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Review

The Latest Progress of Targeting Fibroblast Activating Protein PET/CT Molecular Imaging in Heart Failure

Haoran Guo [1,2] and Jianming Li [1,2,*]

[1] Clinical College of Cardiovascular Disease, Tianjin Medical University, Tianjin 300070, China
[2] Nuclear Medicine Department, TEDA International Cardiovascular Hospital, Tianjin 300457, China
* Correspondence: ichlijm@163.com

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Abstract: Heart failure (HF), the devastating end-stage manifestation of numerous cardiovascular diseases, exhibits alarmingly high morbidity, recurrent hospitalization rates, and mortality. At the core of this pathology lies myocardial fibrosis. Early detection, precise classification, dynamic monitoring, and rigorous assessment of treatment response for myocardial fibrosis are crucial for advancing precision management of HF. In recent years, fibroblast activation protein (FAP)-targeted molecular imaging—specifically fibroblast activation protein inhibitor (FAPI) positron emission tomography/computed tomography (PET/CT)—has garnered considerable attention. This innovative technology uniquely enables the visualization and quantitative assessment of myocardial fibrosis at the molecular level. This review synthesizes the latest research progress on FAPI PET/CT in HF, emphasizing its promising potential for application in the early diagnosis, risk stratification, and prediction of outcomes related to myocardial fibrosis. It also critically examines existing technical limitations and explores prospects for future research.

Keywords: heart failure; HF; myocardial fibrosis; fibroblast activation protein; FAP; positron emission tomography; PET; molecular imaging

1. Introduction

Heart failure (HF) serves as the final common pathway for a wide spectrum of cardiovascular diseases. Characterized by high morbidity, frequent rehospitalizations, and alarming mortality, HF stands as a major global public health crisis [1]. Afflicting more than 64 million individuals worldwide, it carries sobering 1-year and 5-year mortality rates of approximately 20% and 53%, respectively [2,3]. This immense disease burden compellingly underscores the urgent need to optimize prevention and management strategies. Consequently, achieving early diagnosis, precise phenotyping, and truly individualized management has emerged as a paramount priority in contemporary cardiovascular medicine [4].

Within the complex pathophysiology of HF, myocardial fibrosis (MF) is recognized as a central pathological mechanism driving progressive cardiac dysfunction, ventricular remodeling, and decompensation [5–8]. MF has evolved from a purely pathological manifestation into a key intervention focus in the precision management of HF; accurate evaluation of MF is thus essential for risk stratification, treatment monitoring, and clinical decision-making [9–11]. However, current noninvasive imaging modalities remain limited in their ability to comprehensively characterize the dynamic nature of fibrosis. Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR), the current reference standard, effectively delineates established structural scarring, but its ability to monitor early signs of HF and risk stratification is insufficient [12,13]. Similarly, circulating biomarkers such as galectin-3 and soluble growth-stimulated expressed gene 2 protein (sST2) provide insights into systemic inflammatory and fibrotic states but lack cardiac specificity and cannot provide spatial distribution information of lesions [14–16]. Other molecular imaging techniques have not yet been widely used in the fibrotic

assessment of HF due to suboptimal target specificity or insufficient correlation with core fibrotic pathways. Accordingly, there is an unmet clinical need for a novel imaging modality capable of in vivo, specific, and quantitative visualization of ongoing fibrotic activity.

Recently, molecular imaging targeting fibroblast activation protein (FAP) has made remarkable breakthroughs. Building upon this target, fibroblast activation protein inhibitor (FAPI) positron emission tomography/computed tomography (PET/CT) technology has demonstrated immense potential in early studies for noninvasively assessing myocardial fibrosis activity [17,18]. Based on existing evidence, this advancement may contribute to a shift in imaging diagnosis—from visualizing disease consequences toward illuminating the disease process itself. In oncology, FAPI PET/CT has already received preliminary validation for imaging diverse malignant tumors, showcasing significant application value [19,20]. This success provided an exciting opportunity to extend research into cardiovascular diseases, particularly HF. This review synthesizes the latest advances in applying FAPI PET/CT to HF. We highlight the modality's molecular imaging basis and distinct technical advantages, elucidate its critical role in delineating mechanisms of myocardial fibrosis and ventricular remodeling underlying HF, and explore its clinical promise for early diagnosis, precise risk stratification, and effective therapeutic monitoring. Finally, we address current limitations and chart future directions for integrating FAPI PET/CT into the evolving landscape of precision cardiology.

2. Materials and Methods

In this review, a comprehensive literature analysis was performed across multiple academic databases, including PubMed Central (PMC), Springer Nature, Elsevier, and ScienceDirect. A systematic literature search was conducted for publications spanning from January 1979 to November 2025. The main search terms are FAP, FAPI, PET, FAPI PET/CT, myocardial fibrosis, heart failure, molecular imaging, and cardiac remodeling. All retrieved articles were screened, with the final inclusion primarily consisting of recent representative studies on FAPI PET/CT in HF from the past five years, as well as a small number of early seminal works. This review focuses on analyzing and summarizing the molecular mechanisms, diagnostic performance, prognostic significance, and future directions of FAPI PET/CT in HF.

3. Molecular Basis and Technical Advantages of FAPI PET/CT Imaging

3.1. Molecular Basis of Imaging

FAP is a type II transmembrane serine protease that possesses both dipeptidyl peptidase and endopeptidase activities and can specifically degrade components of various extracellular matrices (ECM) [21,22]. In healthy adult tissues, FAP expression is virtually absent or negligible [23]. However, its expression is significantly and specifically upregulated under pathological tissue remodeling conditions such as the tumor microenvironment and fibrotic lesions [24] (Figure 1A). Based on available evidence, this distinct expression pattern is evident in cardiac pathological remodeling, positioning FAP as a potential molecular imaging target [25,26].

In the pathophysiological progression of HF, inflammation-mediated fibrosis plays a central role in the deterioration of cardiac structure and function [27]. Myocardial fibrosis, broadly categorized into reactive and replacement forms mediated by fibroblasts and myofibroblasts, compromises ventricular compliance and induces progressive functional impairment, thereby substantially increasing the risk of cardiovascular mortality and HF-related rehospitalization [28–30]. A recent study using state-of-the-art analyses of large-scale single-cell and single-nucleus transcriptomes of the human heart has revealed the functional heterogeneity of cardiac fibroblasts and established high-resolution cellular atlases [31]. These findings provide a theoretical basis for investigating fibroblast activation markers, including FAP. Mechanistic studies have further demonstrated that fibroblast activation and the resulting dysregulation of collagen metabolism play central roles in ECM remodeling and diastolic dysfunction [32,33].

Clinical observations and animal experimental data jointly suggest that the FAP expression pattern differs in HF depending on the underlying etiology. In acute myocardial infarction (AMI), a leading cause of HF with reduced ejection fraction, FAP expression is typically transient, intense, and regionally confined, consistent with the reparative fibrotic process. In contrast, in chronic pressure overload, such as hypertension-induced HF with preserved ejection fraction, FAP expression is sustained, diffusely distributed, and of lower intensity, reflecting an adaptive fibrotic process [34,35]. Therefore, FAP serves not only as a biomarker of fibrosis presence but also as an indicator of its temporal and spatial dynamics, capturing the active pathological processes underlying HF progression. By linking cellular activation events with macroscopic clinical phenotypes, FAP may provide a biological basis for developing FAP-targeted molecular imaging approaches.

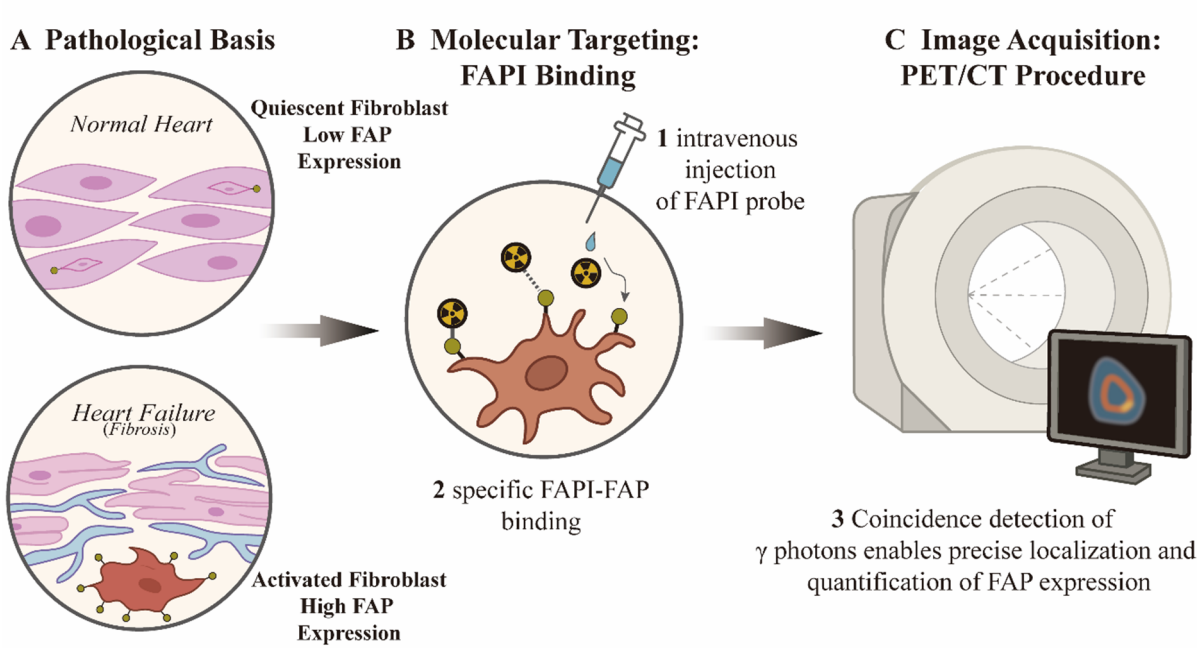

Figure 1. Schematic diagram of FAPI PET/CT imaging targeting the myocardial fibrosis process. (**A**) Under normal physiological conditions, fibroblasts remain quiescent with low FAP expression. When HF occurs, it is accompanied by structural alterations such as fibrosis, which results in activated fibroblasts overexpressing FAP. (**B**) Therefore, when a FAPI imaging agent is injected intravenously, there will be specific FAP-FAPI binding. (**C**) Subsequent coincidence detection of emitted γ-photons allows PET/CT to precisely localize and quantify FAP expression within fibrotic myocardium.

3.2. Technical Advantages

Gallium-68-labelled FAPI serves as a highly specific radiotracer capable of visualizing activated fibroblasts with an excellent target-to-background ratio (TBR) [36,37]. FAPI PET/CT is a molecularly targeted imaging modality whose representative tracers, such as ^{68}Ga-FAPI-04 and ^{68}Ga-FAPI-46, exhibit high affinity and specificity for the enzymatically active site of FAP, thereby enabling precise localization of activated fibroblasts in vivo [38,39]. At present, FAPI-04 has been extensively investigated in clinical research and demonstrates favorable pharmacokinetics [40]. A comparison of several common tracers is presented in Table 1. Following intravenous administration, radiolabeled FAPI probes typically tagged with positron-emitting nuclides such as ^{68}Ga or ^{18}F selectively accumulate in myocardial regions exhibiting high FAP expression. The resultant annihilation photons detected by PET imaging systems enable whole-body visualization of active fibrotic lesions [26] (Figure 1B,C).

Compared with existing imaging modalities, FAPI PET/CT demonstrates several distinct advantages. Endomyocardial biopsy, although considered the diagnostic gold standard, is invasive, subject to sampling error, and incapable of providing a global assessment of myocardial involvement [41,42]; CMR with LGE can delineate fibrotic tissue but primarily reflects focal, end-stage structural alterations, offering limited insight into molecular activity [43,44]; ^{18}F-FDG PET enables the evaluation of inflammatory activity; however, physiologically high glucose uptake in normal myocardium often produces significant background interference, which makes the effective differentiation between pathological and physiological signals challenging [45,46]. ^{13}N-ammonia (^{13}N-NH_3) is a classic imaging agent, commonly used in cardiac PET imaging [47,48]. In one reported case of immune checkpoint inhibitor-associated HF, discordant findings were observed between ^{13}N-NH_3 perfusion and ^{68}Ga-FAPI uptake, which indicated that ^{68}Ga-FAPI PET might provide superior diagnostic information, serving as an indirect marker of fibroblast activation and a potential predictor of myocardial fibroblast activity [49]. Importantly, FAPI tracers exhibit markedly lower uptake in normal myocardium compared with fibrotic or inflamed regions, thereby achieving an exceptionally high TBR; this feature facilitates the clear delineation of pathological lesions and enables dynamic, noninvasive, and quantitative assessment of myocardial remodeling throughout the course of HF [50]. Thus, FAP-targeted imaging is emerging as a potential biomarker of cardiac remodeling and injury, which suggests that it holds promise for clinical translation and implementation in HF management, pending further validation in larger studies.

Table 1. Comparison of common FAPI Tracers.

Ligand	Radionuclide	Kinetics and Biodistribution	Pros	Cons	Ref.
FAPI-04	^{68}Ga	Rapid blood pool clearance with high target-to-background; low physiological myocardial uptake in normal hearts; washout over a few hours; renal clearance.	Wide clinical experience among FAPIs; feasible in centers without cyclotron; low background in blood pool and remote myocardium favors detection of focal fibroblast activation.	Short half-life (68 min); generator capacity limits batch size for large trials and multi-patient dynamic studies; some inter-patient variability in physiologic myocardial signal.	[50–54]
FAPI-46	^{68}Ga	More sustained target retention, theoretically attractive for cardiac fibrosis imaging and delayed imaging; renal clearance.	Improved lesion contrast compared with some earlier FAPIs; increasing target-to-background ratio over time; potentially better suited for late static imaging or simplified protocols (one scan at 60–90 min) in cardiac trials.	Most data derive from oncology; short half-life (68 min); generator capacity limits batch size for large trials and multi-patient dynamic studies.	[51–54]
FAPI-74	^{18}F	High uptake in inflamed/fibrotic myocardium; good blood-pool clearance and low background in non-cardiac tissues; renal clearance.	Longer physical half-life (110 min); cyclotron-produced ^{18}F may favor multicenter trials and standardized SOPs.	Clinical cardiac experience very limited; potentially higher background in certain organs compared with some ^{68}Ga FAPIs; optimal cardiac imaging time not yet defined.	[55,56]
FAPI-42	^{18}F	High binding affinity and in-vivo stability; renal clearance.	Longer half-life supports multi-patient production and distribution; good image contrast; promising for cardiac fibrosis.	Limited clinical validation to date.	[57,58]

4. FAPI PET/CT Visualization and Clinical Correlates of the Pathological Process in Heart Failure

4.1. Visualization of the Dynamic Pathological Process in Heart Failure

A salient advantage of FAPI PET/CT lies in its capacity to noninvasively delineate the dynamic evolution of HF pathology in vivo, transcending the limitations of imaging approaches that capture only end-stage structural changes. Fibroblast activation represents an early and partially reversible event in pathological myocardial remodeling; timely detection of this process will offer a critical window for early therapeutic intervention. Figure 2 provides a conceptual framework linking key stages with the expected evolution of FAPI PET/CT signal, which guides the interpretation of the studies discussed below. Experimental evidence indicates that ^{68}Ga-FAPI PET can effectively identify HF patients at the nascent stages of fibrosis to a certain extent [26]. Furthermore, a separate study demonstrates that the cardiac FAPI signal emerges before detectable functional alterations in the myocardium, suggesting that FAPI PET may serve as a valuable imaging tool for visualizing the incipient stage of fibrosis in cardiac remodeling leading to HF [59]. Related studies have found that FAPI PET/CT has an advantage over other techniques in capturing the early time window of fibrosis initiation. For example, Wang et al. [60] established a rat model of pressure overload–induced HF, and myocardial ^{68}Ga-FAPI-04 accumulation significantly exceeded control levels by the second week, whereas echocardiographic abnormalities did not manifest until the fourth week. Similarly, Diekmann et al. [61] found elevated FAPI uptake in 39 of 78 myocardial segments that appeared normal on LGE imaging. Moreover, they found that fibroblast activation spatially extended beyond the infarcted territory, suggesting that FAPI PET/CT can identify precursor fibroblast activation in non-infarcted myocardium prior to scar formation. Evidence of FAPI signal reversibility further underscores its potential to monitor dynamic pathological activity. In a case report, a patient with acute ischemic injury exhibited a significant reduction in FAPI uptake following successful revascularization, highlighting the ability of this molecular imaging modality to monitor reversible, dynamic fibrotic pathological activity [62]. The utility of FAPI PET/CT in tracking disease progression is further exemplified in myocarditis, a prominent etiology of HF. Zhou et al. [63] reported three patients at different disease stages: focal FAPI uptake during the acute phase, diffuse

FAPI distribution in the subacute phase, and signal overlap with scar tissue in the chronic phase. These patterns vividly delineate the continuum from acute inflammation to chronic fibrosis, providing a longitudinal imaging roadmap of myocardial injury and repair. Collectively, these findings establish FAPI PET/CT as a powerful modality for detecting early pathological events and for tracking the progression from acute injury to chronic fibrotic remodeling. By enabling real-time, in vivo visualization of the evolving disease process, this technique offers unique mechanistic insights into the pathophysiological continuum of HF.

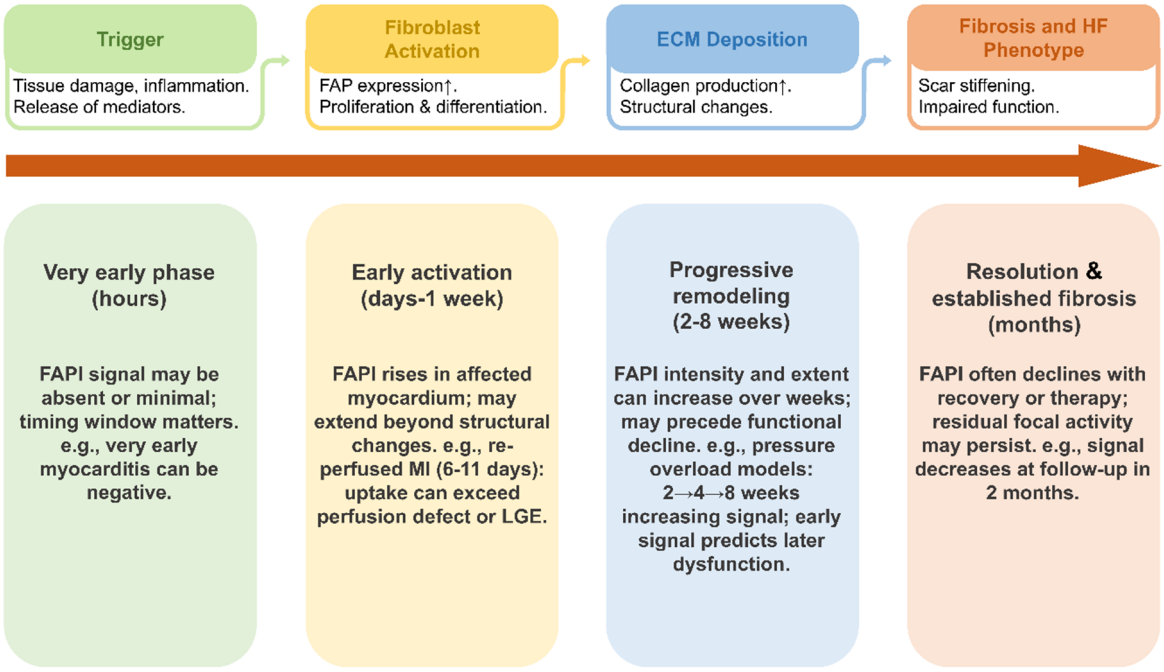

Figure 2. Schematic timeline of FAPI PET/CT signals across stages of myocardial remodeling leading to heart failure.

4.2. Correlations between FAPI Imaging Phenotypes and Clinical Characteristics of Heart Failure

Quantitative parameters derived from FAPI PET/CT showed strong correlations with the clinical severity of HF. In a retrospective analysis of oncology patients, myocardial FAPI uptake showed an inverse correlation with left ventricular ejection fraction (LVEF), indicating that higher FAPI signal intensity corresponds to reduced systolic function [50]. Similarly, Gu et al. [64] reported that right ventricular FAPI uptake was significantly associated with right ventricular dysfunction, and that overall cardiac FAPI activity exhibited a positive correlation with total pulmonary resistance and plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels. Cardiac amyloidosis (CA), once considered rare, is increasingly recognized as an underdiagnosed etiology of HF [65]. In a prospective study involving 27 patients with light-chain cardiac amyloidosis (AL-CA), FAPI uptake correlated significantly with several clinical and imaging biomarkers, including NT-proBNP, LVEF, left ventricular end-systolic volume, extracellular volume fraction, and left ventricular global strain [66]. However, more recent investigations have yielded conflicting results. One study reported no significant correlation between myocardial FAP signal intensity and LVEF, nor with hematocrit, lipoprotein-associated phospholipase A_2, or B-type natriuretic peptide levels [67]. Such discrepancies underscore ongoing uncertainties regarding the strength and consistency of the relationship between FAPI-derived imaging phenotypes and conventional cardiac or biochemical markers. Therefore, while current evidence suggests that FAPI PET/CT provides valuable insight into the molecular and functional substrates of HF, its precise role in disease staging, risk stratification, and prognostic evaluation remains to be validated through large-scale, multicenter studies.

5. Clinical Applications of FAPI PET/CT in Heart Failure

5.1. Assisted Diagnosis and Accurate Classification

For patients presenting with clinical manifestations or imaging abnormalities of HF, FAPI PET/CT has demonstrated substantial potential as a complementary diagnostic tool and as a means to achieve precise disease phenotyping. By delineating distinct imaging phenotypes, FAPI PET/CT facilitates differentiation among various etiologies of HF. In AMI, FAPI uptake typically manifests as focal, intense accumulation spatially concordant with the ischemic territory [50]. In contrast, nonischemic cardiomyopathies, such as dilated cardiomyopathy

(DCM), exhibit multifocal myocardial FAPI accumulation, with the number of affected segments exceeding those identified by LGE, indicating a more diffuse and extensive pathological involvement than is structurally apparent [57]. Moreover, in the context of nonischemic HF, Yang et al. [68] demonstrated significantly increased FAPI uptake across DCM, hypertrophic cardiomyopathy (HCM), and restrictive cardiomyopathy (RCM), with distinct variations in both intensity and extent. These findings indicate that FAPI PET/CT may facilitate differentiation of the underlying fibrotic activation states associated with diverse HF phenotypes. Beyond left ventricular assessment, FAPI PET/CT enables the evaluation of chamber-specific involvement, including the right heart. A single-center clinical study reported pronounced ^{68}Ga-FAPI uptake in the right ventricular free wall and right atrium of patients with pulmonary hypertension–induced right HF [69]. Consistent with these observations, an experimental study employing an animal model of pulmonary hypertension demonstrated that ^{18}F-FAPI-42 PET/CT clearly visualized the progressive fibrotic remodeling of the right ventricle [58]. Collectively, these findings underscore the diagnostic and pathophysiological utility of FAPI PET/CT in characterizing myocardial involvement across HF subtypes, offering a novel molecular approach to refine disease classification and enable precision phenotyping.

5.2. Early Risk Warning and Prognostic Assessment

The clinical utility of FAPI PET/CT has expanded beyond diagnostic evaluation toward prognostic prediction, with emerging evidence suggesting that its quantitative parameters may serve as a novel reference for outcome assessment in HF. In a study of patients with AMI, FAPI PET/CT has demonstrated that the intensity of fibroblast activation in the remote (non-infarcted) myocardium correlates with reductions in LVEF and increases in left ventricular end-diastolic volume [70]. Consequently, FAPI PET may serve as a crucial early imaging marker for predicting adverse ventricular remodeling and the subsequent development of HF. An independent longitudinal study reported a positive correlation between early myocardial ^{68}Ga-FAPI-04 uptake and changes in the left ventricular end-diastolic volume index (LVEDVI) at 6-month follow-up, suggesting that baseline ^{68}Ga-DOTA-FAPI-04 uptake may hold predictive value for future ventricular remodeling [71]. Similarly, Diekmann et al. [72] reported that early FAPI uptake was associated with subsequent functional outcomes, further substantiating the prognostic potential of FAPI metrics. Collectively, these findings demonstrate that by quantifying early fibrotic activity post-infarction, FAPI PET/CT can identify high-risk patients most susceptible to progressing to HF.

Furthermore, FAPI PET/CT has also shown strong potential in risk assessment among other populations predisposed to HF. HCM and DCM are important causes of systolic HF and diastolic HF, respectively. In an experimental study utilizing engineered T cells targeting cardiac fibrosis, Aghajanian et al. [73] confirmed high expression of activated fibroblasts within the left ventricular myocardium of failing human DCM and HCM. In a clinical study of HCM patients who had not yet progressed to end-stage HF, the intensity of myocardial FAPI uptake was found to positively correlate with the 5-year sudden cardiac death (SCD) risk score [74]. Similarly, in patients with AL-CA undergoing ^{68}Ga-FAPI-04 PET/CT, quantitative indices of FAP expression, defined as cardiac fibroblast activation protein volume (CFV) and total cardiac fibroblast activation protein (TCF), were found to be inversely associated with overall survival; in multivariate analysis, higher TCF emerged as a primary determinant of shortened survival [75]. Representative clinical and preclinical investigations of cardiac FAPI PET/CT are summarized in Table 2, outlining study populations, imaging protocols, quantitative parameters, and principal findings. Across animal models and human cohorts, FAPI PET/CT shows a consistent pattern. Myocardial uptake increases during the active remodeling phase and reflects fibroblast activation. In preclinical studies, the signal appears early and can precede measurable functional decline. Clinical studies, especially after acute myocardial infarction, similarly show FAPI uptake beyond perfusion defects or LGE-defined injury, and several cohorts report associations between higher baseline uptake and later adverse remodeling or organ outcomes. Differences across studies are expected because tracers, timing, and quantification methods vary, and FAPI mainly captures cellular activation rather than mature scar. Thus, by quantifying myocardial fibrotic activity before overt functional decline, FAPI PET/CT may facilitate the identification of high-risk individuals and guide timely therapeutic intervention to prevent the progression to overt HF.

Table 2. Summary of Key Studies on FAPI PET/CT in Cardiac Imaging.

Study Type	Study	Population	Imaging Protocol	Quantification Metrics	Main Findings
Preclinical study	Varasteh et al. [35]	20 rats with myocardial infarction induced by permanent ligation of left anterior descending coronary artery.	^{68}Ga-FAPI-04 PET/CT (20–25 MBq; repeated at 1, 3, 6, 14, 23, 30 days post myocardial infarction); dynamic scan around day 7; comparator ^{18}F-FDG around day 3; autoradiography and histology.	Infarct-to-remote uptake ratio; tracer kinetics; fibroblast-related histology.	FAPI uptake peaks early (around day 6) and predominates in border zone, consistent with transient fibroblast activation after myocardial infarction; supports noninvasive monitoring of active remodeling rather than mature scar.
	Sun et al. [34]	Heart failure with preserved ejection fraction (HFpEF) rats.	^{18}F-AlF-NOTA-FAPI-04 PET/CT, serial evaluation during model development; includes dynamic imaging at later time point and histology.	Myocardial SUV-based indices; time-activity analysis; histologic FAP assessment.	Detectable myocardial FAPI uptake emerges during HFpEF development (notably from mid-course timepoints) and reflects activated fibroblasts; suggests feasibility for early HFpEF remodeling visualization.
	Wang et al. [60]	Sprague-Dawley rats with abdominal aortic constriction (AAC) HF; sham controls.	^{68}Ga-FAPI-04 PET/CT at 2, 4, 8 weeks post-surgery; static acquisitions at defined uptake times; echocardiography and immunohistochemistry.	Cardiac uptake indices; FAP and area density.	Cardiac FAPI signal elevated as early as 2 weeks and increases with progression; correlates with FAP expression; early signal associates with later functional deterioration, suggesting predictive value for non-ischemic HF progression.
	Song et al. [26]	HF rat model; 7 HF patients in preliminary clinical study.	Rats: ^{68}Ga-FAPI PET/CT at 0, 7, 14, 21, 28 days; Human: ^{13}N-NH_3 perfusion and ^{68}Ga-FAPI cardiac PET in same subjects.	Rats: heart-to-muscle ratios, fibrosis histology; Human: normalized SUV-type metrics; perfusion–FAPI comparison.	In rats, FAPI signal peaks in the early active remodeling window (around day 7) while histologic fibrosis may still be mild, then evolves with disease course; pilot human data demonstrate feasibility and potential mismatch with perfusion, supporting complementary activity information.
	Zhao et al. [76]	Permanent left anterior descending ligation myocardial infarction (MI) rats.	^{68}Ga-FAPI-04 PET/CT (dynamic at day 7; static at 1, 3, 7, 14, 28 days, 50 min) and ^{177}Lu-FAPI-04 therapy (injection at day 7).	%ID/g; infarct-to-remote ratio; Echocardiogram; MRI.	^{68}Ga-FAPI-04 specifically targets infarct fibroblasts; ^{177}Lu-FAPI-04 improves LVEF and reduces fibrosis with no obvious short-term kidney or liver toxicity; supports activated-fibroblast window after MI.
Clinical study	Diekmann et al. [61]	12 ST-segment elevation myocardial infarction (STEMI) patients, imaged 6–11 days post-percutaneous coronary intervention (PCI).	^{68}Ga-FAPI-46 PET (static 60 min); CMR (LGE).	SUVpeak; LV area above blood-pool–based threshold%; total lesion uptake.	FAPI enrichment at infarct site but FAPI-positive area exceeds perfusion defect; many segments without LGE show FAPI uptake, so fibroblast activation beyond infarct region early after acute myocardial infarction (AMI).
	Kessler et al. [77]	10 patients post-AMI, no prior coronary artery disease.	^{68}Ga-FAPI PET after AMI; visual matching vs. culprit vessel territory.	SUVmax; SUVmean; fibroblast activation volume (FAV).	Focal uptake in all; reasonable alignment with culprit territory; FAV correlates with myocardial injury biomarkers and inversely with systolic function.
	Chen et al. [78]	13 patients with chronic thromboembolic pulmonary hypertension (CTEPH); 13 matched controls.	^{68}Ga-FAPI-04 PET/CT; CMR in subset.	SUVmax; TBR for RV.	Abnormal RV uptake in most CTEPH patients, mainly RV free wall; uptake correlates with RV hypertrophy and impaired RV function; CMR fibrosis surrogates may not fully align.
	Diekmann et al. [72]	35 AMI patients, imaging within 11 days; subset follow-up few months.	^{68}Ga-FAPI-46 PET/CT; CMR (LGE, T1/T2); perfusion SPECT.	FAP volume, extent, segmental SUVs; correlations with baseline and follow-up function.	FAPI extent > perfusion defect and > LGE; imperfect overlap with CMR tissue markers; FAP volume predicts later ventricular dysfunction, supporting prognostic utility.
	Wang et al. [66]	30 patients with biopsy-proven amyloid light chain (AL) amyloidosis (27 with AL cardiac amyloidosis, 3 without).	^{68}Ga-FAPI-04 PET/CT.	SUV ratio-type indices; LV molecular volume; visual pattern classification (patchy/extensive/negative).	Myocardial FAPI uptake common and correlates with staging or biomarkers and remodeling parameters; may provide complementary molecular characterization and staging.
	Wang et al. [74]	50 participants with HCM; 22 healthy controls.	^{18}F-FAPI PET/CT (uptake 60 min).	Intensity; extent; amount.	HCM shows intense heterogeneous FAPI uptake extending beyond hypertrophied segments; uptake amount correlates with 5-year SCD risk score.

6. Current Limitations and Future Directions

6.1. Present Challenges and Technical Bottlenecks

Despite promising preliminary data, current evidence supporting the use of FAPI PET/CT in cardiac imaging remains limited, and standardized imaging protocols have yet to be established. Most existing studies are confined to single-center prospective cohorts with small sample sizes or retrospective analyses derived from oncological populations. The absence of large-scale, multicenter, prospective clinical trials specifically designed for diverse etiologies and stages of HF constrains the validation of its diagnostic and prognostic value. Consequently, imaging acquisition and processing protocols for cardiac applications remain unstandardized. Furthermore, significant variations exist across studies regarding tracer selection, such as ^{68}Ga-FAPI-04, ^{68}Ga-FAPI-46, ^{18}F-FAPI-74, scanning protocols, and quantitative parameters, resulting in limited comparability of findings [79]. Establishing a standardized procedural framework, encompassing tracer administration through image analysis, is therefore a critical prerequisite for facilitating clinical translation. Secondly, the potential for limited specificity of FAP expression warrants attention. Although fibroblast activation and FAP upregulation are important features of cardiac remodeling in HF, elevated FAP expression has also been observed in non-cardiac conditions such as arthritis, tissue repair, and various malignancies; and low-level, nonspecific, or off-target uptake may occasionally occur under physiological conditions [80–82]. Therefore, image interpretation in HF patients must be carefully integrated with clinical history, laboratory data, and anatomical imaging to avoid diagnostic misclassification. Additionally, the inflammatory response during the acute phase of myocardial infarction can also induce transient upregulation of FAP expression. In this context, the observed FAPI signal may reflect both reparative fibrosis and inflammatory components, potentially leading to an overestimation of the fibrotic scope [83]. It should also be noted that the spatial resolution of PET imaging remains inherently limited, which constrains the detection of early, microscopic lesions [84,85]. Finally, clinical translation is also constrained by practical limitations. As an emerging nuclear imaging modality, FAPI PET/CT faces challenges regarding cost-effectiveness, radiotracer availability, and radiation safety considerations. These factors have restricted its widespread application in the routine diagnosis and treatment of HF.

6.2. Future Directions and Technological Outlook

FAPI PET/CT holds considerable promise in the diagnosis, risk assessment, and management of HF. Future advancement of this modality should prioritize the refinement of clinical evidence-based frameworks, facilitate the convergence of multimodal technologies, and explore novel application paradigms for the realization of precision-oriented management of HF. Firstly, the design and execution of large-scale, multicenter prospective clinical studies are essential. Such investigations are expected to generate high-level evidence supporting the role of FAPI PET/CT in early HF diagnosis, risk stratification, and therapeutic monitoring while simultaneously facilitating the establishment and dissemination of standard operating procedures (SOPs) for image acquisition and quantitative analysis [86]. Secondly, advances in multimodal image fusion and artificial intelligence offer novel paradigms for image interpretation. Pixel-wise fusion of FAPI PET/CT molecular and functional data with high-resolution anatomical and tissue characterization information from cardiac magnetic resonance, including LGE and T1/T2 mapping, can enable simultaneous assessment of both fibrotic activity and cumulative burden, and this integrative approach may substantially enhance diagnostic specificity and refine the evaluation of myocardial remodeling [87]. In recent years, hybrid PET/MR has emerged as a potential extension of this integrative paradigm. In selected post-STEMI studies, PET/MR-derived FAPI uptake metrics have been associated with subsequent remodeling and clinical outcomes, and the integrated platform may support more robust co-registration of molecular activity with MR tissue characterization (LGE and mapping) and functional assessment within a single examination. However, FAPI PET/MR evidence in cardiovascular disease remains limited, and clinical adoption is not yet widespread. Larger longitudinal cohorts and standardized acquisition and quantification protocols are still needed before PET/MR can be considered for broader clinical implementation. Furthermore, the exploration of multi-target PET imaging may offer a new avenue for elucidating the multifactorial pathophysiology of HF. For instance, ^{68}Ga-Pentixafor, a new radiotracer targeting C-X-C chemokine receptor 4 (CXCR4), can predict adverse remodeling, with the infarct-to-remote myocardium ratio of maximal standardized uptake values (SUVmax) in AMI serving as an independent predictor of adverse cardiovascular events (HR = 4.9, $p < 0.01$) [88,89]. In the future, the combined use of this target-oriented imaging modality and FAPI PET/CT could maximize their complementary strengths, thereby providing initial imaging evidence for better understanding of HF pathophysiological mechanisms, enhanced risk stratification, and personalized therapeutic regimen optimization. Furthermore, a one-stop ^{68}Ga-FAPI/^{18}F-FDG dual-tracer whole-body imaging regimen allows for concurrent evaluation of myocardial fibrosis states and inflammatory/metabolic activity during a single scan, furnishing more

robust imaging underpinnings for dissecting the pathogenic mechanisms of distinct HF phenotypes and refining personalized therapeutic strategies [90]. Concurrently, artificial intelligence and radiomics can provide crucial support for compensating for the insufficient spatial resolution of PET and improving the accuracy of quantitative analysis. Deep learning algorithms can not only facilitate more precise segmentation and quantification of small lesions but also mine potential radiomic features to construct imaging biomarkers for early pathological identification and prognostic prediction. These advances will help screen high-risk patients, guide treatment regimens, and monitor treatment efficacy, as well as lay a foundation for future explorations of targeted FAP-based theranostic integration.

7. Conclusions

Myocardial fibrosis is intimately associated with the initiation and progression of HF. Early identification and dynamic monitoring of fibrotic processes constitute a pressing, unmet clinical priority. FAP-targeted in vivo molecular imaging offers a noninvasive, visualizable, and quantitative approach for the early detection of fibrosis. Consequently, as an emerging molecular targeted imaging technique, FAPI PET/CT enables noninvasive in vivo characterization of the spatiotemporal distribution of activated fibrosis, thereby mitigating the inherent limitations of conventional imaging modalities and serological biomarkers. Current evidence indicates that this technology may aid in phenotyping, functional stratification, and prognostic prediction across the diverse spectrum of HF etiologies, furnishing novel perspectives for the precision diagnosis and management of HF. Although validation through additional high-quality preclinical and clinical investigations remains essential, the emergence of FAPI PET/CT has suggested a potential to refine HF assessment by integrating molecular information beyond structural imaging to the interrogation of underlying molecular pathological cascades.

Driven by relentless advances in fundamental science, mounting clinical evidence, and increasingly sophisticated imaging techniques, FAPI PET/CT could become a potential complementary approach to precision diagnosis and management of HF. In the near future, it will enable the noninvasive visualization, precise quantitative assessment, personalized management, and therapeutic monitoring of myocardial fibrosis in HF. This emerging molecular imaging technique may contribute to advances in cardiac care by enabling earlier detection and more individualized HF management, though its long-term clinical impact remains to be demonstrated.

Author Contributions

J.L. conceptualized the framework, provided strategic direction for this review, and contributed to manuscript revision and refinement. H.G. drafted the initial manuscript and assisted with revisions. All authors have read and approved the final version and have sufficiently participated in the work, agreeing to be accountable for all aspects of it.

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Conflicts of Interest

The authors declare no conflict of interest. Given the role as editorial board member, Jianming Li had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

During manuscript preparation, we used ChatGPT (OpenAI) for limited wording suggestions and Gemini for language and grammatical refinement, primarily in the Introduction and main review sections, to improve clarity and readability. After using these tools, all content was critically reviewed, verified, and revised by the authors; we take full responsibility for the accuracy, originality, and integrity of the manuscript.

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