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FDA Approval of ^{18}F-Flurpiridaz for PET: Stepping into a New Era of Myocardial Perfusion Imaging?

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Recently, the U.S. Food and Drug Administration (FDA) approved ^{18}F-labeled flurpiridaz as another PET myocardial perfusion imaging (MPI) radiotracer for clinical use in adult patients with known or suspected coronary artery disease (CAD). This decision was based on recent results of a second phase 3 prospective multicenter clinical trial (*1*) and prior trials (*2*,*3*). The FDA approval of ^{18}F-flurpiridaz for PET MPI in patients with known or suspected CAD does not affect existing PET MPI appropriate use criteria (*4*). Recognizing advantages of patient-centered care that may be afforded by ^{18}F-flurpiridaz, the committee on appropriate use criteria has decided to add information on its recent FDA approval in the introduction of the updated document of the Society of Nuclear Medicine and Molecular Imaging (https://snmmi.org/Web/Clinical-Practice/Appropriate-Use-Criteria/Articles/Updated%20Appropriate-Use-Criteria-for-PET-Myocardial-Perfusion-Imaging_2) as follows:

> *"In clinical routine, PET MPI uses clinically validated and established radiotracers, such as ^{13}N-ammonia and ^{82}Rubidium, for the identification of hemodynamically obstructive and diffuse non-obstructive CAD, and/or coronary microvascular disease (CMD). Based on recent results of a second phase 3 prospective multicenter clinical trial (14) and prior trials (15,16), the U.S. Food and Drug Administration (FDA) has approved fluorine-18 (^{18}F) labeled Flurpiridaz, as another PET myocardial perfusion imaging tracer for clinical use in adult patients with known or suspected coronary artery disease (CAD). The physical 110-minute half-life of ^{18}F allows the use of ^{18}F-Flurpiridaz both with exercise and pharmacologic stress (vasodilator and/or dobutamine). In particular, ^{18}F-Flurpiridaz affords the unique advantage that it can be produced as a unit dose from a regional cyclotron and, thus, it can be ordered on an "as needed" basis avoiding the necessity to invest into a ^{82}Rubidium generator, or being dependent on the availability of an onsite cyclotron for ^{13}N-ammonia production; or in centers with such access, ^{18}F-Flurpiridaz could complement their use. The introduction and application of ^{18}F-Flurpiridaz, therefore, will allow a more widespread and flexible clinical use, including medical centers or nuclear laboratories, that perform relatively low volume PET myocardial perfusion studies. Similar to ^{13}N-ammonia and ^{82}Rubidium as myocardial perfusion radiotracers, ^{18}F-Flurpiridaz also allows the concurrent quantification of absolute quantitative myocardial blood flow (MBF) at rest and during hyperemic stress with subsequent derivation of myocardial flow reserve (MFR)."*

Thus, ^{18}F-flurpiridaz further expands the armamentarium of PET MPI radiotracers for clinical application in addition to ^{13}N-ammonia, ^{82}Rubidium, and, in some locations in Europe, ^{15}O-water (*5*). In particular, the comparatively longer half-life of 110 min of ^{18}F-flurpiridaz could afford more widespread clinical use of PET MPI, as it can be transported to more distant regions and ordered on an as needed basis, as it is done routinely with ^{18}F-FDG for oncologic, inflammatory, infectious, or brain PET studies. Conversely, the 110-min half-life of ^{18}F-flurpiridaz may render it unsuitable for same day combined MPI studies with ^{18}F-FDG for assessment of myocardial viability or cardiac inflammation. The FDA approval of ^{18}F-flurpiridaz, however, is expected to accelerate patient-centered clinical applications of PET MPI not only in specialized medical centers but also in facilities of more distant or rural regions. Diagnostic performance of ^{18}F-flurpiridaz PET MPI compares favorably to SPECT MPI for the detection of obstructive CAD. In the recent landmark study, led by Maddahi et al. (*1*), the sensitivity of ^{18}F-flurpiridaz PET was significantly higher than for SPECT (80.3% vs. 68.7%), whereas its specificity was noninferior to SPECT (63.8% vs. 61.7%). Given the substantially higher spatial resolution, image clarity, contrast resolution, and photon attenuation–corrected images of ^{18}F-flurpiridaz PET imaging, one might have expected a higher sensitivity and specificity for ^{18}F-flurpiridaz PET compared with SPECT in the detection of obstructive CAD. The reported results are likely related to the

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comparative study design and specific study population. For example, the lower sensitivity may have been related to the application of cutoff values of 50% for significant stenosis in a study population with a relatively high proportion of patients who had borderline coronary lesions. Another contributing factor to the modestly favorable diagnostic findings of the Maddahi study (*1*) may have been related to the fact that patients with high-risk CAD with more severe CAD were not enrolled because of concerns of patient safety related to performing a second stress test or delaying coronary angiography. Another critical factor impacting the reported specificity may be image interpretation by independent, masked readers rather than consensus interpretations commonly used in clinical practice and in many published retrospective studies (*1*,*6*). The reported specificity likely was impacted by using a less than 50% coronary stenosis rather than patients with a low pretest likelihood of CAD. Some false-positive PET findings were related to the high resolution of ^{18}F-flurpiridaz, rendering it more sensitive to mild flow-limiting downstream effects of diffuse mild-to-moderate CAD, patient motion, respiratory motion, and emission-transmission misregistration. Given these factors impacting the diagnostic accuracy of ^{18}F-flurpiridaz PET MPI in the detection of CAD, further well-designed clinical investigations are needed. Notably, in contrast to ^{82}Rubidium with the 75-s physical half-life, the 110-min physical half-life of ^{18}F also affords the application of ^{18}F-flurpiridaz with exercise stress as a physiologic stimulus, but at the expense of losing myocardial flow reserve (MFR) quantification. This limitation is due to the necessity to acquire a dynamic imaging scan with the concurrent injection of the radiotracer to acquire appropriate arterial input function and myocardial uptake curves needed for the quantification of myocardial blood flow (MBF) in mL/min/g and corresponding MFR (=stress MBF/rest MBF). Conversely, a viable option may be seen in performing supine bicycle exercise stress, in which the patient is already lying in the PET scanner (*7*). This feasibility and precision of this approach to quantify MBF and MFR using ^{15}O-water and PET imaging has been reported to be similar to the use of adenosine stress. Using supine exercise stress, however, is challenging in its performance; it may only allow a mean workload of 130 W, or 70% of the predicted value for upright bicycle exercise, and is likely to introduce substantial patient and respiratory motion artifacts impacting quantification of MBF. These factors may also explain why such an interesting and elegant approach with physiologic exercise stress did not find a more widespread clinical application. Given comparable diagnostic accuracies among established clinical radiotracers (^{13}N-ammonia and ^{82}Rubidium), and potentially ^{18}F-flurpiridaz using PET in the detection and characterization of CAD, the selection of radiotracer in daily clinical routine will depend on the patient volume, available logistics, and cost considerations. For example, centers with relatively higher patient volumes likely will prefer ^{82}Rubidium given its short physical half-life of 75 s, whereas others with lower volumes may give preference to ^{13}N-ammonia, given the availability of an onsite cyclotron, or ^{18}F-flurpiridaz without an available onsite cyclotron. Conceptually, ^{18}F-flurpiridaz could also help to decompress the ^{13}N-ammonia production, as many onsite cyclotrons may also have a demand for other noncardiac PET radiotracers. From the clinical perspective, further investigations are needed to assess the hypothesis that the diagnostic and prognostic value of ^{18}F-flurpiridaz and PET-determined MFR will be enhanced by its near linear myocardial extraction to better detect prognostically important lower-grade stenoses or mild-to-moderate diffuse coronary plaque, the sites of greater plaque rupture and myocardial infarction, missed by relative MPI alone (*8*,*9*). Notably, as competitive modalities offer similar nonexercise approaches to stress testing, a reinvigoration of the value of functional data combined with segmental perfusion information should be an important aim of clinical testing with ^{18}F-flurpiridaz.

Taken together, the FDA approval of ^{18}F-flurpiridaz as a PET MPI radiotracer with its high image quality, near linear extraction, and the 110-min physical half-life of ^{18}F may potentially set a new landmark by enabling a widespread and routine use of PET MPI in clinical practice. Although the diagnostic accuracy of ^{18}F-flurpiridaz PET imaging in the detection and characterization of CAD or coronary microvascular dysfunction needs further investigations in more clinically relevant study populations, its introduction to clinical application holds promise to establish a new era in the field of PET MPI.

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