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Diez, Javier; de Boer, Rudolf A.

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EXPERT OPINION

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Management of cardiac fibrosis is the largest unmet medical need in heart failure

Javier Díez[1,2,3]* and Rudolf A. de Boer[4]

[1]Department of Cardiology, University of Navarra Clinic, Av Pío XX 36, 31008, Pamplona, Spain; [2]Department of Nephrology, University of Navarra Clinic, Av Pío XII 36, 31008 Pamplona, Spain; [3]Program of Cardiovascular Diseases, Center of Applied Medical Research, University of Navarra, Av Pío XII 55, 31008 Pamplona, Spain; and [4]Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

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A diffuse accumulation of collagen fibres within the myocardial interstitium occurs in nearly all chronic cardiac diseases.[1] Because cardiac fibrosis is a key contributor to heart failure (HF) and its progression, it has important prognostic implications both in ischaemic heart disease[2] and non-ischaemic cardiac diseases.[3] In this regard, cardiac fibrosis is a major driver associated with the growing burden of HF, especially in older people.[4] However, integrating cardiac fibrosis in HF management is still an unmet medical need, which may be explained by its high tissue heterogeneity and clinical diversity, and, as a consequence, the very real limitations of its diagnosis and treatment. In this viewpoint paper, we summarize the challenges and requirements in the clinical management of cardiac fibrosis in HF patients (*Figure 1*).

Dealing with tissue heterogeneity and clinical diversity of cardiac fibrosis

Cardiac fibrosis is extremely heterogeneous, as it can develop under very diverse aetiological circumstances and several stages of the fibrotic process exist resulting in variable histomolecular expression and clinical behaviour.[1] In fact, although the major source of collagen fibres in cardiac fibrosis are cardiac fibroblasts, the presence of different subpopulations and their high plasticity enables them to change their behaviour in response to the type of initiating injury (i.e. the aetiology of cardiac disease), thus resulting in variable alterations in fibrillary collagen turnover. This variability translates into fibrotic deposits of specific characteristics with different functional impact and outcomes. This distinction is not academic: a proof-of-concept study showed that in patients with hypertensive HF both the type of predominant collagen fibre (either I or III) and the degree of cross-linking among collagen microfibrils within the deposits defined no less than four different phenotypes of cardiac fibrosis. This resulted in relevant differences in terms of the severity of myocardial stiffness and left ventricular (LV) dysfunction, as well as in terms of prognosis (i.e. risk of HF hospitalization or mortality).[5]

In this conceptual framework, a recent omics-based investigation performed in patients with HF due to hypertrophic cardiomyopathy, integrating functionally important myocardial protein–protein networks, allowed to identify cardiac fibrosis features unique to specific patient networks, that were associated with cardiac clinically relevant morphological and haemodynamic parameters,[6] thereby offering a direct strategy for advancing precision medicine in cardiac fibrosis.

Pursuing an accurate and precise non-invasive diagnosis of cardiac fibrosis

Detection of cardiac fibrosis using current cardiac imaging modalities or circulating biomarkers, usually separately, as has been done so far, does not ensure capture of the subtle aspects of this heterogeneous lesion.[7] Indeed, although the measurements provided by cardiac magnetic resonance or computed tomography (CT) enables reasonable detection of cardiac fibrosis in terms of the extent and topography of fibrotic deposits in different cardiomyopathies,[8] it obviously does not assess the histological and molecular characteristics. In fact, a recent study performed in endomyocardial biopsies from patients with aortic stenosis indicates that the measured extracellular volume (ECV) does not provide insights in the qualitative aspects of cardiac fibrosis.[9] On the other hand, from the proposed circulating biomarkers of cardiac fibrosis in patients with HF, only a few peptides derived from the extracellular processing of collagen type I and type III fulfil the requirement of an association between the systemic level of the biomarker and the extent and/or the histomolecular characteristics of cardiac fibrosis within the heart.[10] In addition, none of these molecules is cardiac specific and changes in their circulating levels might reflect abnormalities in body collagen and/or the influence of comorbidities affecting collagen metabolism in HF.[1,7]

The search of novel biomarkers provided by molecular imaging,[11] omics,[12] and non-coding RNA[13] research might increase the diagnostic accuracy and precision for cardiac fibrosis in HF patients. In the

* Corresponding author. Tel: +34 948 194700; fax: +34 948 194716, E-mail: jadimar@unav.es

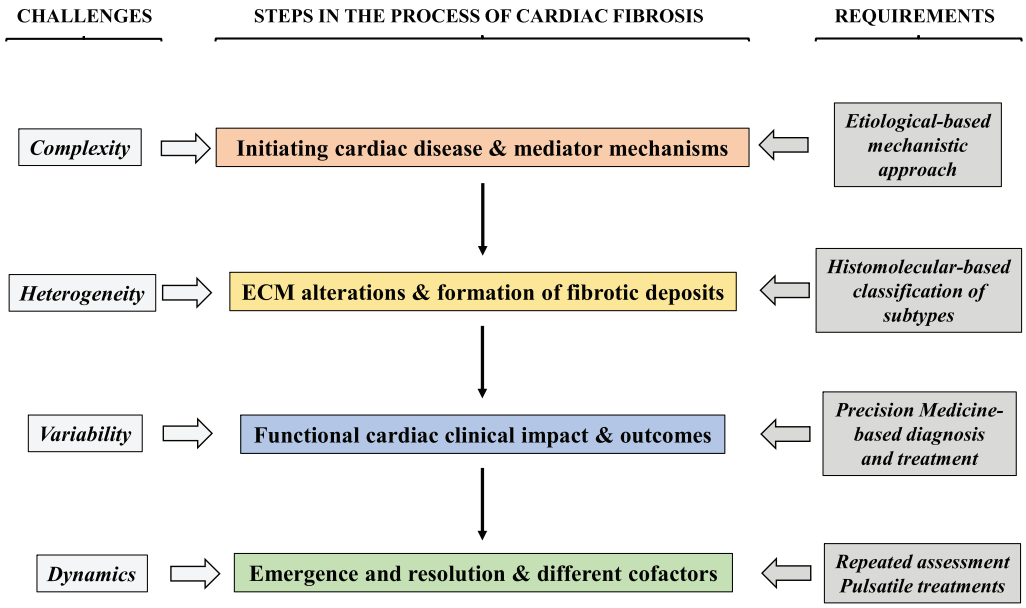

Figure 1 Schematic representation of the challenges posed by the different steps involved in the development and clinical evolution of cardiac fibrosis and the requirements needed to face them. ECM, extracellular matrix.

meantime, the combination of already available imaging and circulating biomarkers (e.g. ECV and collagen type I-derived serum peptides) can aid in the discriminative diagnosis of cardiac fibrosis subtypes.

Searching for personalized treatment and prevention of cardiac fibrosis

Since cardiac fibrosis has been shown to be reversible in HF patients, targeting this lesion has been proposed as part of the treatment of HF.[1,7] However, anti-fibrotic therapies, based either on already existing HF and non-HF pharmacological agents or on compounds still under investigation (e.g. non-coding RNAs),[13] suffer from a lack of precision, given the diversity of pathophysiological mechanisms and clinicopathological phenotypes of the target.[8] Thus, the time has come for studies aimed to investigate the clinical effects of tailored treatment of cardiac fibrosis in HF, based on patients' personalized hallmarks. The possibility exists that the ability of HF drugs to improve LV function in patients with HF can be determined by the histomolecular characteristics of fibrotic deposits. Indeed, it has been reported that the improvement of LV diastolic function induced by spironolactone in patients with HF with preserved ejection fraction depends on the histomolecular phenotype of cardiac fibrosis, as assessed by collagen type I-derived circulating biomarkers.[14]

As it is the case for the treatment of fibrosis in other organs, it can also be anticipated that cardiac fibrosis should be treated with combinations of anti-fibrotic drugs targeting the multiple mechanisms that, jointly, regress this lesion in each individual patient.

In summary, cardiac fibrosis represents a true challenge for transitioning from usual care to biomarker-based personalized treatment and precision medicine in HF. This transition must rely on the biomarker-guided identification of the diverse histomolecular phenotypes of cardiac fibrosis and, accordingly, on the individualization of anti-fibrotic therapies. Since cardiac fibrosis endpoints are currently not included in clinical trials, work in this area should be an urgent research priority for scientists, patients, industry leaders, and regulatory partners alike.

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Authors

Biography: Javier Díez is Professor of Medicine, Scientific Director of the Department of Nephrology and Head of Research of the Department of Cardiology at the University Clinic and the Center of Applied Medical Research of the University of Navarra in Pamplona, Spain. Javier Díez specialized in heart failure and chronic kidney diseases related to local and/or systemic pressure overload-mediated cardiac and renal diseases, and has a background in basic, translational, and clinical research. His research interests include fibrosis, biomarkers, and cardiorenal syndromes.

Biography: Rudolf de Boer is a cardiologist and Professor of Translational Cardiology at the University Medical Center Groningen, the Netherlands. He served as a Board member and Chair of the Basic Section of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), and as a member of the ESC Advocacy, Education, and eHealth committees. He is currently President-elect of the Dutch Cardiac Society. Rudolf de Boer specialized as a cardiologist in heart failure and inherited cardiomyopathies, and has a background in basic, translational, and clinical heart failure research. His research interests include biomarkers, heart failure with preserved ejection fraction, diabetes, fibrosis, and cardio-oncology.