia and hypoxia in the failing heart.

3.5. Disease burden

Three arguments support the medical and public health relevance of cardiac fibrosis. First, reparative fibrosis is part of the pathological substrate of CAD and MI, whose estimated prevalence in subjects older than 20 years in the United States are 7.2% and 3.1%, respectively (Tsao et al., 2022). Furthermore, reactive fibrosis can be detected in many chronic cardiac diseases and in several systemic clinical conditions evolving with cardiac damage (reviewed in (López et al., 2021)). Second, since the severity of cardiac fibrosis is associated with increased risk of HF hospitalization, cardiac events and/or death in patients with HF (Aoki et al., 2011; Arteaga et al., 2009; Ravassa et al., 2017), this lesion could contribute to the burden of HF. The growing importance of these aspects is supported by the evidence that aging favors both the development of cardiac fibrosis (Gazoti Debessa et al., 2001) and the incidence of HF (Conrad et al., 2018). Third, the management of cardiac fibrosis is currently one of the largest unmet medical needs in HF (Díez and De Boer, 2022). It is not being routinely considered in HF management, which may be the reason why fibrosis-related endpoints are not currently included in HF clinical trials. In this context, surrogate markers of cardiac fibrosis could be useful to evaluate antifibrotic effects of drugs in clinical trials.

4. Diagnosis of cardiac fibrosis

4.1. Based on histological findings

The current "gold standard" for quantification of collagen deposition and diagnosis of diffuse myocardial fibrosis is the EMB (Hassan et al., 2020; López et al., 2021). However, the American Heart Association, the American College of Cardiology, and the European Society of Cardiology only indicate EMBs for monitoring rejection after heart transplant, for differential diagnosis, or in patients with rapidly progressive HF despite standard therapy (Cooper et al., 2007; McDonagh et al., 2022), as well as in certain clinical settings when other assessments are not conclusive, such as myocarditis, inflammatory cardiomyopathies, amyloidosis and sarcoidosis (Ammirati et al., 2020; Cooper et al., 2007; Hassan et al., 2020; Mewton et al., 2011).

Several studies have evaluated cardiac fibrosis in patients with other cardiac conditions. The percentage of total myocardial tissue occupied by collagen fibers (CVF o collagen volume fraction) is increased in patients with HF of different etiologies (Aoki et al., 2011; López et al., 2006; Querejeta et al., 2004; Van Heerebeek et al., 2006), and in AS
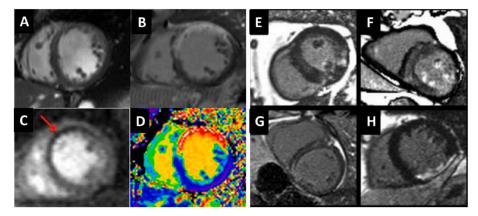
Fig. 2. Cardiac magnetic resonance for the asssement of morphology, function and tissue characteristics. (A) Cardiac magnetic resonance imaging offers non-invasive evaluation of myocardial structure and function. (B) The use of first pass perfusion with gadolinium-based contrast agents during vasodilator stress allows the assessment of stress-induced myocardial ischemia. (C) Utilizing the different wash-in and wash-out kinetics of gadolinium-based contrast agents in normal and diseased myocardium allows visualization of focal scar (white) during late gadolinium enhancement imaging; this technique only allows semi-quantitative evaluation of scar as it requires a difference between diseased and remote myocardium. (D) Quantitative assessment of focal and diffuse myocardial fibrosis is possible through T1 mapping, which allows calculation and visualization of extracellular volume fraction (ECV), with each image voxel representing a quantitative ECV value of the image tissue. (E–H) Patterns of late gadolinium enhancement are typical of the etiology of scar ranging from non-infarct pattern focal scar (E,F) to mid-wall fibrosis of non-ischemic dilated cardiomyopathy (G) to subendocardial scar in myocardial infarction (here a full thickness inferior myocardial infarct; H).

patients (Treibel et al., 2018b), being higher in those with increased LGE (Raafs et al., 2021). However, it is similar in patients with HFpEF or HFrEF and non-CAD (Aoki et al., 2011; López et al., 2006; Van Heerebeek et al., 2006). Myocardial tissue analysis of a large series of patients with HFpEF revealed that 93% of patients presented cardiac fibrosis (Hahn et al., 2020), corroborating the high prevalence of this lesion in HF patients.

Although the EMB is an invasive procedure, it is considered safe, since the overall complication rate is low (<1%), and strictly dependent on the patient's clinical state (Chimenti and Frustaci, 2013). Nevertheless, it presents important limitations such as low representativeness in patchy conditions (failure to obtain samples of the whole myocardium), potential sampling error (miss-localize fibrosis), and the need for a specialized center and operator (Bing and Dweck, 2019; López et al., 2021). These limitations, together with the development of non-invasive techniques for cardiac fibrosis diagnosis, have relegated EMB for diagnosis in routine clinical assessment of HF.

4.2. Critical approach to surrogate assessment of cardiac fibrosis

Surrogate assessment of cardiac fibrosis by imaging techniques and circulating biomarkers potentially allows a non-invasive diagnostic approach to this lesion, being an attractive tool for cardiac fibrosis phenotyping, patient risk stratification and therapeutic management.

Imaging biomarkers offer some clear advantages over EMB. They can be obtained non-invasively, and are repeatable over time, allowing monitoring of disease progression and treatment response. Furthermore, cardiac imaging can capture the whole heart *in vivo*, and is therefore not prone to the sampling errors of the EMB with its very limited size (EMBs = 0.01 mL *vs.* CMR>100 mL). The main limitations of current imaging biomarkers are the resolution (0.5–1 mm for computed tomography [CT], >2 mm for CMR and positron emission tomography [PET]) and the lack of specificity. CMR offers tissue characterization, its biomarkers identify extracellular expansion and the patterns of expansion are used to identify etiologies, however, CMR ultimately does not provide further specificity. Molecular imaging with target-specific radiotracers may promise to overcome this challenge in the future.

The use of circulating biomarkers has the advantage of employing techniques that are broadly available in clinical laboratories, easy to perform in large numbers of patients, reproducible and with an affordable cost. They can also provide information regarding the dynamics of cardiac fibrosis, as well as some mechanistic insights. The search for circulating biomarkers of cardiac fibrosis has grown exponentially in the last years, however, very few biomarkers have shown potential to be translated into clinical practice. Larger studies including multinational

validation across independent cohorts and evaluation in randomized clinical trials are needed to overcome these limitations (González et al., 2022). On the other hand, it should be noted that circulating biomarkers of fibrosis are not cardiac-specific and may be also reflecting systemic fibrosis or fibrosis in other organs. An association with histological cardiac fibrosis should be shown to reinforce their value as cardiac fibrosis biomarkers, however, this is difficult to achieve in the clinical setting given the limitations of EMB accessibility and sampling error. Moreover, considering the heterogeneity of cardiac fibrosis, different biomarkers may better reflect the fibrotic process in different cardiac conditions. Finally, circulating concentrations of biomarkers may be also affected by alterations in the organs responsible for their clearance (i.e. liver or kidney).

Overall, it is unlikely that a single biomarker is likely to capture the heterogeneity and complexity of cardiac fibrosis, and therefore, we should search for differential bioprofiles combining circulating and imaging biomarkers to improve patient phenotyping and advance toward the implementation of personalized medicine targeting cardiac fibrosis.

4.3. Assessment of cardiac fibrosis based on cardiac imaging

4.3.1. Ultrasound

The acoustic impedance of the myocardium is affected by its elastic property. In the case of cardiac fibrosis, collagen deposition reduces tissue elasticity, potentially altering the ultrasound signal. This signal can be measured using the integrated backscatter signal (IBS) (Picano et al., 1990). The reliability of this method has been validated in small studies of various cardiac conditions, including AS, DCM, and post-cardiac transplantation. IBS has also been found to correlate with diastolic function in HCM and end-stage renal disease, as well as with a collagen biomarker in hypertension (Di Bello et al., 2004; Losi et al., 2007; Maceira et al., 2002; Mizuno et al., 2007). IBS is inexpensive and does not require a contrast agent, so it could be widely available. However, it is operator-dependent and requires good image quality (correlation with histology is poor in patients with poor acoustic windows). Furthermore, no studies have yet correlated IBS with functional status or outcomes (Mizuno et al., 2007).

Diastolic assessment and myocardial deformation detect earlier changes in function (Aurigemma et al., 1995; Weidemann et al., 2009). Deformation can be measured in a variety of ways, including long-axis annular excursion, mid-wall fractional shortening, myocardial systolic and diastolic velocities, and global longitudinal strain (GLS) using speckle tracking. Strain abnormalities follow a disease-specific pattern, starting sub-endocardially, becoming mid-wall and then transmural in

Table 1
Association of extracellular volume quantified by cardiac magnetic resonance and histologically-assessed cardiac fibrosis.

Reference	Year	Population	N	Finding
Flett et al. (2010)	2010	AS/HCM	26	Correlation with histological fibrosis in AS ($R^2 = 0.86$) and HCM ($R^2 = 0.62$).
White et al. (2013)	2013	AS	18	Bolus only and infusion ECV correlated with CVF ($R^2 = 0.69$ and 0.71).
Miller et al. (2013)	2013	DCM/CAD (Transplant)	6	Correlation with CVF with the 10-min or 15-min post-contrast T1 ($p < 0.001$).
De Meester De Ravenstein et al. (2015)	2015	AS/AR/MR	31	Correlation with histological fibrosis ($r = 0.78$).
Kammerlander et al. (2016)	2016	Mixed HF	36	Correlation with histological CVF ($r = 0.49$).
Lurz et al. (2016)	2016	Myocarditis	129	ECV associated with LV fibrosis only in patients without inflammation ($r = 0.72$); not in those with inflammation ($r = 0.24$).
ECV by CT				
Bandula et al. (2013)	2013	AS	23	Correlation with histological fibrosis ($r = 0.71$).

AS stands for aortic stenosis; AR, aortic regurgitation; CAD, coronary artery disease; CT, computed tomography; CVF, collagen volume fraction; DCM, dilated cardiomyopathy; ECV, extracellular volume; HCM, hypertrophic cardiomyopathy; HF, heart failure; MR, mitral regurgitation.

advanced disease where they become prognostic in AS patients (Delgado et al., 2009). Worsening of myocardial mechanic indices reflect aggregates of several myocardial insults including intrinsic myocyte dysfunction, fibrosis or ischemia and change early in the disease. Strain parameters of both ventricles have been used to effectively detect cardiac fibrosis (Lisi et al., 2022). Historically, the measurement of strain had high inter-vendor variability, but this has been addressed by standardization task force recommendation (D'hooge et al., 2016).

4.3.2. Cardiac magnetic resonance

CMR using gadolinium-based contrast agents (GBCA) is currently the most effective non-invasive technique for visualizing focal fibrosis due to its high contrast and high spatial resolution. Cardiac CT is an alternative (see below). Both CMR and CT use an extracellular, extravascular contrast agent that remains in extracellular water in areas of scar, due to a higher volume of distribution and slower kinetics. CMR allows non-invasive tissue characterization of the myocardium and as such is being increasingly used to identify the etiology of a range of cardiomyopathies. LGE imaging is the mainstay of this myocardial characterization and allows the detection of focal fibrosis (Kim et al., 2000). LGE imaging relies on the delayed post-contrast difference in T1 between areas of fibrosis (more gadolinium, shorter T1) and healthy myocardium (less gadolinium, longer T1) (Parsai et al., 2012), making it ideal for identifying focal areas of fibrosis. LGE imaging identifies patterns of scar that can be mapped onto etiologies of disease (Fig. 2), although there can be significant overlap. Furthermore, LGE predicts outcome in CAD (Kim et al., 2008), non-ischemic cardiomyopathy (Gulati et al., 2013), HCM (Ismail et al., 2012) and valvular heart disease (Musa et al., 2018).

Diffuse fibrosis visualization has remained challenging until recently, though over the last decade, T1 mapping with ECV quantification (Fig. 2) has been developed and has entered routine clinical practice. T1 mapping and ECV quantification allows measurement and tracking of diffuse interstitial expansion due to diffuse fibrosis, cardiac infiltration and myocardial edema.

Native T1 describes the signal in the whole of the measured myocardium and therefore represents a composite signal from all species present, this signal is swamped by iron or gadolinium if present and in their absence is measuring the signal of both cardiac myocytes and the ECM (Messroghli et al., 2017; Moon et al., 2013). Therefore, fibrosis/edema/amyloid and associated water increase T1, and conversely increased cellularity (athleticism), iron (thalassemia) or fat (Anderson Fabry disease) decrease T1 (McDiarmid et al., 2016; Messroghli et al., 2017; Moon et al., 2013; Puntmann et al., 2016).

The use of extracellular GBCAs in CMR offers the opportunity to quantify the extracellular (i.e. interstitial) space, relative to the intracellular (i.e. myocyte) space, which is the essence of ECV quantification. It dichotomizes the myocardium into myocytes and matrix. In conjunction with myocardial volume, ECV can be used to calculate the relative volumes of each compartment. It is expressed as a volume fraction and provides us with unique insights into the pathophysiology of a range of myocardial diseases (Messroghli et al., 2017). T1 mapping and ECV provide an advantage over conventional LGE imaging, by enabling us to more accurately quantify diffuse fibrosis and potentially detect early fibrosis-related changes not always detectable by LGE (Messroghli et al., 2017). ECV has been found to be associated with histologically-assessed cardiac fibrosis in several studies (Table 1). Increases in ECV seen on CMR are associated with increased mortality and may be as important to prognosis as LV ejection fraction (McDiarmid et al., 2016; Messroghli et al., 2017).

Normal ECV values depend on multiple technical features (field strength, T1 mapping sequence, scanner manufacturer), but range between 20 and 26%, and are slightly higher in women compared to men, likely artefactual due to partial voluming of the blood pool (Sado et al., 2012). With the exception of cardiac amyloidosis and edema (Banypersad et al., 2013), increases in myocardial ECV are generally due to myocardial fibrosis (Moon et al., 2013). Focal scar due to acute or chronic MI results in some of the highest ECV values (acute: $58.5 \pm 7.6\%$; chronic: $51 \pm 8\%$) (Sado et al., 2012; Ugander et al., 2012). Diffuse fibrosis, however, rarely increases beyond 40% and is mildly elevated in AS, HCM and DCM (Sado et al., 2012). Cardiac amyloidosis, which is characterized by the extracellular deposition of misfolded protein, produces large increases in ECV (greater than any other non-ischemic cardiomyopathy) in the region of 40–50% (Martinez-Naharro et al., 2019).

ECV also tracks disease progression and myocardial changes after intervention. In patients with AS, ECV tracks fibrosis progression (Chin et al., 2017) and is able to characterize the components of LV hypertrophy regression (20–30% of LV mass at 1-year) after aortic valve replacement. ECV quantification has confirmed that mass regression is due to both a reduction in cellular and matrix compartments at 1-year, with the cellular response greater than the interstitial matrix response (Treibel et al., 2018a). In patients with light chain cardiac amyloidosis, ECV tracks progressive amyloid deposition and regression in deposits in response to chemotherapy, and can predict outcome after adjusting for known predictors like hematological response, amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and longitudinal strain (Martinez-Naharro et al., 2022). Furthermore, in a randomized controlled trial of pirfenidone in HFpEF, ECV tracked a significant reduction in diffuse fibrosis in the treatment group compared to the placebo group (Lewis et al., 2021).

ECV maps are now routine in some centers (Kellman et al., 2012), but quality control systems, commercial sequences and mega-registries (e.g. Global CMR Registry, HCM Registry, UK Biobank) are still in progress, and will provide high volumes and new insights into the currently most active CMR research area (Kramer et al., 2015; Petersen et al., 2013). On the horizon, magnetic resonance fingerprinting may offer more rapid multi-parametric tissue characterization in the future by providing

Table 2
Relevant associations between circulating biomarkers and cardiac fibrosis evaluated in endomyocardial biopsies or by cardiac magnetic resonance.

	Reference	Year	Population	N	Cardiac Fibrosis Finding (endomyocardial biopsies)	Finding (cardiac magnetic resonance)
miR-21	Villar et al. (2013)	2013	AS	75	Direct correlation with myocardial collagen type I mRNA (r = 0.49)	
miR-29a	Roncarati et al. (2014)	2014	HCM	41		Direct correlation with LGE (r = 0.69)
miR-19b	Beaumont et al. (2017)	2017	AS	28	Inverse correlation with the degree of collagen cross-linking (r = −0.40)	
miR-197-5p	(W. Liu et al., 2018)	2018	HF (Stage C&D)	80		Weak direct correlation with LGE (r = 0.23)
TGF-β	Villar et al. (2009)	2009	AS	39	Direct correlation with myocardial collagen type I mRNA (r = 0.58)	
GDF-15	Lok et al. (2012)	2012	DCM	30	Direct association with collagen deposition (r = 0.61)	
	Kanagala et al. (2020b)	2020	HFpEF/HFrEF/Control	234		Weak direct correlation with LGE (r = 0.24) & ECV (r = 0.21)
CTGF	Rubiś et al. (2016)	2016	DCM	70	NO correlation with collagen deposition.	
	Wu et al. (2014)	2014	Diastolic HF	25		Direct correlation with ECV (r = 0.70)
PICP	Querejeta et al. (2004)	2004	Hypertension with/without HF	65	Direct correlation with collagen deposition (r = 0.87)	
	López et al. (2004)	2004	Hypertensive HF	36	Direct correlation with collagen deposition before and after treatment (r = 0.88)	
	López et al. (2012)	2012	Hypertensive HF	38	Direct correlation with collagen deposition (r = 0.74)	
	(C. Yang et al., 2019)	2019	HCM	52	Direct correlation with collagen deposition (r = 0.33)	
	Raafs et al. (2021)	2021	DCM (LVEF<35%)	109	Direct correlation with collagen deposition ($R^2 = 0.43$)	Direct correlation with LGE ($R^2 = 0.39$)
PIIINP	Klappacher et al. (1995)	1995	DCM	17	Direct correlation with collagen type III (r = 0.78) and type I (r = 0.71) deposition	
	Nagao et al. (2018)	2018	DCM	80	NO correlation with myocardial collagen type III mRNA	
	Raafs et al. (2021)	2021	DCM (LVEF<35%)	109	Weak direct correlation with collagen deposition ($R^2 = 0.08$)	Direct correlation with LGE ($R^2 = 0.14$)
CITP	Klappacher et al. (1995)	1995	DCM	17	Direct correlation with collagen type I deposition (r = 0.60)	
	López et al. (2012)	2012	Hypertensive HF	38	Inverse correlation with insoluble collagen (r = −0.45)	
CITP/MMP-1	López et al. (2016)	2016	Hypertensive HF	38	Inverse correlation with collagen cross-linking (r = 0.46)	
sST2	Tseng et al. (2018)	2018	End-stage HF	38	NO correlation with collagen deposition	
	Gawor et al. (2018)	2018	HCM	60		NO correlation with LGE
	Arrieta et al. (2022)	2022	AS	79		Direct correlation with LGE (r = 0.75)

AS stands for aortic stenosis; CITP, collagen type I carboxy-terminal telopeptide; CTGF, connective tissue growth factor; DCM, dilated cardiomyopathy; ECV, extra-cellular volume; LVEF, left ventricular ejection fraction; Gal-3, galectin-3; GDF-15, growth differentiation factor-15; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, HF with preserved LVEF; HFrEF, HF with reduced LVEF; LGE, late gadolinium enhancement; MMP; matrix metalloproteinase; PICP, procollagen type I carboxy-terminal propeptide; PIIINP, procollagen type III amino-terminal propeptide; sST2, soluble isoform of ST2; TGF-β, transforming growth factor-β.

myocardial T1, T2, and Proton Spin Density in a single breath-hold (Hamilton et al., 2017).

4.3.3. Cardiac computed tomography

Cardiac CT is widely used for the non-invasive assessment of coronary and vascular anatomy. Furthermore, it can provide functional assessment of coronary flow and myocardial tissue characterization in a single modality, which is appealing for diagnostic imaging workflow. Cardiac CT has the ability to detect myocardial fat on the pre-contrast phase, focal myocardial scar on delayed enhancement CT (DECT) (Cochet et al., 2015; Goetti et al., 2011; Ichikawa et al., 2009) and quantification of interstitial expansion due to fibrosis or amyloidosis through iodine mapping by DECT or ECV imaging (Kurita et al., 2016; Nacif et al., 2012; Treibel et al., 2015; Wichmann et al., 2013). The best use case for this modality is in patients with severe AS undergoing cardiac CT as part of their work-up for transcatheter aortic valve replacement. In these patients, cardiac CT with ECV quantification allows not only quantification of diffuse fibrosis, which is prognostic (Scully et al., 2022), but also detection of dual pathology, AS and cardiac

amyloidosis (which occurs in ~10% of elderly AS patients) (Nitsche et al., 2021). However, the poorer signal-to-noise ratio compared to CMR and the use of ionizing radiation have limited the widespread use of cardiac CT for myocardial tissue characterization.

Molecular imaging techniques, such as PET and single-photon emission computed tomography (SPECT), can help to identify the molecular pathways involved in myocardial fibrosis and provide insights into the disease's underlying mechanisms (De Haas et al., 2014). Importantly, the widespread availability of PET imaging for oncology has made this technology more available also for cardiac applications, and is used in the assessment of cardiac infections (endocarditis) and cardiovascular inflammation. By targeting specific molecular markers associated with myocardial fibrosis, these imaging techniques can help in early detection and accurate diagnosis of the disease, as well as in monitoring the treatment response. Over the last few years, novel radiotracers specifically targeting fibrosis have become available (reviewed in (Barton et al., 2023)). Among these targets are ^{18}F-fluciclatide, a novel arginine–glycine–aspartate tripeptide radiotracer that binds the αvβ3 integrin transmembrane receptor, which activation
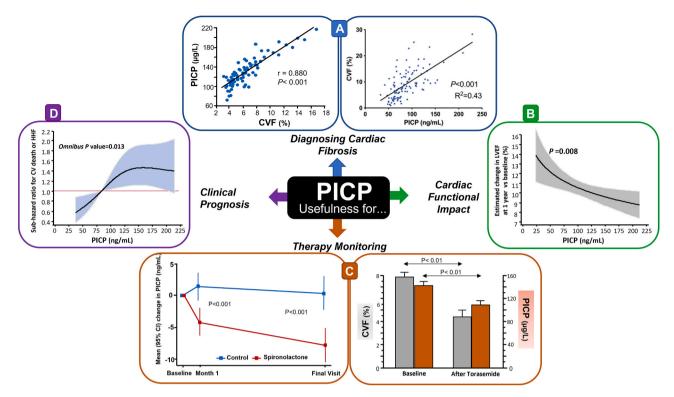
Fig. 3. Procollagen type I carboxy-terminal propeptide (PICP) as a biomarker of cardiac fibrosis. (A) Association between the collagen volume fraction and serum PICP in hypertensive heart failure (HF) patients (left panel) and in patients with dilated cardiomyopathy and a left ventricular ejection fracion (LVEF) below 35% (right panel). (B) Increased baseline serum PICP is associated with lower improvement of LVEF during follow-up in HF patients. (C) PICP decreases in response to spironolactone treatment in patients at risk of HF (left panel), and collagen volume fraction and PICP decrease in parallel in hypertensive patients with chronic HF after treatment with torasemide (right panel). (D) Increased baseline serum PICP is associated with a higher risk of cardiovascular (CV) death or hospitalization for heart failure (HHF). (Adapted from (Cleland et al., 2021; López et al., 2004; Raafs et al., 2021; Ravassa et al., 2023) with permission).

up-regulates ECM modifications and angiogenesis (Jenkins et al., 2017), and ^{18}F-proline, a collagen precursor that is incorporated into mature collagen following hydroxylation to hydroxyproline, which can be radiolabelled to identify areas of fibrotic activity (Geisler et al., 2014). Fibroblast activation protein (FAP) expression is another molecular target, as it reflects myofibroblast activation and active fibrogenesis. FAP inhibitors (FAPIs), previously developed as cancer therapies, can be radiolabelled with gallium-68 (68Ga-FAPI) or fluoride-18 (18F–AlF-FAPI) and are highly specific for FAP-positive fibroblasts. They have been used to image a wide range of fibrotic disease states in the lung, kidney and liver, early cardiac applications in MI (Varasteh et al., 2019), chemotherapy-induced cardiotoxicity (Heckmann et al., 2020) and cardiomyopathy (Shi et al., 2022), suggesting clinical utility; however, further preclinical and clinical studies are required.

4.4. Assessment of cardiac fibrosis based on circulating biomarkers

Although several potential circulating biomarkers associated with fibroblasts activation, stimulation of profibrotic pathways, and ECM remodeling have been proposed, up to date only a few show strong evidence supporting their implementation in clinical practice. Among them, collagen-related biomarkers are the ones that have been more thoroughly studied, showing a stronger association with histologically- or CMR-assessed fibrosis (Table 2), as well as prognostic value and modulation by therapy (potentially reflecting the anti-fibrotic effect of some pharmacological agents; further detailed in section 5).

4.4.1. Biomarkers related to fibroblast activation

4.4.1.1. microRNAs. Non-coding RNAs, mainly microRNAs (miRs), play an important role in the development of cardiac fibrosis (reviewed in (Dong et al., 2022)). Furthermore, circulating microRNAs have been proposed as diagnostic and prognostic biomarker candidates for assessing cardiac fibrosis (Dong et al., 2022).

MiR-21 regulates the activity of cardiac fibroblasts and participates in the development of cardiac fibrosis (Li et al., 2020; Yuan et al., 2017). In patients with AS, myocardial and plasmatic miR-21 levels are associated with myocardial collagen type I and fibronectin expression (Villar et al., 2013). MiR-21 might be also involved in the pathogenesis of atrial fibrosis in atrial fibrillation, showing increased expression in left atrial tissue and a positive correlation with atrial collagen content (Adam et al., 2012).

The miR-29 family is also involved in cardiac fibrosis after MI (Van Rooij et al., 2008), and in patients with HCM, in whom plasma miR-29a correlates with the degree of cardiac fibrosis, evaluated by CMR (Roncarati et al., 2014).

MiR-122 has been implicated in the progression of fibrosis (Liu et al., 2020). Its cardiac expression is decreased in AS patients with severe fibrosis, and its down-regulation was associated with TGF-β over-expression (Beaumont et al., 2014). Of note, its circulating levels are increased in patients with hypertension (Zhang et al., 2020), after acute MI (Cortez-Dias et al., 2016), and in HFrHF patients who died compared to survivors (Stojkovic et al., 2020). In HFrEF patients, circulating miR-122 is associated with right ventricular dysfunction (Stojkovic et al., 2020), and in patients with MI with risk of death or MI recurrence (Cortez-Dias et al., 2016).

MiR-133 down-regulation is related to cardiac fibrosis in Ang II-dependent hypertension, through the modulation of collagen type I expression (Castoldi et al., 2012). In patients treated with the mineralocorticoid receptor antagonist (MRA) eplerenone after MI, its higher circulating levels are associated with a decrease in procollagen type I carboxy-terminal propeptide (PICP), a collagen peptide reflecting

collagen type I synthesis (Stienen et al., 2021).

Myocardial and serum miR-19b levels are inversely correlated with the degree of cardiac fibrosis in AS patients, specifically, with the degree of collagen cross-linking (Beaumont et al., 2017). In addition, circulating miR-19b showed a moderate ability to detect CMR-assessed fibrosis in HCM patients (Fang et al., 2015).

In HF patients, elevated plasma miR-197-5p levels are associated with cardiac fibrosis (CMR-assessed), and with a higher risk of major adverse cardiac events (W. Liu et al., 2018).

4.4.1.2. Growth factors. There is scarce evidence on the direct association between circulating TGF-β and cardiac fibrosis. Plasma TGF-β levels are increased in cardiomyopathies that develop cardiac fibrosis, such as HCM (Ayça et al., 2015), MI (Lin et al., 2019), AS (Villar et al., 2009) or in HF patients with idiopathic DCM or CAD (Mancini et al., 2018). Of note, circulating TGF-β is directly correlated with increased myocardial collagen type I mRNA expression in patients with AS undergoing valve replacement (Villar et al., 2009).

Growth differentiation factor-15 (GDF-15) is a member of the TGF-β superfamily, which is consistently increased in HF and associated with cardiovascular outcomes (reviewed in (González et al., 2022; Meijers et al., 2021)). In addition, in HF patients, plasma GDF-15 is associated with collagen peptides reflecting collagen type I and III formation (PICP and procollagen type III amino-terminal propeptide [PIIINP]) (Li et al., 2018), and with CMR-assessed focal and diffuse fibrosis (Kanagala et al., 2020b). Plasma GDF-15 is also directly associated with CVF in patients with idiopathic DCM (Lok et al., 2012).

Connective tissue growth factor (CTGF) regulates fibrogenesis, activating fibroblasts and increasing the expression of ECM proteins, such as collagen or fibronectin, and of different cytokines, including TGF-β (reviewed in (Chen et al., 2020)). Data on the association of circulating CTGF with cardiac fibrosis are controversial. While plasma CTGF level correlated with CMR-evaluated diffuse fibrosis in diastolic HF patients (Wu et al., 2014), there was no association between circulating CTGF and cardiac fibrosis in patients with chronic idiopathic DCM (Rubiś et al., 2016), although both were increased in these patients.

Myostatin is a member of the TGF-β superfamily that acts as a negative regulator of muscle growth and may play a role in cardiac remodeling. Serum levels of myostatin are correlated with the extent of myocardial scarring as defined by SPECT imaging in patients with HFrEF (Chiang et al., 2022).

4.4.2. Biomarkers related to extracellular fibrillary collagen metabolism

Fragments derived during the processes of synthesis and degradation of collagen fibers (namely collagen type I and III) can be quantified and used as fibrosis biomarkers (reviewed in (López et al., 2021)).

4.4.2.1. Collagen peptides derived from collagen synthesis. PICP has to be necessarily released during the extracellular conversion of procollagen type I into mature fibril-forming collagen type I by procollagen carboxy-proteinase. Increased serum PICP has been reported in HF patients of different etiologies (Querejeta et al., 2004; Raafs et al., 2021). Circulating PICP levels are strongly correlated with histological CVF in hypertensive HF patients (López et al., 2004, 2012; Querejeta et al., 2004), in patients with HCM (C. Yang et al., 2019), and in patients with DCM and severe HF (Raafs et al., 2021). Moreover, in HF patients of hypertensive origin there was a gradient of PICP from coronary sinus blood toward antecubital vein blood, supporting a cardiac contribution to circulating levels of PICP (Querejeta et al., 2004). Of interest, serum PICP and CVF decrease in parallel after treatment with: losartan in patients with hypertensive heart disease (Díez et al., 2002); torasemide in hypertensive patients with HF (López et al., 2004); spironolactone in HF patients with idiopathic DCM (and elevated biomarkers of fibrosis) (Izawa et al., 2005); calcium channel blockers in HCM patients (C. Yang et al., 2019). Finally, high serum PICP is associated with a higher risk of

cardiovascular events in HFrEF patients (Ravassa et al., 2023) and in patients with DCM (Raafs et al., 2021), as well as with a lower probability of reverse remodeling in response to optimal treatment (Ravassa et al., 2023). Overall, cumulative evidence supports the clinical usefulness of PICP to track cardiac fibrosis (Fig. 3).

The procollagen type I amino-terminal propeptide (PINP) is also released from procollagen type I by members of the ADAMTS family (Colige et al., 2002). Compared with PICP, PINP has the disadvantage of delayed release. At present, the relationship between PINP levels and fibrosis remains elusive. In a case-control study, Zile et al. observed that serum PINP was elevated in HF patients (Zile et al., 2019). However, there were no differences between patients with HCM (Ellims et al., 2014; Lombardi et al., 2003), idiopathic DCM (Rubiś et al., 2016) or with advanced HF (Kaye et al., 2013) and control subjects. In addition, none of these studies reported an association between circulating PINP and cardiac fibrosis, neither evaluated in EMBs (Kupari et al., 2013; Rubiś et al., 2016) nor by CMR (Ellims et al., 2014; Münch et al., 2016). Therefore, the potential of PINP as a biomarker of cardiac fibrosis is limited.

During the processing of collagen type III, PIIINP is released into the blood via the lymphatics, although this peptide is not always completely separated from procollagen, which may lead to an underestimation of type III collagen synthesis. The relationship between circulating PIIINP and cardiac fibrosis is not entirely clear. Although Klappacher et al. (1995) found an association between serum PIIINP and CVF in HF patients with CAD or idiopathic DCM, Raafs et al. only found a weak correlation of PIIINP with histological CVF and LGE in patients with idiopathic DCM (Raafs et al., 2021). Of note, in patients with idiopathic DCM (and elevated biomarkers of fibrosis), spironolactone reduced CVF and serum PIIINP in parallel (Izawa et al., 2005).

4.4.2.2. Molecules related to the enzymatic cleavage of extracellular matrix components. Enzymes degrading collagen fibers, such as MMPs, their tissue inhibitors (TIMPs), and the peptides derived from the proteolytic degradation of collagen fibers, are potential biomarkers of collagen metabolism.

During degradation of collagen type I fibers, the collagen type I carboxy-terminal telopeptide (CITP), a cross-linked peptide, is released by MMP-1, allowing an estimation of collagen degradation. However, several studies have highlighted conflicting results regarding its association with cardiac fibrosis. Izawa et al. (2005) found that serum CITP was lower in patients with idiopathic DCM and severe cardiac fibrosis than in those with mild to moderate fibrosis. On the other hand, CITP was directly associated with the extent of type I CVF in HF patients with CAD or idiopathic DCM (Klappacher et al., 1995). However, Nagao et al. found no association between serum CITP levels and cardiac collagen type I mRNA expression DCM patients (Nagao et al., 2018).

The main cardiac collagen degradation system is formed by MMP-1 and TIMP-1, and the gelatinases MMP-2 and MMP-9, but there are no solid data on the performance of these molecules as reliable circulating biomarkers of cardiac fibrosis. In female patients with HCM, while increased serum MMP-2 was associated with lower cardiac fibrosis, MMP-9 was directly associated with LGE (Münch et al., 2016). In hypertensive HF patients, neither MMP-1 nor TIMP-1, or the MMP1/TIMP-1 ratio (an indirect index of active MMP-1), were associated with the CVF (López et al., 2006). However, patients with higher values of serum MMP-1 and MMP-1/TIMP-1 ratio exhibited reduced perimysial and endomysial collagen, suggesting that these molecules may be related to the loss of the physiological collagen scaffold.

Although CITP and MMP-1 separately have not shown a robust performance, the ratio between both molecules has emerged as a potential biomarker of collagen cross-linking. Increased collagen cross-linking makes collagen fibers more resistant to degradation, therefore, the higher the degree of collagen cross-linking the lower CITP will be released for a given quantity of MMP-1. Indeed, lower serum CITP is

Table 3
Clinical studies evaluating antifibrotic therapies.

Drug	Type of study	Disease	Observations	Reference or NCT number
Assessment of cardiac fibrosis in EMBs				
ACEi	Randomizedcontrolled trial	Hypertension	Reduced CVF and improved LV diastolic function	Brilla et al. (2000)
ARB	Retrospective observational case-control study	Hypertension	Reduced CVF and LV stiffness	Díez et al. (2002)
			Reduced CVF and PICP	López et al. (2001)
MRA	Uncontrolled pilot trial	DCM	Reduced CVF and improved LV diastolic function in patients with high PICP/CITP ratio at baseline	Izawa et al. (2005)
Assessment of cardiac fibrosis by CMR				
ACEi/ARB	Case-controlled observational study	DM	Reduced ECV and improved LV systolic function.	Swoboda et al. (2017)
ARB	Randomized controlled trial	HCM	Prevention of LGE increase	Shimada et al. (2013)
	Uncontrolled pilot trial	Radiation-induced HF in breast cancer	ECV determination, ongoing study	NCT05607017
MRA	Randomized controlled trial	DM	Reduced ECV and PINP	Brandt-Jacobsen et al. (2021)
		HCM	Unchanged LGE, PINP, PIIINP and CITP	Maron et al. (2018)
			LGE determinations, ongoing study	NCT02948998
		Obesity	ECV determination, ongoing study	NCT04519164
		Congenital heart disease	ECV and PIIINP determinations, ongoing study	NCT01069510
		Atrial fibrillation	ECV determinations, ongoing study	NCT02764619
		Aortic Stenosis	ECV, PICP, PIIINP and CITP determinations, ongoing study	NCT05230901
		HFpEF	Unchanged ECV but reduced extracellular volume expansion	McDiarmid et al. (2020)
		Chronic right HF	ECV determinations, ongoing study	NCT03344159
ARNI	Randomized valsartan-controlled trial	Hypertension	ECV determinations, ongoing study	NCT03553810
	Randomized controlled trial	Subclinical HF in HIV	ECV determinations, ongoing study	NCT04153136
		HFpEF	ECV determinations, ongoing study	NCT05089539
	Observational study	HFrEF	ECV determinations, ongoing study	NCT05348226
SGLT2i	Uncontrolled pilot trial	DM	Unchanged ECV and non-improved LV dysfunction	Hsu et al. (2019)
	Randomized controlled trial		Reduced ECV and unchanged sST2 and MMP2	Mason et al. (2021)
		Risk of HF	ECV determinations, ongoing study	NCT05084235
		HFpEF	ECV, PICP and CITP:MMP-1 determinations, ongoing study in diabetic patients	NCT04739215
			ECV determinations, ongoing study in non-diabetic patients	NCT05562063
		HFrEF	ECV determinations, ongoing study	NCT04490681
	Substudy of randomized controlled trial	HFrEF	Reduced ECV and inflammation and improved aortic stiffness in non-diabetic patients	Requena-Ibáñez et al. (2021)
	Uncontrolled trial	HFrEF	ECV determinations, ongoing study	NCT05420285
Others				
Pirfenidone	Randomized controlled trial	HFpEF	Reduced ECV	Lewis et al. (2021)
	Randomized controlled trial	MI	ECV determinations, ongoing study	NCT05531955
Colchicine	Randomized controlled trial	Hypertension	ECV determinations, ongoing study	NCT04916522
Anakinra	Randomized controlled trial	Cardiac sarcoidosis	LGE determinations, ongoing study	NCT04017936
Assessment of circulating biomarkers of fibrosis				
ARB	Randomized controlled trial	Hypertension	Reduced PICP and improved LV diastolic function	Müller-Brunotte et al. (2007)
		DM	Reduced PICP/CITP ratio and improved LV diastolic function	Kawasaki et al. (2007)
MRA	Randomized controlled trial	Metabolic syndrome	Reduced PIIINP, PICP and improved LV systolic function	Kosmala et al. (2011)
		Obesity	Reduced PIIINP, PICP and improved LV diastolic function	Kosmala et al. (2013)
		Risk of HF	Reduced PICP and NT-proBNP and improved LA remodeling	Cleland et al. (2021)
		HFpEF	Attenuation of PIIINP increase	Mak et al. (2009)
			Reduced PINP and CITP and improved LV diastolic function	Deswal et al. (2011)
	Substudy of randomized controlled trial	HFpEF	Reduced PICP and improved LV diastolic function	Ravassa et al. (2018)
		HFrEF	Reduced PINP and PIIINP	Iraqi et al. (2009)
			Reduced PINP, PICP and PIIINP	Zannad et al. (2000)
ARNI	Randomized valsartan-controlled trial	HFpEF	Reduced PIIINP, sST2 and TIMP-1 and increased CITP	Cunningham et al. (2020)
			Unchanged sST2, galectin-3, MMP-2 and PIIINP	Zile et al. (2016)
	Randomized controlled trial	HFpEF and HFrEF	sST2 determinations, ongoing study	NCT05164653
		HFrEF	Reduced sST2 and hs-TnT	Morrow et al. (2019)
			Reduced PINP, PIIINP, sST2, TIMP-1 and MMP-9	Zile et al. (2019)
	Non-randomized controlled trial	HFrEF	Attenuation of PICP increase	Wiśniowska-Śmiałek et al. (2020)
	Uncontrolled trial	HFrEF	Reduced PICP	Bolla et al. (2022)

(continued on next page)

Table 3 (*continued*)

Drug	Type of study	Disease	Observations	Reference or NCT number
SGLT2i	Substudy of randomized controlled trial	DM	Reduced serum levels of fibronectin-1	Heerspink et al. (2019)
	Randomized controlled trial	DM	Unchanged sST2 and Gal3	Januzzi et al. (2017)
		HFpEF	PICP, PIIINP and CITP determinations, ongoing study	NCT05676684
		Diabetic HFpEF	PICP and CITP:MMP-1 determinations, ongoing study	NCT04739215
GLP-1 analogue	Randomized-controlled trial	DM or prediabetes	Reduced sST2 and unchanged Gal-3	Simeone et al. (2022)
Others				
Atorvastatin	Uncontrolled trial	Hypertension and atherosclerosis	Reduced PIIINP and TIMP1	Chang et al. (2016)
	Randomized controlled trial	HFrEF	Reduced PIIINP	Abulhul et al. (2012)
Colchicine	Randomized controlled trial	MI	MMP-1 and TGF-β determinations, ongoing study	NCT05709509

ACEi stands for angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin II receptor-neprilysin inhibitor; CITP, collagen type I carboxy-terminal telopeptide; CTGF, connective tissue growth factor; CVF, collagen volumen fraction; DCM, idiopathic dilated cardiomyopathy; DM, diabetes mellitus; ECV, extracellular volume; EMBs, endomyocardial biopsies; Gal-3, galectin-3; GLP-1, glucagon-like peptide-1; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; HIV, human immunodeficiency virus; LGE, late gadolinium enhancement; LV, left ventricular; MI, myocardial infarction; MMP, metalloproteinase; MRA, mineralocorticoid receptor antagonists; PICP, procollagen type I carboxy-terminal propeptide; PINP, procollagen type I amino-terminal propeptide; PIIINP, procollagen type III amino-terminal propeptide; SGLT2i, inhibitors of the sodium-glucose cotransporter-2; sST2, soluble isoform of ST2;; TGF-β, transforming growth factor β; TIMP-1,tissue inhibitor of metalloprotease-1 .

associated with increased insoluble collagen (assessed in EMBs) (López et al., 2012), and lower serum CITP/MMP-1 is correlated with increased myocardial collagen cross-linking (assessed in EMBs) (López et al., 2016) in HF patients of hypertensive etiology. In this study, it was also associated with a higher risk of HF hospitalization. Ravassa et al. showed that hypertensive HF patients with a circulating bioprofile of high PICP and low CITP/MMP-1, reflecting high deposition of highly cross-linked collagen type I fibers, present a higher risk of re-hospitalization for HF or cardiovascular death (Ravassa et al., 2017), as well as a higher risk of atrial fibrillation (Ravassa et al., 2019). Of interest, the presence of chronic kidney disease is associated with increased prevalence of this bioprofile in patients with HFpEF (Eiros et al., 2020).

Several matrikines derived from collagen may contribute to cardiac fibrosis acting directly on fibroblasts (Ricard-Blum and Vallet, 2019). Circulating endostatin is increased in HCM patients (Fernlund et al., 2017) and is associated with HF incidence (Ruge et al., 2018). Endotrophin, a collagen type VI-derived matrikine, has important biological effects such as increasing TGF-β1 expression, promoting adipose tissue fibrosis and metabolic dysfunction (Sun et al., 2014). Increased serum endotrophin reflects the degree of renal fibrosis (Sparding et al., 2022) and is associated with increased mortality in chronic kidney disease (Fenton et al., 2017) and in atherosclerosis (Holm Nielsen et al., 2021). Interestingly, high serum endotrophin is associated with poor outcomes in patients with HFpEF across several independent cohorts (Chirinos et al., 2022).

4.4.3. Other biomarkers

Several matricellular proteins have been associated with fibrotic processes (reviewed in (Pinto, 2021)). Osteoglycin expression in the infarct scar promotes proper collagen maturation and protects against cardiac disruption and adverse remodeling (Van Aelst et al., 2015). Circulating osteoglycin is increased in patients with HF and a previous MI compared with patients with non-ischemic HF and is associated with markers related to collagen turnover (PINP) and with higher mortality (Van Aelst et al., 2015). Cardiac expression of osteopontin is associated with CVF and insoluble collagen (EMBs-assessed) in hypertensive HF patients, but its plasma concentration was not associated with CVF (López et al., 2013). Tenascin-C is generally upregulated during cardiac tissue remodeling (Imanaka-Yoshida et al., 2020). Circulating levels of tenascin-C are elevated in HFpEF patients compared to controls (Kanagala et al., 2020a, 2020b) and directly correlates with diffuse fibrosis evaluated by CMR in HFpEF patients (Kanagala et al., 2020b), with biomarkers associated to profibrotic activation (sST-2, galectin-3, GDF-15) and with clinical severity (NYHA functional class, E/e', BNP) in HFpEF patients (Kanagala et al., 2020a).

Galectin-3, a β-galactoside-binding lectin, activates fibroblasts to increase collagen type I deposition (Yu et al., 2013). Although high circulating galectin-3 was associated with LGE-assessed cardiac replacement fibrosis in non-ischemic DCM (Vergaro et al., 2015) and in HF patients (Kanagala et al., 2020b), there was no association between plasma galectin-3 and cardiac fibrosis (determined in EMBs) in hypertensive patients with HF (López et al., 2015). Similarly, there was no association between cardiac fibrosis and circulating galectin-3 in patients with HF and idiopathic DCM (Besler et al., 2017). Nevertheless, irrespectively of its direct association with fibrosis, serum galectin-3 has shown a good performance as a diagnostic and prognostic biomarker in HF (reviewed in (González et al., 2022; Meijers et al., 2021)).

Cardiotrophin-1 (CT-1) is a member of the IL-6 superfamily that increases the expression of collagen and several profibrotic mediators in cardiac fibroblasts (Martínez-Martínez et al., 2019; Tsuruda et al., 2002) and induces cardiac fibrosis in rodents (Martínez-Martínez et al., 2019). In addition, myocardial expression of CT-1 was associated with collagen types I and III in the fibrotic myocardium of hypertensive patients with HF (López et al., 2014). However, although plasma CT-1 was associated with PICP in these patients, it was not associated with the CVF.

ST2 is an IL-1 receptor family member, and the soluble isoform (sST2) acts as a decoy receptor inhibiting the beneficial cardioprotective effects of IL-33, resulting in cardiac hypertrophy, cardiac fibrosis, and ventricular dysfunction (McCarthy and Januzzi, 2018). Although myocardial expression of sST2 in end-stage HF patients was associated with cardiac fibrosis, no association was observed between sST2 plasma levels and cardiac collagen deposition (Tseng et al., 2018). While there was no association between circulating sST2 and LGE in HCM patients (Gawor et al., 2018), these two parameters were associated in AS patients (Arrieta et al., 2022). Nevertheless, although its usefulness as a fibrosis biomarker is unclear, its utility for HF risk stratification and prognosis has been well established (Aimo et al., 2019; Parikh et al., 2016).

4.4.4. Insights from proteomic studies

Omics approaches, associated with large-scale, high-throughput experiments, have been extensively used in the last decade to decipher the molecular mechanisms associated with cardiac fibrosis (Ricard-Blum and Miele, 2020), and are likely to provide novel biomarker signatures. Interestingly, the development of high-sensitivity methodologies (using proximity extension assays [PEA] or aptamers) has enabled plasma proteomic characterization, overcoming some of the limitations of conventional mass spectrometry analyses. For instance, PEA-based plasma proteomics identified a signature associated with incident HF, which included a cluster of proteins related to ECM remodeling (Ferreira

patients with obesity and HCM, respectively. Moreover, the potential antifibrotic effects (evaluated by ECV) of MRAs on the right ventricle are being examined in patients with chronic right HF (STAR-HF, NCT03344159).

Consistent results have been obtained in studies examining the antifibrotic effects of aldosterone antagonists assessed by changes in circulating biomarkers of fibrosis. Small studies performed in non-HF patients with metabolic syndrome (Kosmala et al., 2011) or with obesity and mild diastolic dysfunction (Kosmala et al., 2013) show significant reductions of PICP and PIIINP accompanying improvements in diastolic function in patients treated with spironolactone compared with those receiving standard Ang II inhibition or placebo, respectively. In addition, the randomized controlled HOMAGE clinical trial recently demonstrated that treatment with spironolactone reduces circulating PICP and improves left atrial remodeling in patients at risk of HF (Cleland et al., 2021). In patients with HFpEF, treatment with eplerenone results in reductions of PIIINP (Mak et al., 2009), PINP and CITP (Deswal et al., 2011) levels compared with placebo. Sub-studies of larger clinical trials have confirmed the antifibrotic effects of aldosterone antagonism, reducing the levels of biomarkers of collagen metabolism in patients with HFrEF (Iraqi et al., 2009; Zannad et al., 2000) and with HFpEF (Ravassa et al., 2018).

Regarding the highly selective non-steroidal MRA finerenone, strong experimental evidences support the antifibrotic renal and cardiac effects, mainly in diabetes mellitus (Lv et al., 2023). Remarkably, finerenone reduced cardiac fibrosis in a model of isoproterenol-induced cardiac damage, while eplerenone had no antifibrotic effects in this model (Grune et al., 2018). Given the cardiorenal protective effects of finerenone (Agarwal et al., 2021; González-Juanatey et al., 2023), it is tempting to speculate that it may exert more potent antifibrotic effects than steroidal MRAs. Nevertheless, further clinical trials are needed to explore this hypothesis.

Interestingly, the CITP/MMP-1 ratio might be used to guide treatment. In patients at risk of HF from the HOMAGE clinical trial (Ravassa et al., 2022) or with HFpEF from the ALDO-DHF trial (Ravassa et al., 2018), the beneficial effects of spironolactone on diastolic function and left atrial remodeling were mostly found in patients with low collagen cross-linking estimated by a high CITP/MMP-1 ratio.

Of note, several of the findings discussed in this section suggest that the anti-fibrotic efficacy of cardiovascular therapies is associated with their clinical benefits. In particular, the therapeutic reduction in circulating biomarkers of myocardial fibrosis is associated with improved cardiac remodeling and function, and with a lower risk of adverse outcomes. For instance, non-HF patients with T2DM showing a decrease in circulating PINP after treatment with MRAs (Brandt-Jacobsen et al., 2021) and a reduced PICP/CITP ratio after treatment with ARBs (Kawasaki et al., 2007), exhibited lower LV mas index and LV chamber stiffness, respectively. In addition, MRA treatment in non-HF patients with obesity (Kosmala et al., 2013) or with metabolic syndrome (Kosmala et al., 2011) resulted in diminished levels of PIIINP and PICP, that accompanied improvements in LV systolic and diastolic function, respectively. Moreover, a decrease in PICP levels in MRA-treated patients at risk of HF was associated with improved LA remodeling (Cleland et al., 2021). In this regard, recent findings in hypertensive patients treated with resveratrol confirm LA remodeling improvement association with a reduction in PICP, along with a lower E/e' ratio and improved contractility, (Zheng et al., 2023). In MRA-treated HFpEF patients exhibiting decreased circulating PINP (Deswal et al., 2011) and PICP (Ravassa et al., 2018), LV diastolic function was improved (reduced E/e' ratio). In addition, treatment with sacubitril/valsartan induced decrements in sST2 levels that were associated with a lower risk of adverse clinical events in HFpEF (Cunningham et al., 2020), in acute decompensated HF (Morrow et al., 2019) and in HFrEF (Zile et al., 2019). In the latter, spironolactone treatment also resulted in reduced PINP, PICP and PIIINP levels and a lower risk of adverse outcomes (Zannad et al., 2000). All the above suggest that the clinical improvements associated with these cardiovascular treatments may be mediated, at least partly, by their actions limiting ECM turnover, and that biomarkers of these processes may help to monitor these beneficial effects.

5.1.1.4. Inhibitors of the sodium-glucose cotransporter-2. Inhibitors of the sodium-glucose cotransporter 2 (i.e. SGLT2 inhibitors) have cardioprotective effects beyond their glucose-lowering effects and have been suggested to decrease cardiac fibrosis as part of their clinical benefits (Sharma et al., 2022; Zelniker and Braunwald, 2020), and to attenuate the remodeling processes leading to HFpEF (de Lorenzi et al., 2023). However, clinical studies evaluating the effects of these drugs on cardiac fibrosis have rendered conflicting results. In particular, whereas 6-month treatment with the SGLT2 inhibitor empagliflozin failed to alleviate myocardial ECV and LV ejection fraction decrease in patients with T2DM (Hsu et al., 2019), results from a larger randomized controlled trial showed significant reductions of ECV in patients with T2DM and CAD (Mason et al., 2021). Antifibrotic actions of SGLT2 inhibitors have also been reported in non-diabetic patients with HFrEF, in whom empagliflozin reduced ECV (Requena-Ibáñez et al., 2021). Currently, studies addressing the antifibrotic role of SGLT2 inhibitors by ECV assessment are being conducted in patients at risk of HF (EMPIRE II, NCT05084235), patients with HFrEF (VERTICAL, NCT04490681; ICARD, NCT05420285) and in HFpEF patients with (CARDIA-STIFF, NCT04739215) and without (SOTA-P-CARDIA, NCT05562063) diabetes.

The modifying effects of SGLT2 inhibitors on circulating biomarkers of fibrosis have been scarcely studied. Whereas diabetic patients chronically treated with the SGLT2 inhibitor canagliflozin exhibited diminished levels of biomarkers related with inflammation (TNFR-1) and fibrosis (fibronectin-1) compared with glimepiride therapy (Heerspink et al., 2019), a larger placebo-controlled clinical trial failed to detect inhibitory effects of canagliflozin therapy on circulating sST2 and galectin-3 (Januzzi et al., 2017). In this regard, further studies are being conducted to clarify the effects of SGLT2 inhibitors on biomarkers of collagen metabolism. In particular, the effects of treatment with dapagliflozin on circulating PICP, PIIINP and CITP are being evaluated in a phase 2 clinical trial in patients with HFpEF (SOGALDI-PEF, NCT05676684). In addition, a placebo-controlled phase 4 clinical trial is analyzing changes in the levels of PICP in diabetic patients with HFpEF treated with dapagliflozin (CARDIA-STIFF, NCT04739215).

5.1.1.5. Antifibrotic effects of other heart failure drugs. Other drugs used for the management of HF may exert some cardiac antifibrotic effects, although little clinical evidence is available. Even though some experimental findings suggest that β-blockers prevent cardiac fibrosis (e.g. in a HFpEF model in Dahl salt-sensitive rats (Kobayashi et al., 2004)), their effectiveness attenuating cardiac fibrosis in HF patients remains unknown. In addition, despite experimental evidences on its antifibrotic potential, isosorbide dinitrate, alone or in combination with hydralazine, was not able to reduce CMR-assessed cardiac fibrosis in HFpEF patients (Zamani et al., 2017).

Stimulators and activators of soluble guanylate cyclase have shown consistent cardiac antifibrotic actions in experimental models (Sandner and Stasch, 2017), suggesting a potential antifibrotic role for vericiguat and similar compounds. However, clinical trials evaluating the effects of these agents on cardiac fibrosis have not yet been conducted.

Likewise, ivabradine, a reducer of elevated resting heart rate, alleviated cardiac remodeling, and in particular cardiac fibrosis, in different animal models of cardiac disease, including HF (Kamisah and Che Hassan, 2023). Consequently, a deeper understanding of its antifibrotic actions in clinical studies evaluating CMR parameters has been prompted to elucidate its role in improving HF (Kamisah and Che Hassan, 2023).
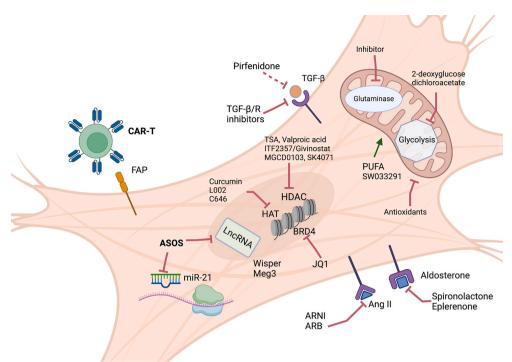
Fig. 4. Graphical overview of potential therapeutic strategies targeting the cardiac fibroblast. Ang II stands for angiotensin II; ARB, angiotensin II receptor blockers; ARNI, angiotensin II receptor blocker and neprilysin inhibitor; ASOs, modified antisense oligonucleotides; BRD4, bromodomain-containing protein 4; FAP, fibroblast activation proteins; HDAC, histone deacetylases; HAT, histone acetyl transferases; PUFA, polyunsaturated fatty acids; SE lncRNA, super enhancer long non-coding RNA; TGF-β, transforming growth factor β; TGF-βR, TGF-β receptor; TSA, trichostatin A (Created with Biorender.com).

5.1.2. Repurposing non-heart failure drugs

Drug repurposing is an attractive approach as it profits from the use of derisked compounds, with lower development costs and time. Examples of non-HF drugs with potential for cardiac fibrosis prevention and treatment are discussed below.

5.1.2.1. Antifibrotic effects of glucose-lowering drugs.
Antifibrotic effects of traditional glucose-lowering therapies in the diabetic and non-diabetic myocardium have been reported (Sharma et al., 2022; Tuleta and Frangogiannis, 2021). Specifically, experimental studies suggest that incretin-based drugs may exert cardiac antifibrotic actions (Tuleta and Frangogiannis, 2021). A recent clinical trial detected reductions in circulating sST2 in obese patients with prediabetes or early T2DM treated with the glucagon-like peptide-1 (GLP-1) analog liraglutide (Simeone et al., 2022).

5.1.2.2. Pirfenidone.
Pirfenidone is approved for the treatment of lung fibrosis in patients with idiopathic pulmonary fibrosis (Bouros, 2011). As this lesion is driven by common pathological mechanisms involved in cardiac fibrosis, an increasing interest in the use of this drug for cardiovascular treatments has emerged (Aimo et al., 2022). In fact, pirfenidone decreases cardiac fibrosis in several experimental models (Graziani et al., 2021). Among the proposed mechanisms mediating pirfenidone antifibrotic actions, TGF-β-dependent and independent pathways have been proposed. In particular, pirfenidone-induced inhibition of the TGF-β1/Smad3 pathway was observed in experimental models of pressure overload-induced HF (Li et al., 2022). On the other hand, TGF-β-independent regulation of the fibrotic response was reported in 3D tissue-engineered constructs containing human cardiomyocytes and cardiac fibroblasts treated with pirfenidone (Bracco Gartner et al., 2022). Altogether, the impact of this drug on cardiac fibrosis in different experimental cardiac conditions has prompted the study of its potential use in HFpEF patients (Graziani et al., 2021). In this regard, the PIROUETTE phase 2 study demonstrated a slight, although significant, reduction in ECV in patients with HFpEF and increased fibrosis (Lewis et al., 2021). In addition, the effects of pirfenidone on ECV are currently being evaluated in a randomized placebo-controlled clinical trial conducted in patients with MI (PROTECT-AMI,

NCT05531955).

5.1.2.3. Inflammation modulators.
Beyond their cholesterol-lowering properties, statins are powerful cardioprotective drugs by interfering with inflammation, fibrosis, apoptosis and angiogenesis-related mechanisms (Tousoulis et al., 2014; Yamamoto et al., 2011)). Small studies in patients with hypertension and atherosclerosis (Chang et al., 2016), and in HFrEF patients with normal cholesterol (Abulhul et al., 2012), showed reductions in PIIINP levels after treatment with atorvastatin. However, conflicting results have been obtained in clinical trials evaluating rosuvastatin, observing higher PIIINP and PINP levels after treatment in patients with chronic HF (Ashton et al., 2011). In this regard, no prognostic benefit from rosuvastatin was observed in chronic HF patients (Kjekshus et al., 2007; Tavazzi L et al., 2008). Therefore, further studies are necessary to clarify the antifibrotic effects of statins in cardiac disease.

Targeting the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome signaling has emerged as a promising therapy for cardiac fibrosis (reviewed in (Fan et al., 2022; Olsen et al., 2021)). Colchicine, a broad-spectrum anti-inflammatory drug, alleviates cardiac fibrosis and diastolic dysfunction, as well as reduces the expression of the NLRP3 pathway, in a rat model of hypertension-induced HFpEF (Shen et al., 2022). In this regard, a currently ongoing placebo-controlled randomized phase 2 clinical trial is evaluating the effects of colchicine on CMR-assessed cardiac fibrosis in hypertensive patients (COHERENT, NCT04916522). In addition, changes in the circulating levels of profibrotic factors, including TGF-β, are being examined in patients with MI treated with colchicine (NCT05709509). Nonetheless, as a risk of dose-related serious adverse side effects has been attributed to this drug, the applicability of chronic treatments based on colchicine should be carefully considered.

Inhibitors of the NLRP3-inflammasome pathway have also been proposed as potential tools to treat HF (Wu et al., 2021). The specific NLRP3 inhibitor MCC950 reduces cardiac inflammation, alleviates cardiac fibrosis (by inhibiting the TGF-β/Smad4 pathway) and improves cardiac function after TAC (Zhao et al., 2021). Blocking downstream mediators like IL-1β or its receptor, prevents cardiac fibrosis in models of chronic viral myocarditis (Kraft et al., 2019) and cardiac pressure

bromodomain-containing protein 4 (BRD4) to gene regulatory elements (Travers et al., 2021). Antifibrotic effects were found with the class I and II HDAC inhibitor valproic acid, and with the selective class I inhibitor SK-7041 after aortic banding (Kee et al., 2006). Indeed, in a model of hypertension (by Ang II) specific class I HDAC inhibition with MGCD0103, but not class II inhibitors, prevents the development of cardiac fibrosis and the proliferation of cardiac fibroblasts (Williams et al., 2014). Despite these promising results, little is known about the specific molecular mechanisms responsible for the profibrotic actions of HDACs or the specific HDAC members involved. In addition, HDAC inhibition is likely to also regulate fibrosis through additional mechanisms such as the immunoregulation of macrophages (Kimbrough et al., 2018) or of T regulatory cells (Wang et al., 2018). As a note of caution, while HDAC inhibitors are generally well tolerated, adverse events and toxicity have been reported (Bondarev et al., 2021), raising concerns about their chronic use in conditions such as HF.

BRD4, a member of the BET family of acetyl-histone binding proteins, regulates TGF-β-induced activation of cardiac fibroblasts and is involved in the formation of dynamic, specific enhancers, known as super-enhancers (Stratton et al., 2019). JQ1, an acetyl-lysine mimetic that competitively displaces BRD4 from chromatin, prevents changes in chromatin accessibility (identified by single-cell accessible chromatin sequencing) in cardiac fibroblasts after TAC, which is associated with reduced cardiac fibrosis and improved cardiac function (Alexanian et al., 2021). JQ1 also reduces inflammatory and profibrotic transcriptional networks in HF models of TAC and MI, reducing cardiac fibrosis after cardiac remodeling had developed (Duan et al., 2017).

While histone methyltransferases and demethylases are involved in pathological cardiac remodeling, and their inhibition has shown cardioprotective effects in experimental models of HF, including a decrease in cardiac fibrosis, whether this effect is directly mediated by specific actions on cardiac fibroblasts is still under evaluation (reviewed in (McKinsey et al., 2023)).

5.2.1.4. Targeting non-coding RNAs. Oligonucleotide-based therapies targeting non-coding RNAs, alone or associated with nanoparticles or exosomes to improve delivery, have emerged as promising therapeutic tools in cardiovascular disease (reviewed in (Lu and Thum, 2019)).

MiR-21 was one of the first microRNAs shown to be upregulated in cardiac fibroblasts in conditions of cardiac damage and to increase fibroblast survival (Thum et al., 2008). MiR-21 inhibition with antagomirs prevents the development of cardiac fibrosis after TAC if administered early after surgery and attenuates fibrosis progression if administered 3 weeks after surgery (Thum et al., 2008). In pigs subjected to ischemia/reperfusion, anti-miR-21 therapy reduces cardiac fibrosis and improves cardiac function, which is associated with decreased macrophage and fibroblast numbers (Hinkel et al., 2020). Of note, a phase II clinical trial targeting miR-21 with lademirsen was recently completed in patients with renal fibrosis (NCT02855268), and the publication of results is pending. Similarly, an optimized synthetic antisense oligonucleotide inhibitor of miR-132 (CDR132L) attenuates cardiac fibrosis after TAC (Hinkel et al., 2021) or in the remote region after MI in pigs, affecting the expression of ECM-related genes (Batkai et al., 2021). Nevertheless, whether this is the result of a direct effect on fibroblasts or the consequence of the beneficial impact on cardiomyocytes requires further investigation. Of interest, a phase 1b clinical trial with CDR132L in patients with CAD showed a trend toward a decrease in circulating biomarkers associated with fibrosis after treatment (Täubel et al., 2021).

Long non-coding RNAs (lncRNAs) function as indirect modulators of DNA/histone complexes, trigger chromatin remodeling and influence post-transcriptional and translational pathways (Bär et al., 2016). Enhancer-associated lncRNAs provide the possibility for focusing on cardiac fibroblast-specific targets, overcoming some of the challenges related to antifibrotic therapies. Wisp2 super-enhancer-associated RNA (Wisper) is a cardiac fibroblast-specific lncRNA, which shows increased cardiac expression after MI and in hypertension models (Micheletti et al., 2017). Wisper depletion with gapmers in neonatal murine myofibroblasts and in human cardiac fibroblasts down-regulates the expression of α-SMA and other profibrotic genes. Moreover, Micheletti et al. also showed that *in vivo* inhibition of Wisper after MI inhibits the development of fibrosis and improves cardiac function (Micheletti et al., 2017). Similarly, inhibition of the cardiac fibroblast-enriched lncRNA maternally expressed gene 3 (Meg3) by intraperitoneal injection of modified antisense oligonucleotides prevents the development of cardiac fibrosis after TAC and preserves diastolic function (Piccoli et al., 2017).

5.2.1.5. Targeting the mitochondria and the cellular metabolism. Mitochondrial alterations play a relevant role in fibroblasts activation and function. TGF-β-induced differentiation of fibroblasts is accompanied by energy remodeling with an increase in mitochondrial respiration and content (Negmadjanov et al., 2015). Increased production of reactive oxygen species (ROS) by mitochondria may play a role in cardiac fibroblasts activation. Indeed, mitochondrial-targeted antioxidants attenuate TGF-β-induced changes in lung fibroblasts (Jain et al., 2013).

Glycolytic reprogramming has been described in different fibroblast populations, and the mechanisms involved have been recently reviewed (Gibb et al., 2020). Fibroblasts activation is associated with increased glycolysis and lactate production, and TGF-β induces the expression of most glycolytic enzymes, glucose transporters and lactate dehydrogenase (Nigdelioglu et al., 2016). In embryonic fibroblasts, profibrotic stimuli like TGF-β or Ang II decrease mitochondrial Ca^{2+} uptake and induce increased glycolysis and glutaminolysis, which are involved in fibroblast activation (Lombardi et al., 2019). In a model of renal fibrosis induced by unilateral ureter obstruction, shikonin and 2-deoxyglucose (glycolysis inhibitors) attenuate the development of renal fibrosis, as well as TGF-β-induced myofibroblast activation (Ding et al., 2017). Right ventricular fibroblasts from a model of pulmonary arterial hypertension show increased mitochondrial fission, increased expression of pyruvate dehydrogenase kinase 1 (PDK1) and a shift to aerobic glycolysis, which are prevented by dichloroacetate, a potent PDK1 inhibitor (Tian et al., 2020). Fibroblast proliferation and collagen production are also prevented by dichloroacetate in this study. In addition, dichloroacetate significantly attenuates bleomycin-induced pulmonary fibrosis (Goodwin et al., 2018) and right ventricular fibrosis secondary to pulmonary arterial hypertension (Tian et al., 2020).

On the other hand, glutamine may play a role in cardiac fibroblasts activation and function since it is an essential factor for *de novo* collagen synthesis and it also contributes to increased α-ketoglutarate (a co-factor of epigenetic modifiers) linking glutaminolysis to chromatin remodeling (Gibb et al., 2020). Of interest, pharmacological inhibition of glutaminase-1 prevents and reverses myofibroblast differentiation of human cardiac fibroblasts isolated from HF patients (Gibb et al., 2022a, 2022b), and *in vivo* genetic deletion of glutaminase-1 reduces cardiac fibrosis after TAC (Gibb et al., 2022b).

However, the antifibrotic potential of interfering with these pathways *in vivo,* in experimental models of HF, has been scarcely studied. Drugs targeting metabolic enzymes related to glycolysis, glutaminolysis, or ROS are currently being tested in clinical trials for cancer (reviewed in (Hamanaka and Mutlu, 2021)), providing already available tools to be tested in the cardiovascular field.

On a different note, supplementation with omega-3 polyunsaturated essential fatty acids like docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or an inhibitor of the free fatty acid receptor 4, prevents cardiac fibroblasts activation and collagen synthesis in response to TGF-β (Chen et al., 2011; Eclov et al., 2015). More recently, Rubino et al. showed that SW033291 (an inhibitor of the eicosanoid-degrading enzyme 15-hydroxyprostaglandin dehydrogenase) inhibits TGF-β-dependent activation of human cardiac fibroblasts, reverses

constitutive activation of cardiac fibroblasts isolated from HF patients and prevents the development of cardiac fibrosis in hypertension induced by Ang II (Rubino et al., 2023). High doses of DHA and EPA reduced cardiac fibrosis with an improvement in cardiac function after TAC (Chen et al., 2011), while only lower doses of EPA achieved a similar result (Eclov et al., 2015). In addition, fish oil, rich in omega-3 polyunsaturated fatty acids, prevents the development of cardiac fibrosis in a rat model of diabetes mellitus (Mayyas et al., 2018). Importantly, omega-3 polyunsaturated fatty acids supplementation in addition to guideline-directed therapy was associated with a reduction in diffuse cardiac fibrosis (assessed by CMR) in the non-infarcted region after MI in the OMEGA-REMODEL trial (Heydari et al., 2016).

5.2.1.6. Targeting the fibroblast secretome and the extracellular matrix. Inhibition of excessive collagen cross-linking by targeting LOX and LOX-like (LOXL) proteins is being explored (González et al., 2019). Irreversible inhibition of LOX with β-aminopropionitrile, prevents the development of cardiac fibrosis in a rat model of volume overload by aortocaval fistula (El Hajj et al., 2018). In addition, the pan-LOX inhibitor PXS-5505, has shown potent antifibrotic effects in different organs (Yao et al., 2022). The LOXL-2/3 inhibitor PXS-5153A reduces LOXL2-mediated collagen oxidation and collagen cross-linking *in vitro,* and diminishes collagen content and cross-linking in models of liver fibrosis, as well as cardiac fibrosis after MI (Schilter et al., 2019). A neutralizing antibody against LOXL2 attenuates cardiac fibrosis in response to TAC (Yang et al., 2016). However, the disappointing results from clinical trials testing the antifibrotic effects of simtuzumab (an antibody against LOXL-2) in different organs have cooled down the enthusiasm for this therapeutic approach (Fickert, 2019). Nevertheless, it has to be considered that other enzymes of the LOX family may compensate for the blockade of LOXL-2, making a more comprehensive approach needed.

On the other hand, ALT-711, a breaker of advanced glycation end-products (AGEs), showed promising preclinical results in diabetic models decreasing collagen content and increasing its solubility (Candido et al., 2003). However, the BENEFICIAL clinical trial in patients with HFrEF obtained neutral results, not showing improvements in exercise tolerance or systolic and diastolic function with this treatment (Hartog et al., 2011).

5.2.2. Other antifibrotic strategies
The complex crosstalk and feedback loop of fibroblasts and the ECM with other cardiac cells such as cardiomyocytes, endothelial cells or immune cells also plays a key role in the development of cardiac remodeling and fibrosis (Smolgovsky et al., 2021; Tzahor and Dimmeler, 2022). On the other hand, extracardiac comorbidities like chronic kidney disease (Romero-González et al., 2022), metabolic alterations such as obesity (Kruszewska et al., 2022), or gut dysbiosis (Xu et al., 2023) also contribute to the development of cardiac fibrosis in HF. As an example, we will describe strategies addressing immunomodulation and dysbiosis.

5.2.2.1. Immunomodulation. Immune cells infiltrate the heart in response to injury and release several proinflammatory and profibrotic cytokines (reviewed in (Adamo et al., 2020)). The mechanistic pathways involved in this cellular crosstalk have been elegantly addressed in recent reviews (Baci et al., 2020; Weiβ et al., 2022; Zaidi et al., 2021) and are beyond the scope of this review.

Adoptive transfer of regulatory T cells, a subset of lymphocytes with cardioprotective properties (Theall and Alcaide, 2022), is being tested in several inflammatory non-cardiovascular conditions (Raffin et al., 2020). However, their impact may depend on the etiopathogenic cause of cardiac fibrosis. In conditions of pressure overload, either by hypertension (Ang II) (Kvakan et al., 2009) or TAC (Kanellakis et al., 2011), administration of regulatory T cells limits cardiac infiltration of inflammatory cells, reduces cardiac fibrosis and improves cardiac function. On the other hand, activation of regulatory T cells after MI with an anti-CD28 antibody induces a M2-like macrophage phenotype associated with myofibroblast activation, increases *de novo* collagen expression within the infarcted region and decreases the rate of LV ruptures (Weirather et al., 2014). Metabolic reprogramming of T cells by NG52 (a phosphoglycerate kinase 1 inhibitor) leads to reduced infiltration of Th17 and Th1 cells and to increased T regulatory cells, associated with less inflammation and fibrosis and with improved systolic function (Lu et al., 2023).

In aging mice, treatment with abatacept (FDA-approved drug, cytotoxic T lymphocyte-associated antigen 4 (CTLA4)-IgG), which prevents T lymphocytes co-stimulation, reduces cardiac inflammation and fibrosis, which is associated with improved cardiac function (Martini et al., 2020).

EPA, beyond the direct effects in fibroblasts, reduces the development of cardiac fibrosis in spontaneously hypertensive rats, at least partially, by mediating phenotypic polarization of macrophages toward an anti-inflammatory M2 subtype (Gharraee et al., 2022). Specialized pro-resolving lipid mediators of unsaturated fatty acid, such as resolvins, may also exert antifibrotic effects by modulating macrophage phenotypes and infiltration (Kain and Halade, 2019; Liu et al., 2018). Treatment with resolvin 1 in hypertensive mice (by Ang II) reduces neutrophil and macrophage infiltration, as well as cardiac fibrosis (Olivares-Silva et al., 2021). Similarly, exogenous resolvin administration reduces cardiac fibrosis after MI and improves cardiac function (Kain et al., 2015).

Han et al. used graphene oxide to develop a macrophage-targeting/polarizing graphene oxide complex (MGC) with antioxidant properties that modulates macrophage polarization by reducing intracellular ROS (Han et al., 2018). In addition, MGC functionalized with an IL-4 plasmid attenuates inflammation, mitigates fibrosis, and improves cardiac function after MI (Han et al., 2018). To enhance M2 macrophage polarization, hyaluronan-sulfate nanoparticles complexed with a miR-21 mimic were administered intravenously after MI to passively target macrophages, reducing cardiac fibrosis (Bejerano et al., 2018). On the other hand, delivery of nanoparticle-encapsulated siRNA for CSF-1 in myocarditis inhibits cardiac monocyte infiltration leading to reduced cardiac fibrosis and improved function at later stages (Meyer et al., 2018). Likewise, lipidoid nanoparticles with a siRNA for CCR2 reduce inflammatory macrophages and fibrosis in myocarditis (Leuschner et al., 2015). Finally, in a model of Ang II-dependent hypertension liposomes carrying clodronate, known to cause monocyte apoptosis, lead to decreased macrophage infiltration and reduce cardiac fibrosis independently of hypertension (Falkenham et al., 2015).

Despite these promising experimental results, several of these approaches have failed in their translation to clinical trials (reviewed in (Adamo et al., 2020)), toning down the expectations regarding immunomodulation and anti-cytokine therapy. However, the promising cardioprotective results from inflammasome-pathway inhibitors in clinical trials have sparked the interest in this approach (Olsen et al., 2021). In addition, identification of patients with a high proinflammatory phenotype could be useful to select responders to anti-inflammatory therapies.

5.2.2.2. Gut microbiota. The identification of an association between gut microbiota and cardiovascular disease has opened a new area of research in recent years (Xu et al., 2023), although the knowledge on its contribution to cardiac fibrosis is still scarce and with conflicting results. For instance, microbiota depletion by antibiotic treatment at the onset of TAC prevented the development of cardiac fibrosis and preserved cardiac function (Carrillo-Salinas et al., 2020), while antibiotic treatment after MI increased collagen synthesis (Song et al., 2021). Interestingly, dietary modifications can have an impact on gut dysbiosis and cardiac fibrosis. In hypertensive mice (uninephrectomy plus deoxycorticosterone acetate), a high-fiber diet or supplementation with acetate decrease

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Box 1
Challenges and knowledge gaps regarding the management of cardiac fibrosis in heart failure

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Multiplicity of pathophysiological mechanisms triggering cardiac fibrosis
- Deeper knowledge on triggering mechanisms needed.

Histomolecular heterogeneity of cardiac fibrosis
- More accurate phenotyping and stratification needed.
- Access to myocardial tissue needed.

Cardiac fibrosis as a dynamic process with variable functional impact
- Longitudinal (time-adjusted) approaches needed.

Limited tissue availability for accurate diagnosis and phenotyping
- Improved accessibility and cost-effectiveness of imaging techniques needed.
- Multinational studies for the validation of circulating biomarkers needed.
- Multimarker panels needed to identify phenotypes of cardiac fibrosis.

Assessment of anti-fibrotic effects of heart failure drugs
- Including fibrosis surrogate biomarkers as endpoints in clinical trials needed.

Specific targeting of pathological cardiac fibrosis while preserving the physiological ECM
- Evaluation and prioritization of new antifibrotic strategies needed, including better knowledge on the targets and improved cost-effectiveness.
- Better understanding of cardiac fibrosis dynamics and mechanisms at different stages of disease needed.
- More selective and effective methods of delivery of antifibrotic drugs needed.
- Understanding extracardiac effects in the long-term needed.
- Better animal and *ex vivo* models needed.

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gut dysbiosis, measured by the ratio of Firmicutes to Bacteroidetes, which is associated with decreased cardiac fibrosis and hypertrophy (Marques et al., 2017). On the other hand, obese rats fed a high-fat diet show dysbiosis, characterized by a decrease in Firmicutes to Bacteroidetes ratio, and increased expression of markers of fibroblast activation, these effects being corrected by the mitochondrial antioxidant MitoTempo (Ortega-Hernández et al., 2020).

Trimethylamine N-oxide (TMAO), a gut microbe-derived metabolite, induces neonatal cardiac fibroblast differentiation and collagen production (W. Yang et al., 2019). Moreover, TMAO or a high choline diet (a main source of TMAO) exacerbate cardiac fibrosis and dysfunction after TAC (Organ et al., 2016, 2020), whereas treatment with a choline trimethylamine lyase inhibitor (iodomethylcholine) prevents these detrimental effects in the high choline diet model (Organ et al., 2020). Similarly, a high choline diet increases cardiac fibrosis after MI and further deteriorates cardiac function, while treatment with 3-dimethyl-1-butanol, another inhibitor of trimethylamine lyases, reverses this damage (W. Yang et al., 2019).

5.2.3. Future avenues of research

Further preclinical studies are needed to unravel the mechanisms regulating cardiac fibroblasts activation and fibrosis and to identify targetable molecules, in order to specifically inhibit pathological fibrosis while preserving the physiological and reparative functions of the ECM. Additional pathways may emerge from a deeper study of mechanosensing mediators (Pesce et al., 2023), the crosstalk with the endothelium, cardiomyocytes or the adipose tissue (Anthony et al., 2019; Tzahor and Dimmeler, 2022), or the possibility of *in vivo* reprogramming of cardiac fibroblasts into induced cardiomyocytes to reduce scar formation and preserve cardiac function after MI (Tani et al., 2023; Yamada et al., 2023).

Novel strategies of delivery of RNAs, small molecules or biologicals with nanoparticles (Passaro et al., 2021), engineered exosomes (Hohn et al., 2021), or viral vectors (Cannatà et al., 2020; Lu and Thum, 2019) may increase the efficacy and targeted-specificity of the compounds, limiting unwanted effects in other organs.

Finally, novel methodological approaches, like organ-on-chip technologies show great promise as human disease modeling platforms, powerful for screening human antifibrotic drugs, which may outperform animal models and reduce animal testing (Mourad et al., 2023).

6. Conclusions

Cardiac fibrosis is a major lesion involved in cardiac remodeling, contributing to the growing socioeconomic burden of HF and having an impact on cardiac dysfunction and clinical outcomes. Although preventing or reverting cardiac fibrosis is an unmet need, effective therapeutic strategies targeting cardiac fibrosis are lacking. However, the challenges and hurdles of antifibrotic therapies should be carefully considered as fibrosis is a highly heterogeneous and dynamic process that can be reparative at some stages of disease (Box 1). Moreover, fine-tuned strategies aimed at preventing excessive activation of fibroblasts and excessive collagen deposition, while preserving the key physiological role of the ECM, should be pursued. In this context, a more precise and accurate phenotyping of cardiac fibrosis is needed to advance toward the implementation of personalized medicine approaches for the management of this lesion. In the future, biomarker signatures combining imaging and circulating biomarkers are likely to capture the complexity and dynamic changes of cardiac fibrosis in different pathophysiological conditions. Finally, further research is needed to develop more specific targeted-strategies, combined with improved delivery methods, which are expected to exert cardiac antifibrotic effects while preventing detrimental side effects in the heart and in other organs.

In summary, academia, industry, and regulators are urged to develop a broad research agenda that spans the spectrum of basic, translational, and clinical studies repurposing known diagnostic tools and drugs of cardiac fibrosis for new indications, and investigating novel therapies and their effects among HF patient subgroups, defined according to biomarkers of cardiac fibrosis, in the application of personalized/precision medicine to prevent the progression of HF.

Sources of funding

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