Current Cardiology Reports (2020) 22: 40
https://doi.org/10.1007/s11886-020-01284-3

NUCLEAR CARDIOLOGY (V DILSIZIAN, SECTION EDITOR)

Advances in PET-Based Cardiac Amyloid Radiotracers

Cesia Gallegos[1] · Edward J. Miller[1]

Published online: 19 May 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

The gold standard for diagnosis of cardiac amyloidosis (CA) is endomyocardial biopsy showing Congo red staining followed by mass spectroscopy, but the diagnosis can also be made with high certainty by demonstration of typical cardiac imaging features along with amyloid on biopsy of another involved organ. The use of cardiac imaging techniques to detect amyloid deposits may frequently obviate the need for invasive methods in order to ascertain the presence, and potentially the type, of amyloid deposition.

Purpose of Review We aim to review the evidence behind the development of novel positron emission tomography (PET) radiotracers for demonstrating cardiac amyloid deposition and potentially distinguishing between light-chain (AL) or transthyretin (ATTR) cardiac amyloidosis.

Recent Findings Multiple recent studies have shown that thioflavin-analogue tracers such as ^{18}F-florbetapir, ^{18}F-florbetaben, ^{18}F-flutemetamol, and ^{11}C-labeled Pittsburg Compound-B (PiB) may be able to fulfill the unmet need of elucidating the presence of amyloid deposition in the heart. Because they bind to the beta-pleated motif of the amyloid fibril due to their similarity to the thioflavin structure, they could potentially be used to image CA (Table 1).

Summary The use of PET amyloid radiotracers shows promise; however, further data is needed to define their overall accuracy and additive value to the care of patients with suspected systemic and/or cardiac amyloidosis.

Keywords Amyloid · Transthyretin · Radiotracers · Positron emission tomography · Bone scintigraphy

Introduction

Amyloidosis is a term used to describe a family of protein-folding disorders in which organs are infiltrated by deposits derived from misfolded precursor protein, with characteristic histopathological features of apple-green birefringence with polarized light on Congo red staining. Amyloid infiltration causes expansion of the extracellular space, causing cellular toxicity and organ damage [1]. In the heart, amyloid deposition commonly causes hypertrophy with progression to diastolic dysfunction and heart failure, initially with preserved ejection fraction but can progress to systolic dysfunction [2].

Though there are multiple types of systemic amyloidosis defined by their specific precursor protein, cardiac amyloidosis (CA) is most frequently caused by acquired immunoglobulin-derived light chain deposition (AL) or by transthyretin (ATTR) protein accumulation. ATTR CA appears to be much more prevalent than AL CA [3]. ATTR can be subclassified as genetically normal (e.g., "wild type" (WT)) previously referred to as "senile," or genetically abnormal or mutant (hATTR) caused by any of the > 120 known *TTR* gene mutations [1, 2, 4, 5].

There are three goals for imaging of cardiac amyloidosis. The first is to have diagnostic sensitivity to detect whether or not any amyloid deposits (AL, ATTR, etc.) are present in the heart. The second is to differentiate between AL and ATTR, as the prognosis and treatments are very different. Lastly, is to assess total systemic disease burden in order to better understand prognosis and/or response to treatment [6]. While the diagnostic gold standard for CA remains endomyocardial biopsy showing Congo red positivity followed by mass spectroscopy for amyloid typing, biopsy can be avoided in many

This article is part of the Topical Collection on *Nuclear Cardiology*

✉ Edward J. Miller
edward.miller@yale.edu

Cesia Gallegos
cesia.gallegoskattan@yale.edu

[1] Section of Cardiovascular Medicine, Yale University School of Medicine, 333 Cedar Street, PO Box 208017, New Haven, CT 06520-8017, USA

patients if amyloid is confirmed in another organ or if cardiac amyloid involvement can be ascertained using an imaging method. For example, there have been many recent advances in the use of technetium-99m (^{99m}Tc)-labeled SPECT "bone avid" radiotracers (^{99m}Tc-DPD [3,3-diphosphono-1,2-propanodicarboxylic acid], ^{99m}Tc-HMDP [hydroxymethylene diphosphonate], and ^{99m}Tc-PYP [pyrophosphate]), that can differentiate between ATTR and AL [7]. Despite their increasingly wide-spread use, the SPECT "bone avid" radiotracers are limited in their ability to primarily identify ATTR disease only in the heart.

There is rapidly increasing interest to develop positron emission tomography (PET) tracers that satisfy both the need to detect the presence of amyloidosis and quantify the disease burden and the response to treatment. Thus, this review will focus on emerging PET radiotracers developed for imaging amyloidosis, including four thioflavin analogue agents initially developed for imaging Alzheimer's disease (AD) and β-amyloid that have shown promise for the diagnosis of CA: ^{11}C-labeled Pittsburg Compound-B (PiB), ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol [8, 9•, 10, 11] (Fig. 1). They are similar in structure to thioflavin and they bind to the beta-pleated motif of the amyloid fibril, making them able to image both AL and ATTR amyloid in the heart [12]. The following sections will discuss each novel tracer in detail and will provide insight into their imaging protocols, uses, and limitations.

^{11}C-Labeled Pittsburg Compound-B

^{11}C-PiB was developed by modifying the amyloid-binding histological dye, thioflavin-T, which led to the finding that a neutral benzothiazole could bind to amyloid and allow for direct visualization and quantification of the β-amyloid in

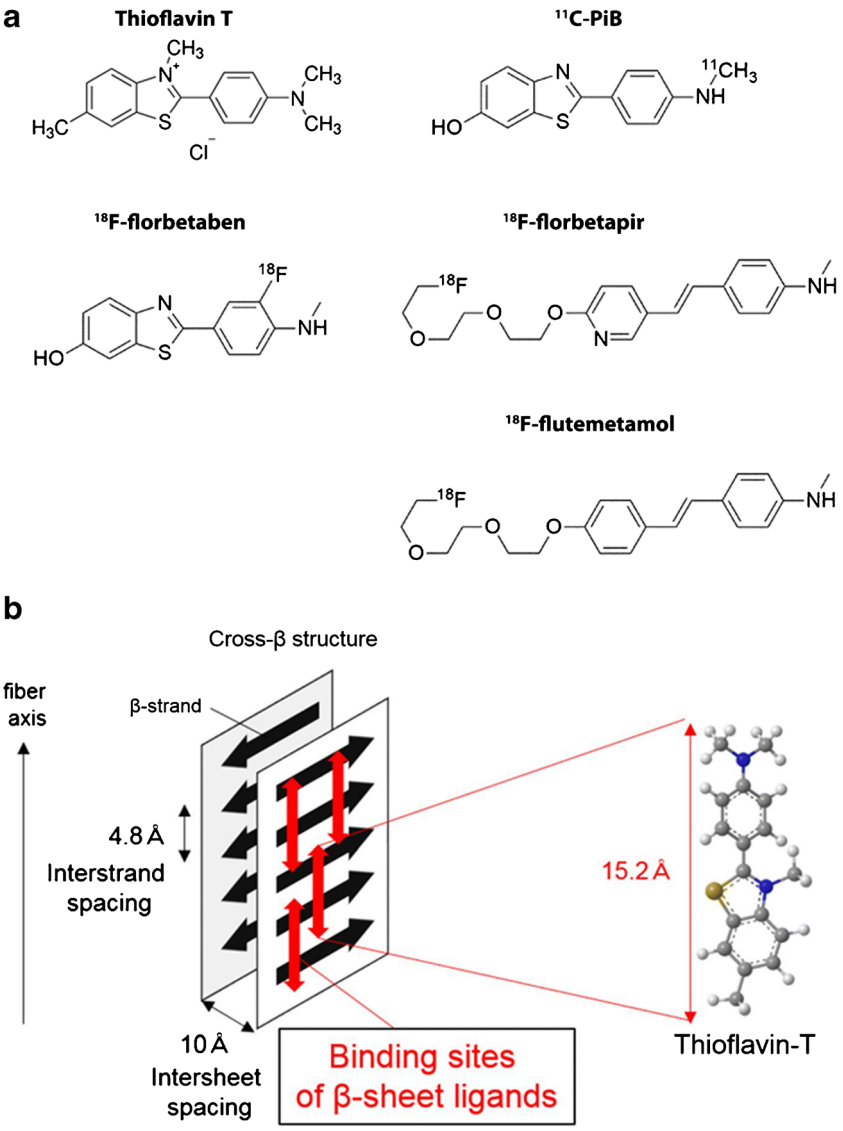

Fig. 1 **a** Thioflavin-T derived amyloid PET tracers. ^{18}F-florbetapir (Amyvid™), ^{18}F-florbetaben (Neuraceq™), ^{18}F-flutemetamol (Vizamyl™), are FDA approved, while ^{11}C-labeled Pittsburg Compound-B (PiB) is not. **b** Proposed mechanism of binding to amyloid fibrils. Given their similarity to the thioflavin-T structure, they likely bind to the B motif of the fibril. (Reproduced with permission from: Singh V, et al. Journal of Nuclear Cardiology. 2019;26(1):158–73. doi:https://doi.org/10.1007/s12350-018-01552-4, permission conveyed through Copyright Clearance Center, Inc.) [12]

Alzheimer's disease. Klunk et al. reported the first-in-human study of amyloid-imaging using the PET tracer ^{11}C-PiB in 16 patients with mild Alzheimer's disease [13•]. Even though it has not been FDA approved, it is a widely studied and specific PET agent that may allow earlier diagnosis of AD [14]. Speculating on its potential use in other amyloidogenic disorders, Antoni et al. were the first to investigate whether the use of ^{11}C-PiB could allow for visualization of amyloid in the heart. Ten patients with either AL or ATTR cardiac amyloid and five healthy volunteers were studied using ^{11}C-PiB to visualize cardiac amyloid deposits and ^{11}C-acetate to measure myocardial blood flow and its relation to ^{11}C-PiB retention. They found that myocardial ^{11}C-PiB uptake was evident in all amyloidosis patients, but no uptake was present on the healthy volunteers. This finding was reproduced by Lee et al. in a study in which twenty-two patients with monoclonal gammopathy with suspected CA were enrolled. They underwent ^{11}C-PiB PET/CT along with echocardiography, cardiac magnetic resonance, and endomyocardial biopsy within a 1-month period. In this study, ^{11}C-PiB PET/CT uptake was present in thirteen out of fifteen biopsy-proven patients with CA, but in none of the patients without CA [15]. This data suggests that ^{11}C-PiB may be a sensitive tracer for determining the presence of CA.

Further intriguing data with ^{11}C-PiB suggest that it may also be helpful with understanding ATTR biology. In a study by Pilebro et al., ten patients with biopsy-proven ATTR amyloid and the V30M mutation were grouped according to their TTR fiber type (fibril type A, early onset, or type B, late onset) [16]. All underwent ^{11}C-PiB PET/CT and ^{99m}Tc-DPD scintigraphy. They found that ^{11}C-PiB retention was increased in all patients but was significantly higher in those with type B, commonly associated with less cardiac involvement. However, ^{99m}Tc-DPD uptake was elevated in type A and absent in type B. This study showed that ^{11}C-PiB PET/CT is a sensitive method for detecting ATTR amyloid deposits, but DPD appears only to detect fragmented TTR which is associated with more severe clinical heart disease. This data suggests that ^{11}C-PiB might be a sensitive marker for early detection and raises the possibility of studying this agent in carriers of mutations to detect early onset of disease.

Despite its uses, ^{11}C-PiB has some disadvantages. First, its use is restricted to centers with an on-site cyclotron. Additionally, the 20-min half-life of ^{11}C and high synthesis cost makes it challenging for use in routine clinical practice. To offset these limitations, amyloid PET tracers labeled with ^{18}F will be discussed below realizing their potentially more widespread clinical use [17].

^{18}F-Florbetapir

^{18}F-florbetapir is structurally different from ^{11}C-PiB, with a styrylpyridine structure and use of ^{18}F [18]. It was developed and FDA approved in 2012 for imaging β-amyloid protein in the brain in AD [19, 20]. In 2014, Dorbala et al. presented a pilot study in which they studied the feasibility of ^{18}F-florbetapir for imaging in CA and whether its uptake in the heart could help distinguish AL from ATTR CA [9•]. They also explored the kinetics of this tracer in the liver, lung, and bone to assess its potential use to diagnose amyloidosis in other organs in fourteen patients: Nine with confirmed cardiac amyloid and five control subjects. They found that the left ventricular signal after injection with ^{18}F-florbetapir was diffuse and uniform in both ventricles in the amyloid patients compared with controls. Despite the lower myocardial mass, the retention index also tended to be higher in patients with AL compared with the ATTR cohort without clearly distinguishing between them. They speculated that the higher uptake might reflect amyloid disease activity [9•]. This same group also studied endomyocardial biopsy specimens with autopsy-documented AL and ATTR using ^{18}F-florbetapir and digital autoradiography. They demonstrated the specific in vitro binding of the tracer to myocardial amyloid fibers with significantly higher uptake particularly in those with AL amyloid, suggesting that the concentration of available binding sites for the tracer may be different in AL and ATTR [21•].

With this background and given the lack of modalities to identify multi-organ involvement in AL amyloidosis accurately, Ehman et al. sought to evaluate the additive value of ^{18}F-florbetapir when in conjunction with international consensus in the largest study of this tracer and systemic AL amyloidosis to date [22]. They prospectively studied 40 subjects with biopsy-proven systemic amyloidosis both with active disease and those with hematologic remission with the aim of determining the distribution and frequency of systemic amyloid [22]. In this study, ^{18}F-florbetapir uptake identified organ deposition of amyloid, even in those patients without clinically evident involvement and in patients with complete remission for more than 1 year, potentially allowing for early diagnosis as well as monitoring of antifibrillar treatments.

These data suggest that ^{18}F-florbetapir holds promise for evaluating fibril deposition in systemic AL amyloidosis, even in patients where there is no obvious organ involvement. It may also be successful to monitor organ response to plasma cell and antifibrillar therapies.

^{18}F-Florbetaben

^{18}F-florbetaben is a stilbene derivative that shares similar structural features to PiB. It was also studied first in patients with AD, where it was found to bind specifically to the amyloid β-pleated sheets [23]. In CA, it was first studied by Law et al. in a small number of patients with both AL and ATTR CA and controls with hypertensive heart disease [10]. They

found that target-to-background SUV ratio and percentage tracer retention were higher in the patients with CA when using a cutoff of 40% of retention, proposing the possibility of this tracer in differentiating between CA and hypertensive heart disease in clinical practice. However, ^{18}F-florbetaben does not appear to effectively differentiate between AL and ATTR despite having significantly higher myocardial SUV variability for AL patients [10]. This was also the first ^{18}F-florbetaben study to show a correlation between tracer retention and biventricular contractive function via an inverse curve relationship, suggesting it may have a role in monitoring burden of amyloid plaque and response to therapies.

Another small study with nine patients with suspected AL CA evaluated the use of ^{18}F-florbetaben PET/MR whole-body imaging in the diagnosis of AL systemic involvement. Accumulation of the radiopharmaceutical was noted on delayed whole-body imaging in the bone marrow, stomach, brain, salivary glands, tongue, spleen, skeletal muscle, ocular muscles, thyroid, pleura, kidneys, and lungs, suggesting that this method may provide guidance of organ involvement for treatment and histological examination [24].

Most recently, the performance of ^{18}F-florbetaben PET/CT imaging was studied to assess the amyloid burden response in twenty-two patients with clinically proven or suspected CA. This technique was compared with echocardiography, cardiac MRI (CMR), and DPD scintigraphy. They found that amyloid subtypes demonstrated different characteristic retention patterns, with AL being highest. Myocardial tracer retention correlated with parameters as measured by CMR and echocardiography, but not with cardiac biomarkers (troponin T and N-terminal proBNP). In four patients, a follow-up PET/CT done after treatment initiation showed changes in tracer retention from baseline to follow-up correlating with treatment response [25]. Though a small sample size and heterogeneous group of patients without histological confirmation of CA, the results of this pilot study are promising in suggesting the possibility of this tracer to differentiate between subtypes of CA and accurately assess amyloid burden and response to treatment.

These data suggest that ^{18}F-florbetaben is a feasible technique for differentiating among CA subtypes with the added value of possible burden quantification and deserves further investigations to assess its suitability for assessment of treatment response.

^{18}F-Flutemetamol

^{18}F-flutemetamol is another thioflavin derivative used for evaluation of β-amyloid plaque density in patients with cognitive impairment being evaluated for AD and other dementia disorders [26]. Dietemann et al. retrospectively studied twelve patients: Nine with CA (one with AL and the rest with ATTR) and three control subjects. ^{18}F-flutemetamol uptake was higher in eleven of the patients with CA. The target to background ratio was also significantly higher, showing promise of this radiotracer in the diagnosis and perhaps treatment response in patients with CA [27•].

In summary, the ^{18}F-labeled PET amyloid tracers (Table 1) appear to be sensitive for CA given their ability for imaging amyloid independent of the type of amyloid precursor protein. The quantitative nature of the PET holds promise for disease quantification and therapy monitoring. Further studies are warranted to determine their additive value in clinical practice.

Other Tracers Under Investigation

As described in the previous sections, there has been extensive work on developing imaging tracers for cardiac amyloidosis based on their ability to bind to β-amyloid fibrils. However, another potential basis for tracer development is the interaction of amyloid precursor proteins and local calcium homeostasis, as it has been postulated that ATTR fibrils have higher calcium content leading to the ability to potentially bind calcium-sensitive probes. Such is the case for ^{18}F-labeled sodium fluoride (^{18}F-NaF), which is approved for prostate cancer imaging as well as for detecting microcalcification in coronary plaques and progression of disease in patients with calcific aortic stenosis [2, 28]. Besides possibly detecting presence of CA as well as allowing for treatment monitoring, ^{18}F-NaF has the advantage of being more readily available than other F-labeled tracers. Preliminary results on the use of ^{18}F-NaF to distinguish between mutant ATTR and AL had been discordant as published in two European case reports [29, 30]. This was followed by an exploratory study in seven patients with biopsy-proven CA (two with AL and five with ATTR) and five patients with prostate cancer and no amyloid as controls who were enrolled to undergo ^{18}F-NaF PET imaging [28]. The principal finding of the study was greater uptake in amyloid patients compared with controls, which was more accentuated in patient with ATTR CA. Though a novel quantitative approach with intriguing findings, this study had important limitations: It was small and with a small proportion of AL that is difficult to understand whether ^{18}F-NaF PET imaging can reliably differentiate between the two entities. More recent data aimed to examine the use of this tracer in patients with AL and ATTR CA using qualitative and quantitative analysis with average left ventricular SUV and TBR. They found that the TBR was significantly increased in those with ATTR compared with AL and controls with varying degrees of sensitivity depending on the cutoff for diagnosing ATTR [31].

Table 1 PET radiotracers studied in cardiac amyloidosis

First author	Tracer	*N* and cohort	Method	Outcome
Antoni et al. [10]	^{11}C-PiB	10—ATTR and AL CA 5—healthy volunteers	Tracer retention and myocardial flow quantification	Retention in all CA patients and no uptake on healthy volunteers
Lee et al. [14]	^{11}C-PiB	22—monoclonal gammopathy and suspected CA	^{11}C-PiB PET/CT + TTE + cMRI + EMB	^{11}C-PiB Uptake was present in 3/15 biopsy-proven CA None in non-CA patients
Pilebro et al. [15]	^{11}C-PiB	10—ATTR CA (according to fibril type A or B) and V30M mutation	^{11}C-PiB PET/CT and ^{99m}Tc-DPD scintigraphy	^{11}C-PiB increased in all but > in fibril type B (less cardiac involvement) DPD elevated in type A ^{11}C-PiB: Sensitive to detect earlier onset of disease?
Dorbala et al. [8]	^{18}F-florbetapir	9—ATTR and AL CA 5—control subjects	Cardiac uptake of ^{18}F-florbetapir and tracer kinetics in the liver, lung, and bone	Diffuse uptake of tracer in both amyloid types with increased retention index in AL patients.
Park et al. [20]	^{18}F-florbetapir	30—myocardial autopsy specimens (AL, ATTR, and control)	^{18}F-florbetapir and digital autoradiography	First time in vitro specific binding of tracer in amyloid specimens AL > ATTR
Ehman et al. [21•]	^{18}F-florbetapir	40—AL CA	^{18}F-florbetapir PET/CT	Tracer detected widespread organ amyloid deposition in subjects with both active AL and AL hematologic remission.
Law et al. [9•]	^{18}F-florbetaben	5—AL CA 5—ATTR CA 4—control with hypertensive heart disease	^{18}F-florbetapir PET/CT	Increased retention in patients with CA with no difference between types.
Baratto et al. [23]	^{18}F-florbetaben	9—CA	^{18}F-florbetapir PET/MRI of the heart and whole body	High early and delayed cardiac uptake Increased abnormal accumulation in multiple organs
Kircher et al. [24]	^{18}F-florbetaben	5—proven CA 17—suspected CA	$^{-18}$F-florbetaben-PET/CT in detection of CA vs TTE, cMRI and scintigraphy. $^{-18}$F-florbetaben-PET/CT for quantification of amyloid burden and monitoring of treatment response was assessed.	Tracer retention consistent with CA in 14/22 patients with characteristic retention patterns AL > AA > ATTR
Dietemann et al. [26]	^{18}F-flutemetamol	8—ATTR CA 1—AL CA 3—control	^{18}F-flutemetamol pilot study determining SUV in the left ventricular myocardium and blood pool	Uptake noted in 8/9 CA patients and none in control

Overall, though significant advanced have been made as proof-of-point of ^{18}F-NaF PET imaging as an emerging modality for evaluation of CA, there current data is limited. Comparison with the current available bone tracers like ^{99m}Tc-PYP might be useful to advance the application of this radiotracer.

Conclusions

Despite the growing armamentarium in the imaging of CA, the use of PET technique for its diagnosis and management continues to develop. Though the use of thioflavin analogue PET agents shows promise, data is still lacking regarding their additive clinical role. However, there is unmet and critical need to develop tracers to distinguish between amyloid types and quantify response to treatment.

Compliance with Ethical Standards

Conflict of Interest Cesia Gallegos declares no conflict of interest.

Edward J. Miller reports grants from Bracco, Eidos, Alnylam, and Pfizer; and has been a consultant for Bracco, Pfizer, GE, and Alnylam.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance

1. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis. J Am Coll Cardiol. 2016;68(12):1323–41. https://doi.org/10.1016/j.jacc.2016.06.053.
2. Gallegos C, Miller EJ. Use of fluorine-18 sodium fluoride for the diagnosis of transthyretin cardiac amyloidosis: the birth of a new technique. J Nucl Cardiol. 2018;25(5):1568–70. https://doi.org/10.1007/s12350-017-0847-6.
3. Kyriakou P, Mouselimis D, Tsarouchas A, Rigopoulos A, Bakogiannis C, Noutsias M, et al. Diagnosis of cardiac amyloidosis: a systematic review on the role of imaging and biomarkers. BMC Cardiovasc Disord. 2018;18(1):221. https://doi.org/10.1186/s12872-018-0952-8.
4. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. J Am Coll Cardiol. 2015;66(21):2451–66. https://doi.org/10.1016/j.jacc.2015.09.075.
5. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy. Neurology. 2012;79(8):785. https://doi.org/10.1212/WNL.0b013e3182661eb1.
6. Dorbala S, Bokhari S, Miller EJ, Bullock-Palmer RP, Soman P, Thompson RC (2019) 99mTechnetium-pyrophosphate imaging for transthyretin cardiac amyloidosis. American Society of Nuclear Cardiology Practice Points Webpage. https://www.asnc.org/content.asp?contentid=182.
7. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404–12. https://doi.org/10.1161/circulationaha.116.021612.
8. Vandenberghe R, Van Laere K, Ivanoiu A, Salmon E, Bastin C, Triau E, et al. ^{18}F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. Ann Neurol. 2010;68(3):319–29. https://doi.org/10.1002/ana.22068.
9. • Dorbala S, Vangala D, Semer J, Strader C, Bruyere JR Jr, Di Carli MF, et al. Imaging cardiac amyloidosis: a pilot study using (1)(8)F-florbetapir positron emission tomography. Eur J Nucl Med Mol Imaging. 2014;41(9):1652–62. https://doi.org/10.1007/s00259-014-2787-6. **First study to show the feasibility of ^{18}F-Florbetapir for imaging cardiac amyloidosis.**
10. Law WP, Wang WY, Moore PT, Mollee PN, Ng AC. Cardiac amyloid imaging with 18F-florbetaben PET: a pilot study. J Nucl Med. 2016;57(11):1733–9. https://doi.org/10.2967/jnumed.115.169870.
11. Antoni G, Lubberink M, Estrada S, Axelsson J, Carlson K, Lindsjö L, et al. In vivo visualization of amyloid deposits in the heart with 11C-PIB and PET. J Nucl Med. 2013;54(2):213–20. https://doi.org/10.2967/jnumed.111.102053.
12. Singh V, Falk R, Di Carli MF, Kijewski M, Rapezzi C, Dorbala S. State-of-the-art radionuclide imaging in cardiac transthyretin amyloidosis. J Nucl Cardiol. 2019;26(1):158–73. https://doi.org/10.1007/s12350-018-01552-4.
13. • Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. Ann Neurol. 2004;55(3):306–19. https://doi.org/10.1002/ana.20009. **First-in-human study of the thioflavin PET tracers in the the diagnosis of brain amyloid.**
14. Benadiba M, Luurtsema G, Wichert-Ana L, Buchpigel CA, Busatto FG. New molecular targets for PET and SPECT imaging in neurodegenerative diseases. Braz J Psychiatry. 2012;34(Suppl 2):S125–36. https://doi.org/10.1016/j.rbp.2012.07.002.
15. Lee SP, Lee ES, Choi H, Im HJ, Koh Y, Lee MH, et al. 11C-Pittsburgh B PET imaging in cardiac amyloidosis. J Am Coll Cardiol Img. 2015;8(1):50–9. https://doi.org/10.1016/j.jcmg.2014.09.018.
16. Pilebro B, Arvidsson S, Lindqvist P, Sundström T, Westermark P, Antoni G, et al. Positron emission tomography (PET) utilizing Pittsburgh compound B (PIB) for detection of amyloid heart deposits in hereditary transthyretin amyloidosis (ATTR). J Nucl Cardiol. 2018;25(1):240–8. https://doi.org/10.1007/s12350-016-0638-5.
17. Villemagne VL, Ong K, Mulligan RS, Holl G, Pejoska S, Jones G, et al. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. J Nucl Med. 2011;52(8):1210–7. https://doi.org/10.2967/jnumed.111.089730.
18. Yao T, Li Z. Facile synthesis of TEG-substituted 4-(N-methyl-N-Boc-amino)styrylpyridine and PET imaging agent [F]florbetapir ([F]AV-45). Synth Commun. 2018;48(4):422–7. https://doi.org/10.1080/00397911.2017.1404107.
19. Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA. 2011;305(3):275–83. https://doi.org/10.1001/jama.2010.2008.
20. Yang L, Rieves D, Ganley C. Brain amyloid imaging–FDA approval of florbetapir F18 injection. N Engl J Med. 2012;367(10):885–7. https://doi.org/10.1056/NEJMp1208061.
21. • Park M-A, Padera RF, Belanger A, Dubey S, Hwang DH, Veeranna V, et al. ^{18}F-Florbetapir binds specifically to myocardial light chain and transthyretin amyloid deposits: autoradiography study. Circ Cardiovasc Imaging. 2015;8(8). https://doi.org/10.1161/CIRCIMAGING.114.002954. **Cross-sectional study demonstrating binding of ^{18}F-Florbetapir to cardiac amyloid by autoradiography.**
22. Ehman EC, El-Sady MS, Kijewski MF, Khor YM, Jacob S, Ruberg FL, et al. Early detection of multiorgan light-chain amyloidosis by whole-body (18)F-florbetapir PET/CT. J Nucl Med. 2019;60(9):1234–9. https://doi.org/10.2967/jnumed.118.221770.
23. Rowe CC, Ackerman U, Browne W, Mulligan R, Pike KL, O'Keefe G, et al. Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof of mechanism. Lancet Neurol. 2008;7(2):129–35. https://doi.org/10.1016/s1474-4422(08)70001-2.
24. Baratto L, Park SY, Hatami N, Gulaka P, Vasanawala S, Yohannan TK, et al. (18)F-florbetaben whole-body PET/MRI for evaluation of systemic amyloid deposition. EJNMMI Res. 2018;8(1):66. https://doi.org/10.1186/s13550-018-0425-1.
25. Kircher M, Ihne S, Brumberg J, Morbach C, Knop S, Kortum KM, et al. Detection of cardiac amyloidosis with (18)F-florbetaben-PET/CT in comparison to echocardiography, cardiac MRI and DPD-scintigraphy. Eur J Nucl Med Mol Imaging. 2019;46(7):1407–16. https://doi.org/10.1007/s00259-019-04290-y.
26. Leuzy A, Savitcheva I, Chiotis K, Lilja J, Andersen P, Bogdanovic N, et al. Clinical impact of [(18)F]flutemetamol PET among memory clinic patients with an unclear diagnosis. Eur J Nucl Med Mol Imaging. 2019;46(6):1276–86. https://doi.org/10.1007/s00259-019-04297-5.
27. • Dietemann S, Nkoulou R. Amyloid PET imaging in cardiac amyloidosis: a pilot study using ^{18}F-flutemetamol positron emission tomography. Ann Nucl Med. 2019;33(8):624–8. https://doi.org/10.1007/s12149-019-01372-7. **Pilot study using ^{18}F-flutemetamol for evaluation of cardiac amyloidosis.**
28. Morgenstern R, Yeh R, Castano A, Maurer MS, Bokhari S. ^{18}Fluorine sodium fluoride positron emission tomography, a potential biomarker of transthyretin cardiac amyloidosis. J Nucl Cardiol. 2018;25(5):1559–67. https://doi.org/10.1007/s12350-017-0799-x.

29. Van Der Gucht A, Galat A, Rosso J, Guellich A, Garot J, Bodez D, et al. [18F]-NaF PET/CT imaging in cardiac amyloidosis. J Nucl Cardiol. 2016;23(4):846–9. https://doi.org/10.1007/s12350-015-0287-0.
30. Gagliardi C, Tabacchi E, Bonfiglioli R, Diodato S, Nanni C, Guidalotti P, et al. Does the etiology of cardiac amyloidosis determine the myocardial uptake of [18F]-NaF PET/CT? J Nucl Cardiol. 2017;24(2):746–9. https://doi.org/10.1007/s12350-016-0457-8.
31. Martineau P, Finnerty V, Giraldeau G, Authier S, Harel F, Pelletier-Galarneau M. Examining the sensitivity of 18F-NaF PET for the imaging of cardiac amyloidosis. J Nucl Cardiol. 2019:1–10. https://doi.org/10.1007/s12350-019-01675-2.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.