Am J Nucl Med Mol Imaging 2026;16(2):67-76
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0170704

Review Article

^{18}F-Flurpiridaz PET in myocardial perfusion imaging: comparing effectiveness against traditional tracers

Shreyas Bulusu[1], Albab S Uddin[1], Oluwaseyi M Oderinde[2,3], Qi-Huang Zheng[1]

[1]Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IN, USA; [3]Advanced Molecular Imaging Research Laboratory, Purdue University, West Lafayette, IN, USA

Received December 12, 2025; Accepted March 8, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: Myocardial perfusion imaging (MPI) has served as a cornerstone of coronary artery disease (CAD) evaluation for over four decades, including many other cardiac diseases. MPI is extremely valuable for both diagnostic and prognostic purposes in clinical environments, enabling clinicians to evaluate a patient's coronary health. Perfusion scanning utilizes two primary imaging techniques: single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Each relies on radioactive tracers, which are radioactive substances injected into a patient that spread across myocardial tissue and emit photons or positrons detectable by cameras. Traditional radiotracers include ^{15}O-water, ^{13}N-ammonia, and ^{82}Rb-chloride for PET and ^{99m}Tc-sestamibi for SPECT, which vary in physical and biological properties, including half-life and extraction fraction, influencing image quality, workflow, and clinical utility. Recently, a new PET radiotracer called ^{18}F-Flurpiridaz has shown promise for increased efficiency among traditional radiotracers, such as a substantially longer half-life. Additional advantages of this radiotracer include, but are not limited to, improved cost-effectiveness due to the use of a pre-existing delivery system, superior image quality, mid-exercise testing, and solving "imaging deserts", which are regions with a lack of medical imaging services that rural areas face. We aim to review the advantages and disadvantages of ^{18}F-Flurpiridaz PET and compare its effectiveness against traditional PET and SPECT tracers in this article.

Keywords: ^{18}F-Flurpiridaz, positron emission tomography (PET), single-photon emission computed tomography (SPECT), radiotracer, myocardial perfusion imaging (MPI), coronary artery disease (CAD)

Introduction

Myocardial perfusion imaging (MPI) is completed through comparing a patient's imaging scans during rest (no stress) and activity (causing stress, such as running on a treadmill) [1]. The steps for an MPI are listed in **Figure 1**. There are differences between the types of radiotracers and imaging type used. ^{99m}Tc-sestamibi is the most common used radiotracer for single-photon emission computed tomography (SPECT) due to its widespread availability and a lower upfront cost but fluctuates because of supply issues. Positron emission tomography (PET) scans with radiotracers offer faster acquisition times and lower radiation doses compared to SPECT, such as ^{82}Rb-chloride, ^{15}O-water, and ^{13}N-ammonia; they also provide clear image resolution and flow quantification [2]. Nevertheless, the major limitation of traditional PET perfusion tracers is extremely short half-lives, which ultimately limits their use to centers with specialized infrastructure.

Current radiotracers for MPI can best be characterized by their various extraction and retention fractions. Extraction fractions (EF) measure the efficiency of tracer's initial absorption into the bloodstream then moving into the target tissue. Retention fractions (RF) measure how well the tracer is withheld or "trapped" in the target tissue after being extracted. A higher EF and RF is favorable of radiotracers. **Table 1** refers to the EF and RF of current traditional PET and SPECT radiotracers for MPI [2, 3]. The listed radiotracers have their own advantages and disadvantages, correlating to various factors such as EF, RF, half-life, etc.

A new PET radiotracer named ^{18}F-Flurpiridaz, as shown in **Figure 2**, has been identified for imaging of coronary artery disease (CAD). This review intends to provide an update on ^{18}F-Flurpiridaz PET in MPI, comparing its effectiveness against traditional tracers.

Background of radiotracers in MPI

^{15}O-water

^{15}O-water is a PET radiotracer and has an extremely high EF, but virtually zero RF [4, 5]. This allows for ^{15}O-water to be a strong radiotracer for myocardial blood flow (MBF)-the rate of blood flow through the heart muscle-since its uptake directly reflects perfusion. Because it is not retained and is diffused freely, ^{15}O-water is less effective for MPI [2, 3, 6]. ^{15}O-water has a short half-life of approximately 2 minutes and requires an on-site cyclotron [2, 7].

^{13}N-ammonia

^{13}N-ammonia is a PET radiotracer requiring an on-site cyclotron and has a relatively high EF and moderate RF,

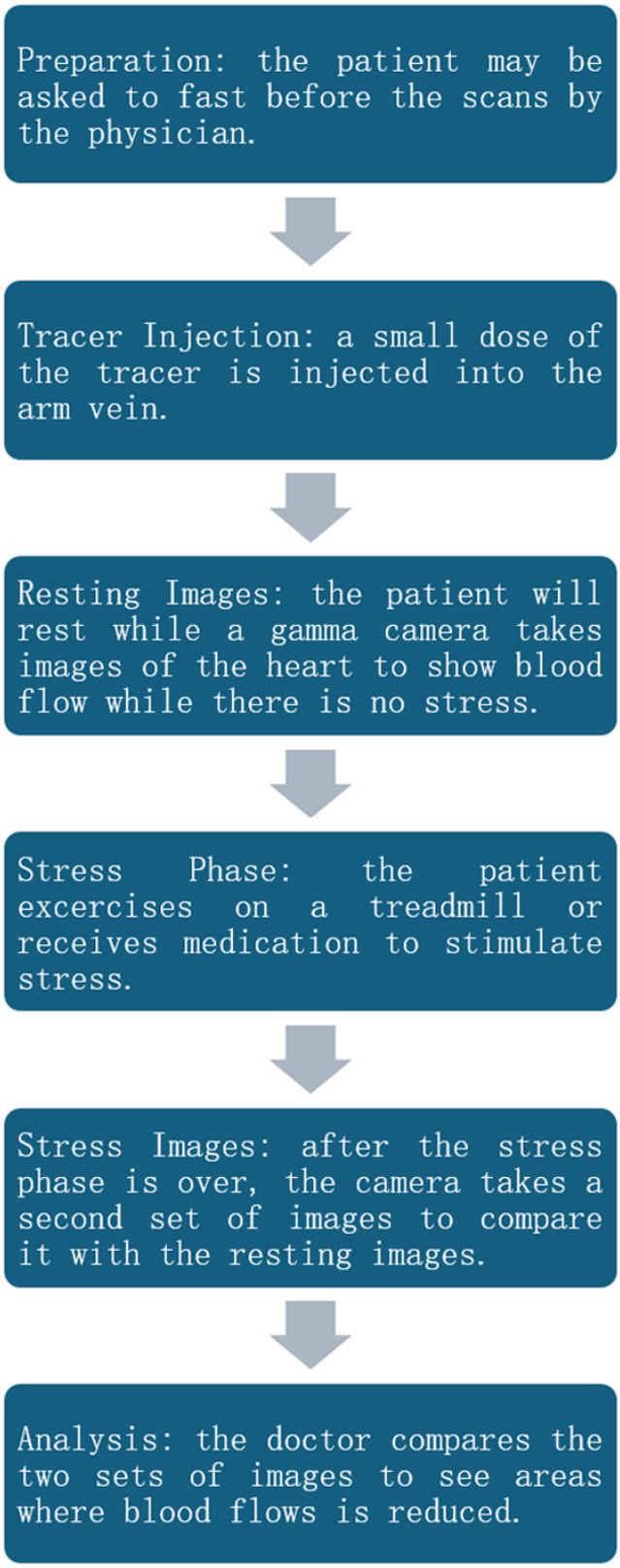
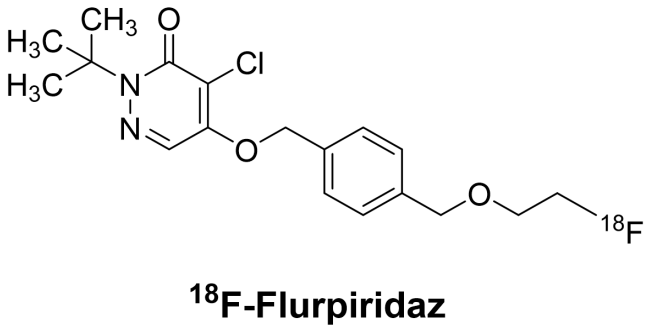


Figure 1. The steps a patient must go through to obtain an MPI, including the resting and stress phases.

making it effective for MPI and MBF [6, 7]. After uptake, ^{13}N-ammonia converts to glutamine within myocardial cells; this leads to partial metabolic trapping and strong

Table 1. Extraction fraction and retention fractions of PET and SPECT radiotracers for myocardial perfusion imaging (MPI)

Radiotracer	Extraction Fraction	Retention Fraction
^{15}O-water (PET)	~1.0	~0.0
^{13}N-ammonia (PET)	~0.95-0.99	~0.5-0.9
^{82}Rb-chloride (PET)	~0.4-0.7	~0.3-0.7
^{99m}Tc-sestamibi (SPECT)	~0.15-0.50	~0.10-0.45



^{18}F-Flurpiridaz

Figure 2. Chemical structure of ^{18}F-Flurpiridaz.

image contrast [7]. ^{13}N-ammonia has been referred to one of the most accurate radiotracers, despite its short half-life of approximately 10 minutes, upon its ability to assist with simultaneous perfusion and flow assessment [2, 7].

^{82}Rb-chloride

^{82}Rb-chloride is a PET radiotracer produced from a generator and enters myocardial cells through the Na^+/K^+-ATPase pump [7]. This radiotracer has a moderate EF and moderate RF but can provide rapid imaging due to its short half-life of around 75 seconds [6]. Since it is not a cyclotron-produced radiotracer, it can be more conveniently used, which has made it more clinically popular.

^{99m}Tc-sestamibi

^{99m}Tc-sestamibi is a SPECT radiotracer with a low EF and low RF [2, 3, 6]. This is a lipophilic and cationic compound that passively diffuses through myocardial and accumulates in the mitochondria. The compound remains trapped here due to the negative transmembrane potential, hence creating for a stronger image contrast and stability over time [2, 8]. The lower extraction limits its ability to quantify MBF precisely, and thus ^{99m}Tc-sestamibi remains as more suitable for MPI. ^{99m}Tc-sestamibi is widely available and has a half-life of around 6 hours [2, 3].

Tracer kinetics

Tracer kinetics is defined as the mathematical study of how a substance (specifically a radiotracer) moves

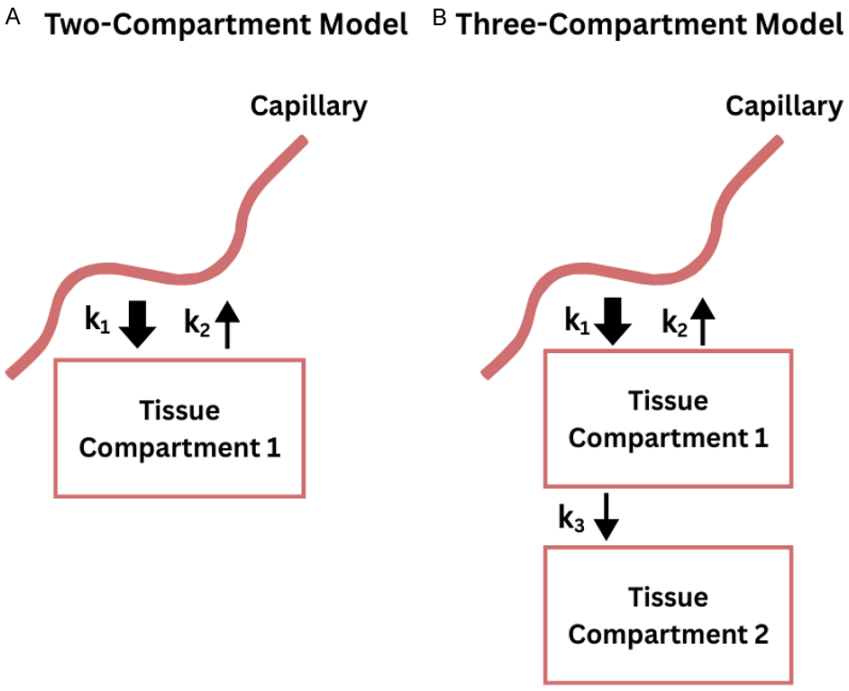


Figure 3. A two-compartmental model on the left (A) and a three-compartmental model on the right (B).

through a biological system over time. In PET MPI, the tracer's kinetic behavior reflects perfusion to the myocardium. PET MBF uses compartmental kinetic models, which simplifies the complex physiology of tracers into distinct "compartments"-each representing a homogenous region where the tracer concentration is uniform. There are two models, known as the two-compartment model and three-compartment model [4].

The two-compartmental model relies on two kinetic parameters, *k1* and *k2*. *k1* (mL/min/g) is the uptake rate constant from blood to tissue and reflects myocardial blood flow multiplied by the extraction fraction. *k2* (1/min) is the washout rate constant from tissue to blood. The three-compartmental model relies on a third kinetic parameter, *k3*. *k3* (1/min) is the metabolic trapping rate constant and represents the rate at which tracer in myocardial tissue becomes irreversibly bound or metabolized [4]. This provides information of intracellular retention. ^{82}Rb-chloride is considered using a two-compartment model, and ^{13}N-ammonia qualifies as either a two- or three-compartment model. ^{15}O-water is a special one-compartment model due to its free diffusion process (very high EF). ^{99m}Tc-sestamibi uses an irreversible one-compartment model, which is a simplified retention model [4]. **Figure 3** shows a visual representation of the two types of compartment models. Tracer kinetic modeling is important because it provides quantitative MBF, enables coronary flow reserve calculations, and improves diagnostic accuracy for multivessel CAD.

New ^{18}F tracers

Development of ^{18}F tracers

The development of ^{18}F tracers has shown promise with a better MPI and MBF efficiency. Among ^{18}F tracers, ^{18}F-Flurpiridaz has shown the greatest improvement across traditional tracers [9].

A defining feature of ^{18}F-Flurpiridaz is that it binds specifically to the mitochondrial complex I (MC-1). The MC-1 is a key protein in the electron transport chain. Unlike the other PET and SPECT tracers which rely on metabolic trapping (^{13}N-ammonia) or cation exchange (^{82}Rb-chloride or ^{99m}Tc-sestamibi), ^{18}F-Flurpiridaz rather binds with high affinity to MC-1 [9-14]. ^{18}F-Flurpiridaz has been clinically tested and has reported a very high EF of 94% with a slow washout rate and high myocardial uptake [9-12, 14-16]. It has a short positron range of around 1.03 mm in water, which has led to a high image quality [9, 10, 12-14]. Coupled with these advantages, ^{18}F-Flurpiridaz also has an acceptable effective dose that is safe to be administered to patients of around 6.3 millisievert (mSv). The long half-life of approximately 109.8 minutes of F-18 also allows ^{18}F-Flurpiridaz for centralized production and unit-dose distribution. This removes the need for an on-site cyclotron [9-11, 13-15]. This benefits patients by allowing them to get images at the peak of their stress phase, too, as detailed in **Figure 1**. As a result, more information is provided of the blood flow with respect to the heart to the physician as they can also assess during the middle of the exercise. ^{18}F-Flurpiridaz was found to also have a higher sensitivity than ^{99m}Tc-sestamibi specifically for detecting 25% stenosis (narrowing or constriction of passageway) [13, 17]. The kinetics of ^{18}F-Flurpiridaz was tested with a study in mice. The *k1* constant was found to be high, which reflects its high extraction. The *k2* constant was low, and this is due to the strong binding to the MC-1. This low *k2* reflects on ^{18}F-Flurpiridaz's high myocardial retention. A two-compartmental model is used for ^{18}F-Flurpiridaz, where in compartment one is the free tracer in blood and interstitial space, and in compartment two is where the tracer is bound to MC-1 [5].

There are also additional ^{18}F tracers such as ^{18}F-fluorobenzyl-triphenyl phosphonium (^{18}F-FBnTP) and ^{18}F-fluorodihydrorotenone (^{18}F-FDHR), but they do not have as promising evidence as ^{18}F-Flurpiridaz yet. Predominant data with respect to these are based on animal studies. **Table 2** lists the existing research on ^{18}F-FBnTP and ^{18}F-FDHR [12, 18, 19].

Table 2. The existing research and limitations of additional ^{18}F tracers

^{18}F Tracer	Existing Research	Limitations
^{18}F-FBnTP	High first-pass extraction fraction and high imaging quality based on animal testing. Potential dual role in assessing both perfusion and cell apoptosis.	Not yet human approved, and still in pre-clinical phases.
^{18}F-FDHR	Shows to be a potential MPI agent.	Not yet advanced and significant human data and follow up data limited.

Ultimately, due to its advantages and improved efficiency of traditional tracers in various aspects, it is very likely for ^{18}F-Flurpiridaz to become a reliable radiotracer for MPI imaging. The evolution from traditional PET and SPECT tracers toward ^{18}F-labeled compounds highlights the ongoing push in nuclear cardiology to combine safety, accuracy, and convenience, potentially transforming how myocardial perfusion is assessed in the future.

Data of ^{18}F-Flurpiridaz with clinical trials

To test the effectiveness of ^{18}F-Flurpiridaz as a novel PET radiotracer, one Phase II and two Phase III clinical trials were conducted. A Phase II clinical trial attempts to determine the effectiveness, safety, and optimal dosing of a drug. It typically involves approximately 100 to 300 patients who have the condition or disease the drug is meant to address. A Phase III clinical trial takes further steps, where there is a larger number of participants for a study, involving several hundred to several thousand patients for whom the drug is intended. Phase III trials provide information that is needed for the labeling of a medicine, intended for the U.S. Food and Drug Administration's (FDA) approval to be used in clinical settings. Once the Phase III is complete, a company can request for the FDA to market the drug [20].

Phase II clinical trial

To further the progress of ^{18}F-Flurpiridaz, a Phase II clinical trial was conducted in 2013. This initial trial enrolled 143 patients from 21 centers and provided a direct comparison between the effectiveness of ^{18}F-Flurpiridaz and ^{99m}Tc-sestamibi [21]. There were notable improvements reported.

Image quality: The stress image quality, which was recorded by three experienced nuclear cardiologists, was reported to be 99.2% for ^{18}F-Flurpiridaz PET and 88.5% for ^{99m}Tc-sestamibi SPECT, respectively. The rest image quality was recorded as 96.9% for ^{18}F-Flurpiridaz PET and 66.4% for ^{99m}Tc-sestamibi SPECT [21], respectively. Statistical analysis demonstrated a highly significant difference between modalities ($P < 0.01$), confirming that ^{18}F-Flurpiridaz provided superior image quality [21].

Sensitivity: Sensitivity describes the ability of the imaging test to correctly identify people who have the disease. The clinical trial also compared the ability to detect CAD between ^{18}F-Flurpiridaz and ^{99m}Tc-sestamibi. The investigators found that ^{18}F-Flurpiridaz PET had achieved a sensitivity of 78.8% and ^{99m}Tc-sestamibi SPECT had achieved a sensitivity of 61.5% [21]. The difference in sensitivity was statistically significant ($P = 0.02$), indicating that 18F-Flurpiridaz more reliably detected CAD [21]. The improved sensitivity was consistent across the readers and attributes to the ^{18}F-Flurpiridaz's higher myocardial EF of 0.94 [9-11, 15]. Overall, this clinical trial also concludes that ^{18}F-Flurpiridaz detects ischemic myocardium more reliable.

Diagnostic certainty: The phase II trial compared the diagnostic certainty between ^{18}F-Flurpiridaz PET and ^{99m}Tc-sestamibi SPECT. Diagnostic certainty is defined as the percentage of scans rated by blind readers as "definitely normal" or "definitely abnormal". This was significantly higher for ^{18}F-Flurpiridaz PET, with 90.8%, compared to ^{99m}Tc-sestamibi SPECT, with 70.9% [21]. A highly significant difference ($P < 0.01$) demonstrated that clinicians could interpret ^{18}F-Flurpiridaz images with greater confidence [21].

Ischemic regions: The trial also indicated that ^{18}F-Flurpiridaz PET showed a greater magnitude of perfusion defects compared to ^{99m}Tc-sestamibi SPECT. This shows that ischemic regions (areas of the body where blood flow and oxygen supply are reduced) were able to be more visually apparent due to the ^{18}F-Flurpiridaz radiotracer [22]. This was recorded using the summed difference scores (SDS), which measures the change in perfusion between stress and rest images [21]. Across all three blinded readers, the mean SDS values were significantly higher for ^{18}F-Flurpiridaz PET, which yielded 8.9 ± 7.98, 9.4 ± 7.51, and 6.8 ± 5.75, than for ^{99m}Tc-sestamibi SPECT, which yielded 4.8 ± 5.61, 5.7 ± 6.51, and 4.1 ± 4.75 ($P = 0.01$-0.02) [21]. ^{18}F-Flurpiridaz's ability to detect larger and more intense areas of reversible ischemia attributes to its high myocardial extraction fraction, excellent spatial resolution, and more accurate attenuation correction.

Safety: The safety of ^{18}F-Flurpiridaz was tested amongst all 132 patients in the study. Overall, 61 patients reported 108 adverse events (AE), which is around 42.7% of the total patients. 8 patients who reported AEs were possibly related to the tracer, but all were mild and resolved spontaneously. Examples of those AEs included transient hypertension, dysgeusia, and mild cough. 2 patients reported 2 serious adverse events (SAE) which were later found as unrelated to the tracer [21].

Table 3. Analysis of different subgroups when comparing effectiveness between ^{18}F-Flurpiridaz PET and ^{99m}Tc-Sestamibi SPECT

Subgroup	Sensitivity (F-18 PET)	Sensitivity (Tc-99m SPECT)	Specificity (F-18 PET)	Specificity (Tc-99m SPECT)	*p*-value	Interpretation
Women (2020)	64.4%	35.6%	N/A	N/A	$P < 0.001$	F-18 PET showed higher sensitivity in women.
Women (2023)	82.9%	65.9%	72.8%	66.0%	$P = 0.0448$ (sensitivity) $P = 0.0091$ (specificity)	F-18 PET is again superior for women, with higher sensitivity and specificity.
BMI ≥ 30 (2020)	72.2%	53.3%	N/A	N/A	$P < 0.001$	F-18 PET retained diagnostic power despite obesity.
BMI ≥ 30 (2023)	76.9%	69.2%	66.9%	61.9%	$P = 0.0641$ (sensitivity) $P = 0.0008$ (specificity)	F-18 PET continued to have a better accuracy overall.
Diabetic (2023)	75.8%	71.4%	61.2%	51.5%	$P = 0.2164$ (sensitivity) $P = 0.0006$ (specificity)	F-18 PET did not show significant difference for sensitivity but did for specificity.
Multivessel CAD (2020)	41.0%	27.5%	N/A	N/A	$P = 0.21$	PET detected larger ischemic burden but not statistically significant.
≥ 70% Stenosis (2023)	92.1%	79.5%	55.5%	56.6%	$P < 0.01$ (sensitivity)	PET remained highly sensitivity for severe CAD, equally for specificity.

Phase III clinical trials

Two phase III clinical trials were conducted to further study the effectiveness of ^{18}F-Flurpiridaz. The first clinical trial results were published in 2020 and enrolled 795 patients in 72 sites across the United States, Canada, and Finland [16]. The second clinical trial results were published in 2023 and enrolled 755 patients in 72 centers across the United States, Canada, and Europe [15]. Notable improvements present in the phase II clinical trial continued to be apparent in the phase III clinical trials. The primary endpoints were sensitivity and specificity in both trials. There were subgroups analyzed, too, such as women and obesity [15, 16].

Sensitivity: The sensitivity in the 2020 trial was reported to be 71.9% for ^{18}F-Flurpiridaz PET and 53.7% for ^{99m}Tc-sestamibi SPECT. A highly significant difference was observed ($P < 0.001$) [16]. For the 2023 study, the sensitivity was 80.3% for ^{18}F-Flurpiridaz PET and 68.7% for ^{99m}Tc-sestamibi SPECT. Again, the difference was significant ($P \approx 0.0003$) [15]. Therefore, ^{18}F-Flurpiridaz having a greater sensitivity is beneficial for clinicians as this means a fewer false negatives, making it less likely to miss the disease.

Specificity: Specificity describes the ability of the imaging test to correctly identify people who do not have the disease. The specificity in the 2020 clinical trial as reported to be 76.2% for ^{18}F-Flurpiridaz PET and 86.6% for ^{99m}Tc-sestamibi SPECT [16]. For the 2023 study, the sensitivity was 80.3% for ^{18}F-Flurpiridaz PET and 68.7% for ^{99m}Tc-sestamibi SPECT. The 2023 differences were statistically significant ($P \approx 0.0004$) [15]. Overall, a higher specificity means fewer false positives, where the test can be less likely to label healthy people as sick. This is valuable for confirming diseases and avoiding unnecessary tests.

Safety: All patients in the 2020 clinical trial were assessed for safety. 70% reported any AE, most of which were related to stress procedures. 7.4% were possibly related to the ^{18}F-Flurpiridaz radioactivity injected and none were serious. 0.5% of AEs were definitely related, which were 2 cases of dysgeusia and 1 injection site pain. There were no cases of SAEs [16]. 604 patients were monitored for safety complaints in the 2023 clinical trial, of which 45.4% of patients (274 of patients) had treatment emergent AEs (TEAEs). 31% of patients had clinically expected TEAEs, such as from flushing from stress. There were 19 patients with 25 events that were possibly related to the radioactivity and none were serious. There was one death but was unrelated to ^{18}F-Flurpiridaz [15]. The mean radiation exposure based on mean effective dose was 6.25 ± 0.74 mSv for ^{18}F-Flurpiridaz PET and 9.86 ± 2.74 mSv for ^{99m}Tc-sestamibi SPECT; the PET dose is approximately 50% lower, leading to a lesser radiation exposure [15].

Additional clinical trial results

Table 3 describes the additional tests conducted on specific individuals (subgroups) to further differentiate the effectiveness between ^{18}F-Flurpiridaz and ^{99m}Tc-sestamibi [15, 16].

Based on the 2013 Phase II and 2020 and 2023 Phase III clinical trials, there is sufficient evidence to prove that ^{18}F-Flurpiridaz PET is superior to ^{99m}Tc-sestamibi SPECT in its radiotracer properties, particularly in its ability to detect CAD. It has shown to have a higher sensitivity and specificity, among numerous other benefits. Based on this clinical data, **Figure 4** displays the unique properties

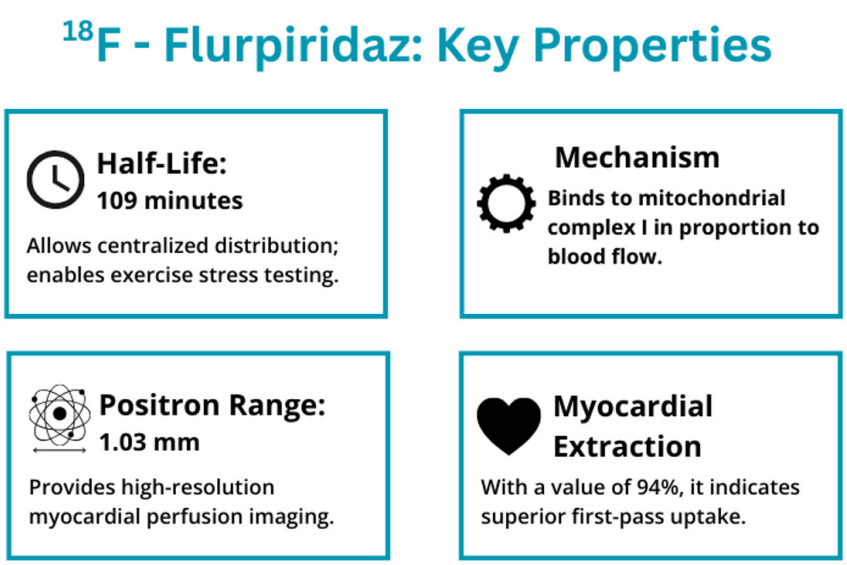


Figure 4. The key properties of ^{18}F-Flurpiridaz against traditional MPI tracers.

of ^{18}F-Flurpiridaz. The next step is to evaluate how ^{18}F-Flurpiridaz PET compares with other traditional PET tracers, to determine whether it offers superior diagnostic performance.

Comparing effectiveness against traditional PET tracers

The phase II and III clinical trials predominately compare ^{18}F-Flurpiridaz (F-18) with ^{99m}Tc-sestamibi (Tc-99m). However, there are more tracers that are being used for MPI, including ^{15}O-water (O-15), ^{13}N-ammonia (N-13), and ^{82}Rb-chloride (Rb-82).

Production and practicality

The half-lives of F-18, O-15, N-13, and Rb-82 are approximately 110 minutes, 2 minutes, 10 minutes, and 75 seconds, respectively [2, 3]. Due to this, O-15 and N-13 require an on-site cyclotron. Therefore, O-15 and N-13 are limited to be used in only highly specialized PET centers. Unlike these two tracers, F-18 does not need an on-site cyclotron and can be shipped from centralized sites, predominately reducing the costs of building and maintaining a cyclotron [23, 24]. Due to this benefit, F-18 has the potential to solve "imaging deserts". The lack of advanced nuclear medicine diagnostic tools and associated radiopharmaceuticals can be solved with the help of F-18, where the ability to ship the radiotracer offers more flexibility. Therefore, the widespread access of F-18 will allow for rural areas around the world to be able to have access to MPI and cardiovascular diagnosing. Rb-82 does not require a cyclotron but is rather a generator-based tracer [25, 26]. This generator is also expensive, with annual costs of approximately $120,000 to $432,000. Rb-82 is widely available in PET-equipped hospitals. Overall, F-18 provides the best logical advantages, where a longer half-life allows for centralized production.

Biological mechanism and target

F-18's MC-1 binding produces high extraction and strong retention, which provides clear contrast and durable imaging windows [2]. It uses a two-compartment model when compared to the traditional tracers [4]. O-15 freely diffuses and uses a one-compartment mode with no primary binding target, accounting for a high EF but virtually zero RF [2]. Rb-82's primary binding target is through intracellular cation exchange and uses the Na^+/K^+ ATPase pump for its uptake mechanism, leading to strong perfusion quantification [2]. However, it also has limited retention and extraction efficiency, reducing image quality and quantification reliability. N-13 diffuses and is metabolically trapped, using glutamine synthesis as its primary binding target [27]. N-13 is relatively equal in terms of EF and image quality compared to F-18, but F-18 prevails to be stronger.

Extraction and retention fraction

Due to F-18 binding to MC-1, it has a very high EF (94%) and high RF (70-80%) [9-15]. Referring to **Table 1**, this proves benefits over O-15's RF (0%) as well as Rb-82's EF (40-70%) and RF (30-70%) [6, 7]. However, F-18 seems to have a slightly less EF than N-13 and within the margin of error of its RF. Despite this, F-18 does have strong EF and RF.

Image quality and resolution

F-18 has a positron range of approximately 1.03 mm [9, 10, 12-14]. The short range allows for an excellent spatial resolution and high-quality and high-contrast image quality. O-15, N-13, and Rb-82 have a positron range of approximately 4.14 mm, 2.5 mm, and 8.6 mm respectively [2]. These lead to lesser image qualities, especially Rb-82 due to its very long positron range. A shorter positron range indicates that the positron travels a smaller distance before it hits an electron and gives off the PET signal. This translates to sharper perfusion delineation and better detection of small perfusion defects. F-18 succeeds in having a greater image quality and resolution.

One of the first few scans taken and published featuring the advantages of F-18 is shown in **Figure 5** [21]. The SPECT scans indicate that there is a possible reversible defect in the basal inferior wall, which means there is abnormality detected. However, with no CAD by invasive coronary angiography (ICA) of the patient, there should

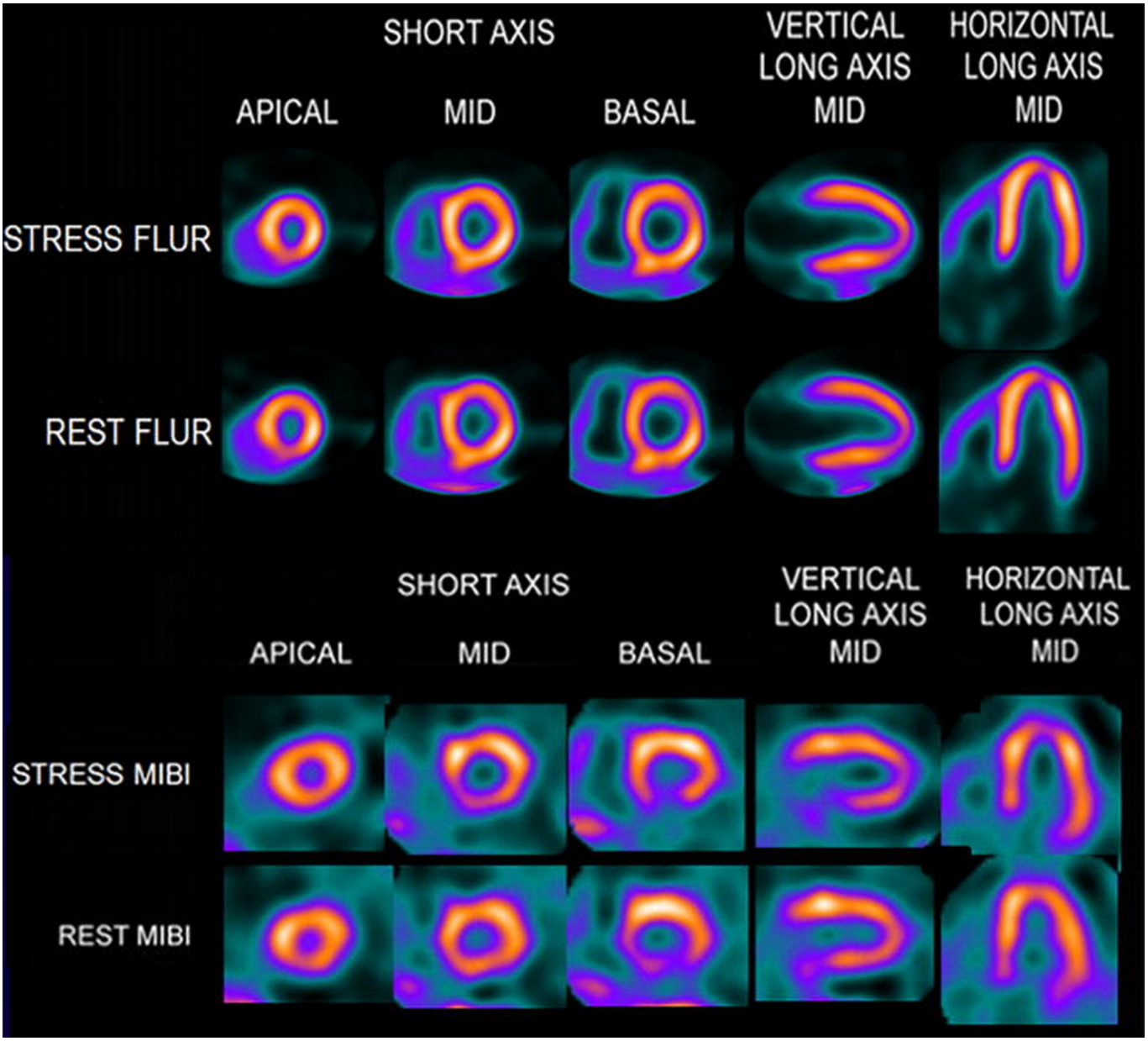


Figure 5. ^{18}F-Flurpiridaz (FLUR) PET (top) and ^{99m}Tc-sestamibi (MIBI) SPECT (bottom) show the scans taken of a 75-year-old male, with a body mass index of 32.6 and no coronary artery disease on invasive coronary angiography. The FLUR images indicate that the scans are normal, while the MIBI scans indicate abnormality (adapted from literature [21]).

Table 4. Radiation dosages between F-18, 0-15, N-13, and Rb-82

Tracer	Typical effective dose (mSv)
F-18	~6.3 mSv
0-15	~1-2 mSv
N-13	~2-3 mSv
Rb-82	~2-3 mSv

be no abnormality. This is shown in the F-18 PET scans, where the scans indicate normality. This indicates how F-18, with its superior image quality, avoids false positives that can otherwise appear with MPI radiotracers like Tc-99m SPECT.

Radiation dose and safety profile

The radiation dosages between the tracers vary, which is an important measure to the amount of radiation exposure to patients. **Table 4** details the radiation doses of the different tracers [16, 27-29]. The mean radiation exposure for 0-15 is approximately 1-2 mSv, 2-3 mSv for N-13, and 2-3 mSv for Rb-82. While other PET tracers have lower radiation exposure, the diagnostic gains of ^{18}F-Flurpiridaz outweigh the increased exposure for specific patient populations, where the safest average dose for a F-18 scan is approximately 6-9 mSv [7]. Therefore, the higher effective dose does not significantly impact the patient.

Figure 6. The supply chain for ^{18}F-Flurpiridaz.

As indicated in **Table 4**, F-18 has a higher radiation dose than traditional PET tracers, but its dose is still acceptable for clinical use given the diagnostic benefits. Compared to SPECT MPI, F-18 has demonstrated a favorable safety profile with excellent tolerability. The radiation exposure was much lower as found by the clinical trials, representing an important consideration for patient safety, particularly those requiring serial imaging studies and SPECT tracers.

Overall comparative summary

In terms of logistical practicality, image resolution, perfusion retention, and overall diagnostic power, F-18 tracer is the stronger tracer. Its properties clearly make it superior for comprehensive MPI. F-18 tracer represents a next-generation PET myocardial perfusion tracer that bridges the gap between the high physiological accuracy of ^{15}O-water and ^{13}N-ammonia and the practical accessibility of ^{82}Rb-chloride.

Limitations

Cost and accessibility

Upfront costs for starting or expanding a cardiac PET program (scanner time, staffing, radiopharmacy operations) and variability in reimbursement create financial barriers [30]. For example, annual Rb-82 generator costs have been reported in the range of $120,000-$432,000, translating into substantial per-scan expense that is highly dependent on study volume and generator utilization efficiency. In contrast, cyclotron-produced ^{18}F-labeled tracers such as ^{18}F-flurpiridaz are distributed in unit doses, and preliminary economic analyses suggest that per-scan tracer costs may be comparable to or potentially lower than generator-based approaches in moderate- to high-volume centers, although definitive real-world pricing data remain limited. Payer coverage and real-world reimbursement practices have been evolving but can differ by region and institution; this complicates broad deployment even when clinical performance is strong [15]. Economic models suggest possible cost offsets from improved diagnostic accuracy and downstream reductions in unnecessary invasive testing, but the overall budget impact remains dependent on local tracer pricing, reimbursement rates, and institutional case volumes [15].

Logistical hurdles

While the ~110-minute half-life of F-18 permits regional distribution-allowing the tracer to be produced at a cyclotron and shipped to imaging centers rather than requiring an on-site cyclotron-real-world implementation will depend on establishing reliable distribution networks similar to those used for ^{18}F-fluorodeoxyglucose (^{18}F-FDG) [10]. Although many production centers already manufacture F-18 oncology tracers, expanding capacity for cardiac PET will require coordinated development of PET manufacturing facilities (PMFs), site-specific regulatory approvals, transport logistics, decay management during transit, and consistent radiochemical yields. For example, company filings note that each PMF must obtain individual FDA approval, and delays in site authorization could affect product rollout timelines [30].

Importantly, while F-18 tracers must be produced in a cyclotron, they do not require an on-site cyclotron. This differentiates ^{18}F-flurpiridaz from short-half-life tracers such as O-15 and N-13, which necessitate on-site production due to rapid radioactive decay. Thanks to its longer half-life, ^{18}F-flurpiridaz can be manufactured at a regional cyclotron and distributed within a practical delivery radius, substantially lowering infrastructure barriers compared with tracers that mandate local cyclotron access. Thus, although production logistics remain complex, the distribution model is far more scalable than that required for true on-site tracers [23].

Overall, the dependence on a cyclotron is less of a "must be on-site" in this case but is still a logistical barrier. The whole supply chain (detailed by **Figure 6**) must be robust and cost-effective for F-18 to reach its full potential.

Need for long-term data

Large, randomized data showing that using ^{18}F-Flurpiridaz to guide management improves hard clinical outcomes (e.g., myocardial infarction, mortality) are limited. Phase II/III diagnostic performance and image-quality data are strong, but longer-term trials directly linking ^{18}F-Flurpiridaz-based strategies to improved patient outcomes or cost-effective care pathways are still emerging. That limits immediate adoption as a standard of care in some guideline frameworks until outcome data accumulate [15].

Future outlook

As mentioned during a discussion of the limitations of ^{18}F-Flurpiridaz, there needs to be long-term data continuing to prove this radiotracer's advantages. Specifically, there were similarities found between ^{18}F-Flurpiridaz and ^{13}N-ammonia, specifically the extraction and retention fractions. In the future, there needs to be a further analy-

sis between these two radioactive tracers to determine which provides better image quality and resolution, among other features.

Major professional societies including the American Society of Nuclear Cardiology (ASNC), Society of Nuclear Medicine and Molecular Imaging (SNMMI), European Association of Nuclear Medicine (EANM), and American College of Nuclear Medicine (ACNM) have jointly issued comprehensive guidance for ^{18}F-Flurpiridaz PET MPI, covering patient selection, imaging protocols, interpretation, and quantification [20]. This coordinated effort aims to standardize clinical practice and ensure optimal implementation as the tracer becomes more widely available. The potential impact of ^{18}F-Flurpiridaz PET extends beyond improved diagnostic accuracy for focal CAD. Its high first-pass extraction fraction and linear uptake across a wide range of myocardial blood flow allows for ^{18}F-Flurpiridaz to be an ideal tracer for precise myocardial blood flow quantification. Unlike Rb-82, which demonstrates a reduced extraction at higher flow rates, ^{18}F-Flurpiridaz maintains high efficiency despite elevated flow states. This enhances its sensitivity for detecting subtle impairments in coronary flow reserve, making it ideal for evaluating conditions characterized by microvascular dysfunction, such as ischemia with no obstructive coronary artery disease (INOCA), heart failure with preserved ejection fraction, and cardiac allograft vasculopathy.

As research continues, the widespread adoption of ^{18}F-Flurpiridaz PET will need to collect more evidence and defeat its limitations. Educational initiatives, training workshops, and the development of streamlined protocols will allow for this, and ultimately expand the role of ^{18}F-Flurpiridaz PET.

Conclusion

^{18}F-Flurpiridaz represents a significant improvement in the field of MPI, proving to hold many advantages over traditional PET and SPECT tracers. Its ability to have properties such as longer half-life or much clearer image quality allows it to be a better option in clinical settings. Robust evidence from multicenter clinical trials consistently demonstrates enhanced sensitivity for CAD detection compared to SPECT, with particular benefits for women, obese patients, and those requiring comprehensive flow quantification.

The recent development of international guidelines and standardization of imaging protocols provides a framework for the appropriate integration of this promising tracer into clinical practice. While challenges related to availability and implementation persist, the unique advantages of ^{18}F-Flurpiridaz position it to expand access to high-quality cardiac PET imaging and transform the evaluation of CAD. As clinical experience grows and new applications emerge, ^{18}F-Flurpiridaz heralds a new frontier in cardiovascular imaging, offering the potential for more precise diagnosis, improved risk stratification, and personalized management for patients with known or suspected CAD.

Disclosure of conflict of interest

None.

Address correspondence to: Shreyas Bulusu and Dr. Qi-Huang Zheng, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 1345 West 16th Street, Room 206, Indianapolis, IN 46202, USA. E-mail: sbulusu125@marian.edu (SB); qzheng@iu.edu (QHZ)

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