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**Angaben zur Veröffentlichung / Publication details:**

Higuchi, Takahiro, Xinyu Chen, Sophie C. Siegmund, Konrad Klimek, Daniel Gröner, Steven P. Rowe, Michael Fischereder, and Rudolf A. Werner. 2025. "Recent advances and future trends of[18F]-labeled PET agents for renal imaging." Seminars in Nuclear Medicine. https://doi.org/10.1053/j.semnuclmed.2025.09.008.

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# Recent Advances and Future Trends of [$^{18}$F]-Labeled PET Agents for Renal Imaging

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**Recent years have seen substantial advancements in renal positron emission tomography (PET) imaging. Targets for PET imaging include, but are not limited to, angiotensin receptors, norepinephrine transporters, and sodium-glucose cotransporters. All of those novel radiotracers inherit advantages of F18 radiochemistry, thereby allowing for higher clinical throughput or potentially increased diagnostic accuracy. The potential of such novel F18-labeled agents to yield imaging biomarkers, and their potential role for future renal molecular imaging, will be presented in the following article.**



## Introduction

Various novel radiotracers for renal radionuclide imaging have been developed that go beyond assessments of renal function and more deeply probe the underlying kidney physiology and pathophysiology.[1] Although overall renal functional imaging remains highly relevant and can be evaluated with PET radiotracers, target-specific agents that allow for interrogation of varying target distributions of the renal parenchyma, including angiotensin type I receptor (AT1R), norepinephrine transporters (NET), and sodium-glucose (co) transporters (SGLT),[2-4] may be of increasing importance in the future. Those targets have also been exploited in recent major clinical trials focusing on (cardio)renal protection. For instance, the EMPA-KIDNEY trial reported on lower rates of cardiovascular-related death or slower progression of chronic kidney disease (CKD) in a group of patients treated with SGLT-inhibitors relative to placebo.[5] Of note, SGLT-targeted PET agents can quantify SGLT activity *in vivo*,[4] thereby paving the way for improved risk stratification that goes beyond established conventional risk assessment tools, such as Thrombolysis In Myocardial Infarction (TIMI) Risk Score.[6] In that regard, read-out of the target is not part of current risk assessments and that gap may be addressed by novel SGLT-directed PET radiotracers and associated biomarkers,[4] which may then improve therapeutic efficacy based on an image-based assessment of retention capacities.

Of note, radiotracers developed to bind to those targets also leverage advantages of fluorine-18 (F-18, $^{18}$F) radiochemistry, in particular due to their long physical half-lives of 110 min.[7] Further, with the use of radiofluorinated agents, molecular imaging specialists benefit from an improved spatiotemporal resolution, higher flexibility in clinical scheduling, or delivery from radiopharmaceutical production sites to distant hospitals without access to a cyclotron.[7] In the present review, we will report on those $^{18}$F-labeled radiotracers targeting varying

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Funding: Funding by the German Research Council (DFG grants RAW, TH, 507803309; 424778381, TH). Partially supported by the Okayama University RECTOR Program and a KAKENHI Grant (TH, 23K24288) from the Japan Society for the Promotion of Science (JSPS).
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https://doi.org/10.1053/j.semnuclmed.2025.09.008

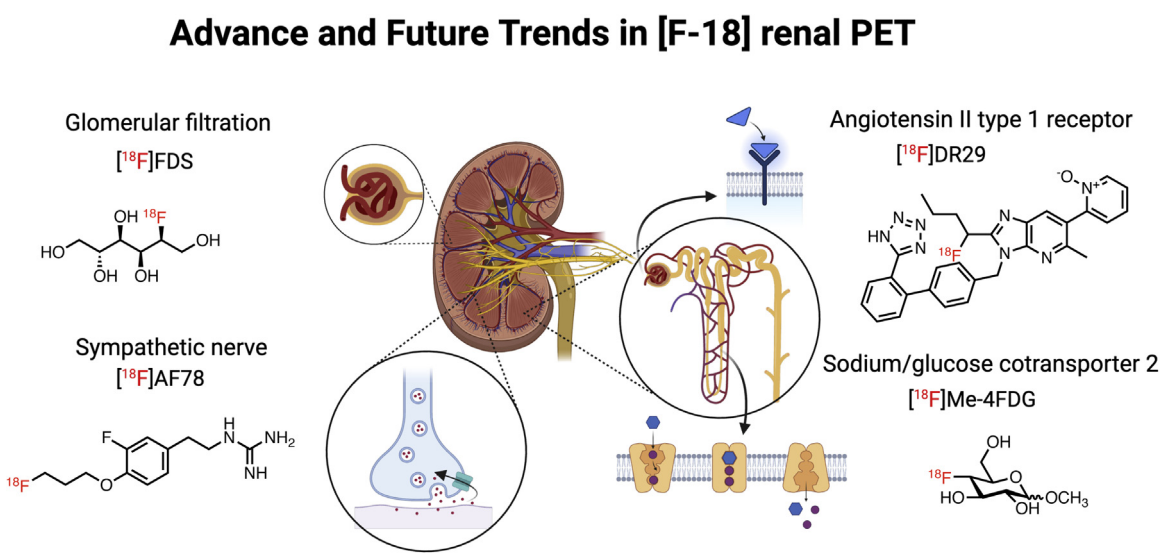


**Figure 1** Overview of recently developed 18F-labeled PET radiotracers for assessing renal pathophysiological pillars. alpha-methyl-4-deoxy-4-[$^{18}$F]-fluoro-D-glucopyranoside ([$^{18}$F]Me-4FDG), 2-deoxy-2-[$^{18}$F]-fluoro-D-sorbitol ([$^{18}$F]FDS). Created with biorender.com.

pathophysiological pillars in the kidney, including AT1R, NET, and SGLT. Novel PET agents assessing renal function will also be briefly discussed (Figs. 1 and 2).

## Functional Renal Assessment

Glomerular filtration rate can be assessed using 2-deoxy-2-[$^{18}$F]-fluoro-D-sorbitol ([$^{18}$F]FDS), which can be easily synthesized by isomerization of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose ([$^{18}$F]FDG).[8] That simplified process requires minimal specialized knowledge or technique, making [$^{18}$F]FDS accessible at nearly every PET center. That accessibility allows a relevant number of scans on a daily basis. In addition, it is freely filtered at the glomerulus, rendering this PET agent as a promising substitute for the renal scintigraphy radiotracer [$^{99m}$Tc]diethylenetriaminepentaacetic acid ([$^{99m}$Tc]DTPA).[8] [$^{18}$F]FDS has already provided excellent imaging properties including normal renograms to determine split renal function in healthy rats, with tissue counting providing similar activities relative to [$^{99m}$Tc]DTPA.[8] In rats with impaired kidney function (unilateral obstruction model, acute renal failure), [$^{18}$F]FDS revealed expected time-activity curves (TAC; obstructed and renal failure renograms).[9] In healthy kidney patients, TAC of the medulla and pelvis activity showed respective transit through the renal parenchyma, thereby offering the potential to perform localized evaluations of specific areas of interest in a single kidney or split renal function of both kidneys (Fig. 3).[10] To date, further evaluation of [$^{18}$F]FDS in larger clinical trials are still lacking.

## AT1R-Directed Renal Molecular Imaging

Crucially involved in vasoconstriction, the renin-angiotensin system has been exploited for varying cardiovascular and renal targeted reparative interventions by the use of angiotensin-converting enzyme inhibitors or AT1R inhibition.[11] Refined dosing, however, may further improve cardiorenal outcome[11] and thus, *in vivo* quantification of the receptor capacities may address this unmet clinical need. Among others, the AT1R-targeting agent [$^{11}$C]KR31173 has already been investigated in pigs with renal artery stenosis, but the short physical half-life of 20 minutes renders this compound impractical for clinical use outside of specialized centers with cyclotron and radiochemistry facilities.[12] Based on the known potent AT1R antagonist SK-1080, the novel PET agent [$^{18}$F]DR29 has recently been investigated. It leverages the advantages of $^{18}$F radiochemistry, shows optimal radiolabeling yield, and is readily translatable to automated radiosynthesis for clinical application.[2] In healthy rats, candesartan (an AT1R inhibitor) led to a relevant reduction of renal uptake. Of note, inhibition of interfering liver and kidney uptake by blockage of organic anion transporting polypeptides and organic anion transporters improved renal contrast, highlighting the complexity of achieving high diagnostic accuracy for assessing renal AT1R read-out (Fig. 4). In hypertensive rats, renal uptake was substantially higher relative to normotensive animals[2] and thus, potential clinical applications could be anticipated, e.g., in hypertension. Other $^{18}$F-labeled compounds targeting AT1R include a derivative of the AT1R blocker losartan ([$^{18}$F]FPyKYNE-losartan) and valsartan-based compounds (eg, [$^{18}$F]FV45), which have also been applied to rats and provided high affinity to the target in the kidneys.[13,14]

## NET-Directed Renal Molecular Imaging

Primarily developed to identify cardiac innervation, NET-directed radiotracers which evaluate NE clearance from the synaptic cleft of cardiomyocytes, have been applied to patients with arrhythmia and heart failure (HF).[15-17] The most commonly used radiotracer applied to determine NET capacities is the single-photon emission compound [$^{123}$I]-*meta*-iodobenzylguanidine ([$^{123}$I]MIBG). Missing cardiac

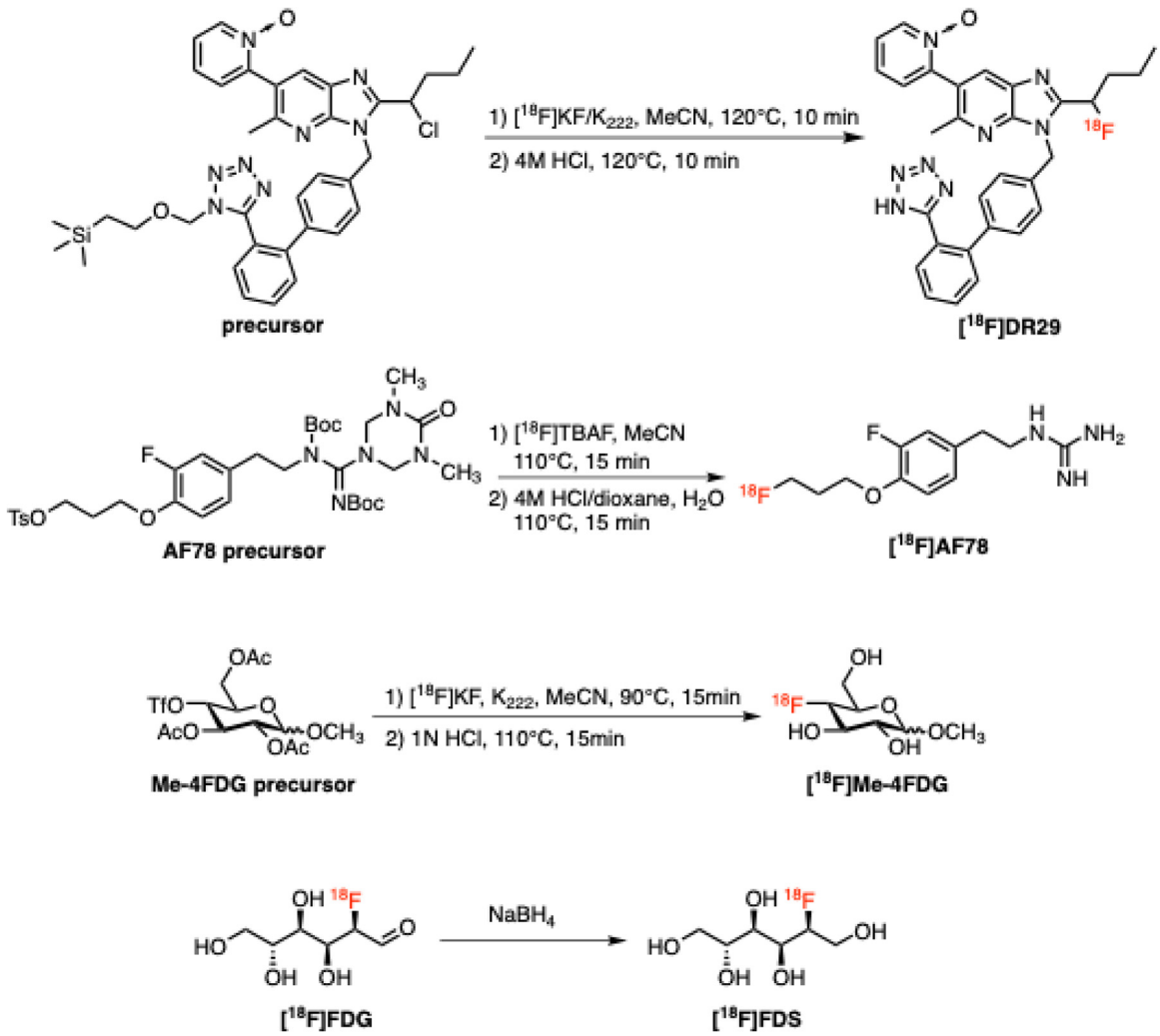


**Figure 2** Synthesis and radiochemical structures of the herein presented $^{18}$F-labeled radiotracers for renal PET imaging. The figure illustrates the radiosynthesis of key tracers employed in renal PET imaging. [$^{18}$F]DR29, an angiotensin II type 1 receptor (AT1R)-targeting tracer, is synthesized by nucleophilic substitution with [$^{18}$F]KF/$K_{222}$ followed by acidic hydrolysis. [$^{18}$F]AF78(F), a norepinephrine transporter tracer, is produced via radiofluorination of a protected precursor under tBuOH/MeCN conditions, with subsequent acidic deprotection. [$^{18}$F]Me-4FDG, a glucose analogue, is obtained from a peracetylated precursor through nucleophilic substitution and deprotection. [$^{18}$F]FDS, a sorbitol analogue, is generated by reducing [$^{18}$F]FDG with sodium borohydride. Collectively, these tracers highlight diverse 18F-labeling strategies that expand the molecular imaging toolbox for investigating renal physiology and disease. alpha-methyl-4-deoxy-4-[$^{18}$F]-fluoro-D-glucopyranoside ([$^{18}$F]Me-4FDG), 2-deoxy-2-[$^{18}$F]-fluoro-D-sorbitol ([$^{18}$F]FDS).

uptake reflects impaired NE clearance and those findings have been tied to increased risk of fatal cardiac events in HF during short- and long-term follow-up.[16,17]

Renal sympathetic overactivity has long been implicated in the pathophysiology of hypertension, CKD, and cardiorenal syndrome. Therapeutic interventions such as renal sympathetic denervation (RDN) have therefore been investigated as a strategy to reduce sympathetic drive. However, clinical data have been rather discouraging. In the IMPROVE-HF-I trial, patients with HF and reduced ejection fraction (HFrEF) randomized to RDN versus optimal medical therapy showed no significant change in cardiac [$^{123}$I]MIBG uptake at 6 months (late HMR: −0.02 in both groups, washout rate change +2.34% vs. −2.59%, $P = .09$), despite the procedure being safe.[18] Similarly, in vasospastic angina, RDN improved angina symptoms and quality of life, but again, no significant changes were observed in cardiac [$^{123}$I]MIBG indices (late HMR: 2.56 vs. 2.36, $P = .22$; washout rate unchanged).[19] Those studies suggest that while sympathetic modulation may hold therapeutic potential, the ability to identify appropriate patient populations and monitor the completeness of denervation remains rather limited.

A central issue is that current monitoring strategies often rely on cardiac imaging as a surrogate. Yet, the kidney itself is the origin of sympathetic hyperactivation in many conditions, including CKD.[20] Takamura et al.[21] directly investigated renal [$^{123}$I]MIBG imaging in primary hypertension and showed that renal washout rate (WR) correlated strongly with muscle sympathetic nerve activity (MSNA, $r = 0.68$, $P < .001$), whereas the cardiac WR correlation was weaker

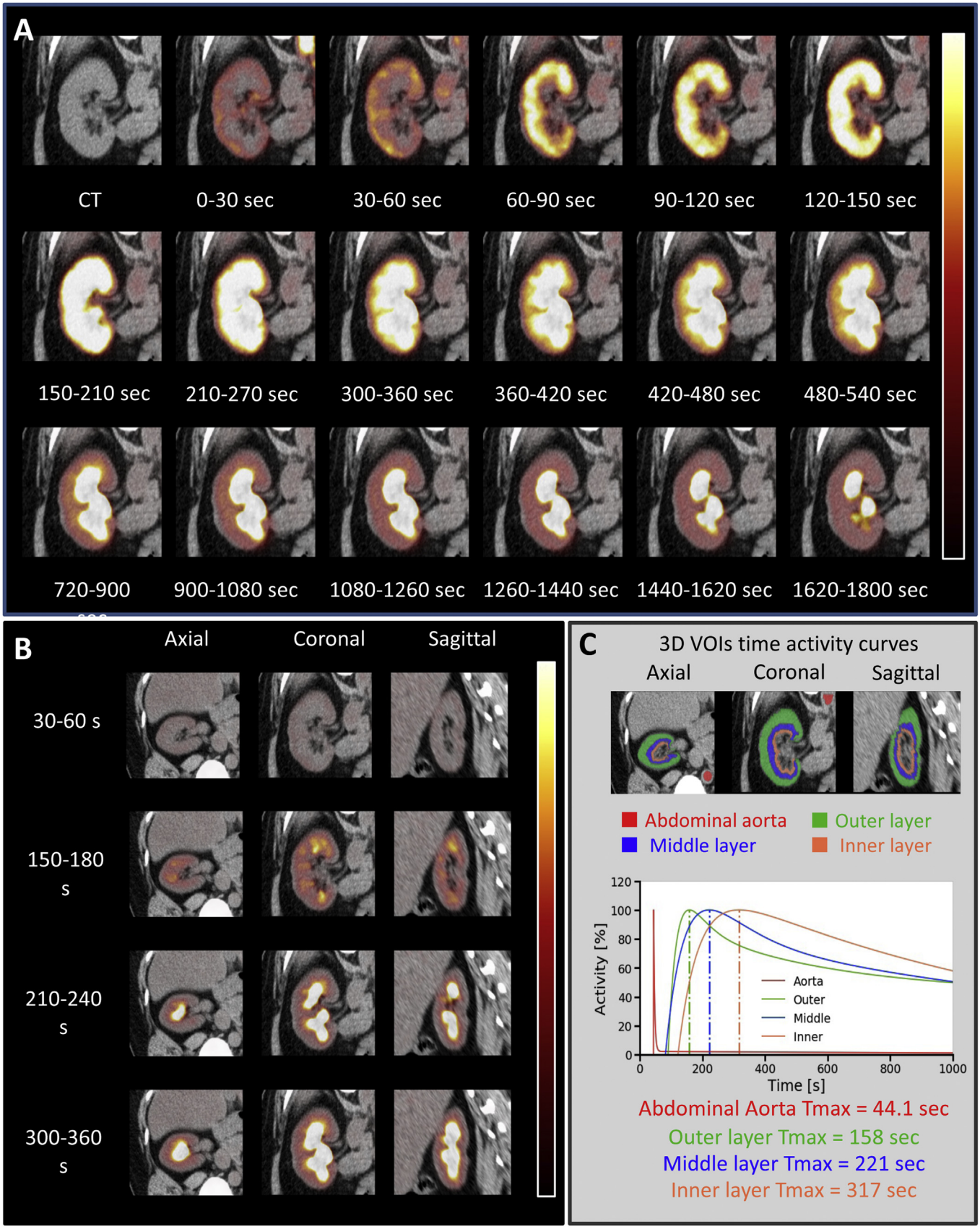


**Figure 3** [$^{18}$F]FDS PET/CT imaging in volunteer (right kidney). As indicated by (A) coronal and (B) axial, coronal, and sagittal views, [$^{18}$F]FDS first accumulated in the renal cortex and was then excreted via the pelvis. (C) Volumes of Interest (VOIs) included the outer layer (i.e., cortex, green), the middle (blue) and inner portion (orange), i.e., the medulla. Respective time-activity curves showed a rapid transit trough the kidneys, as indicated by the different layers. Reproduced from *Werner* et al., Novel Functional Renal PET Imaging With 18F-FDS in Human Subjects. Clin Nucl Med. 2019;44(5):410-1 (10). Published by Wolters Kluwer Health, Inc. Licensed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

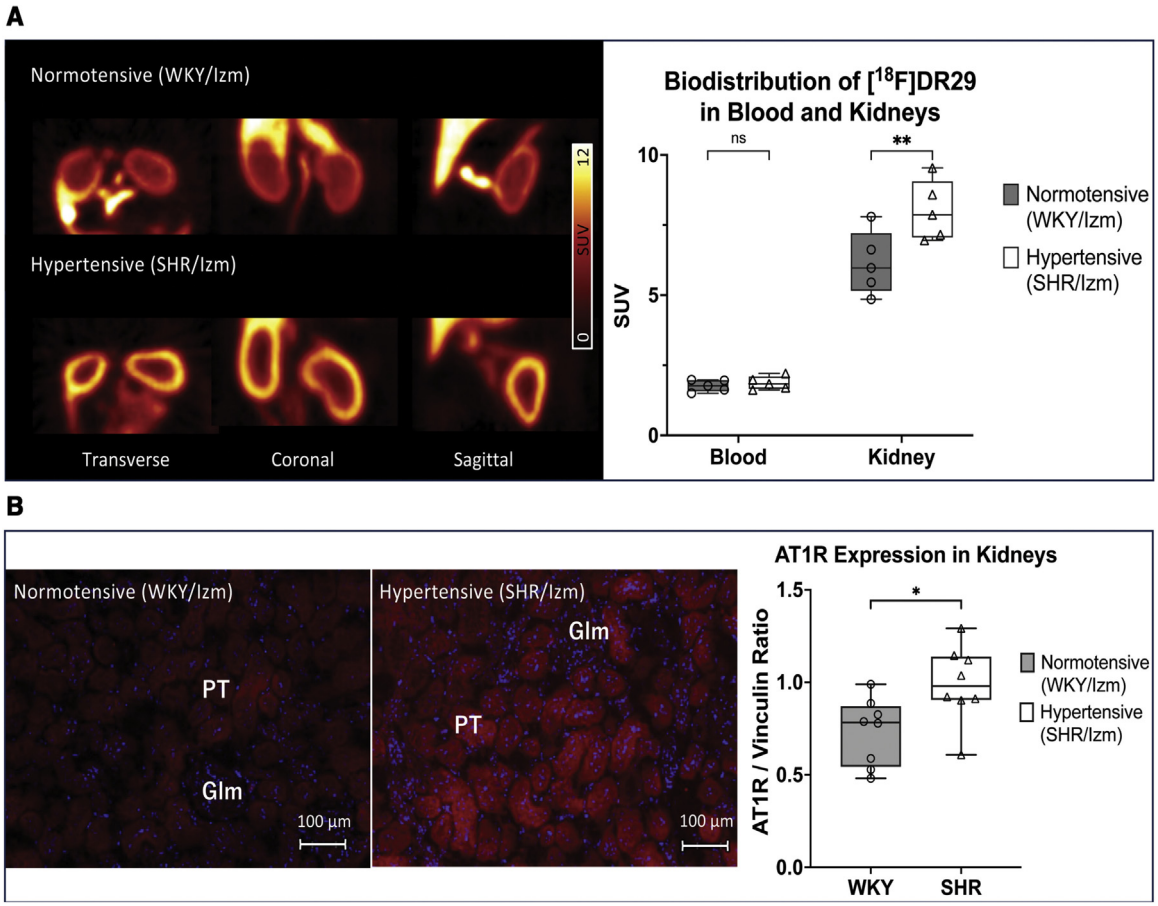


**Figure 4** Angiotensin II type 1 receptors (AT1R)-directed PET using [$^{18}$F]DR29 in a hypertensive rat model in an in- and ex-vivo setting. (A) AT1R-targeting radiotracer [$^{18}$F]DR29 applied to normotensive (WKY/Izm, upper rows) vs hypertensive rats (SHR/Izm, lower rows), with the latter animals exhibiting increased radiotracer accumulation in the kidneys (*left*). This was also corroborated quantitatively, along with significantly higher uptake relative to the blood pool (*right*). (B) Immunohistochemical staining of AT1R expression in kidneys of both animal models, indicating upregulation of the AT1R in SHR/Izm rats as revealed by fluorescent intensity (*left*). AT1R protein levels (assessed by Western Blot), determined by a ratio using Vinculin as a standard, also showed significant increase of AT1R expression in hypertensive rats (*right*). Reproduced from *Chen* et al. (2), Redefining AT1 Receptor PET Imaging: Introducing the Radiotracer [$^{18}$F]DR29. Hypertension. 2025 Aug 8 doi: 10.1161/HYPERTENSIONAHA.124.24441. Licensed under CC BY-NC-ND 4.0 https://creativecommons.org/licenses/by-nc-nd/4.0/

(r = 0.45, $P$ = .0035). Moreover, renal WR values were substantially higher than cardiac WR (43.2% vs. 25.8%, $P$ < .001), which suggests that the kidney may exhibit more pronounced sympathetic turnover detectable by imaging and indicates that sympathetic innervation of the kidneys can be assessed non-invasively.[21] Nevertheless, that imaging approach comes with multiple drawbacks, including high renal clearance, potential off-target uptake by organic cation transporters (OCT), and interference from antihypertensive medications.[16,22,23] In addition, [$^{123}$I]MIBG-derived planar scintigraphy has inherent difficulties in reliably assessing renal uptake due to overlapping activity from surrounding organs, while single-photon emission computed tomography (SPECT) suffers from limited quantitative accuracy, further restricting its utility for precise evaluation of renal sympathetic innervation.[24,25]

Those unmet needs create a rationale for developing next-generation PET radiotracers with improved specificity. Using *in vitro* cell assays, the NET-targeting compound [$^{18}$F]AF78 has markedly reduced renal OCT-mediated accumulation compared to earlier NET radiotracers (based on preclinical and unpublished data), while maintaining high affinity and specificity for sympathetic nerve terminals.[3,14,26] Importantly, [$^{18}$F]AF78 is now undergoing clinical translation in a first-in-human Phase I trial in Japan (jRCTs051250025, AF78-P1), enrolling healthy volunteers and designed to evaluate safety, biodistribution, and dosimetry. That trial will provide crucial insights into whether [$^{18}$F]AF78 can offer reliable quantification of sympathetic activity in humans, potentially extending beyond the heart to directly image the kidney.[27]

## SGLT2-Directed Renal Molecular Imaging

Beyond cardiovascular benefit in diabetes type 2 patients, SGLT inhibition also exerted reno-protective effects by

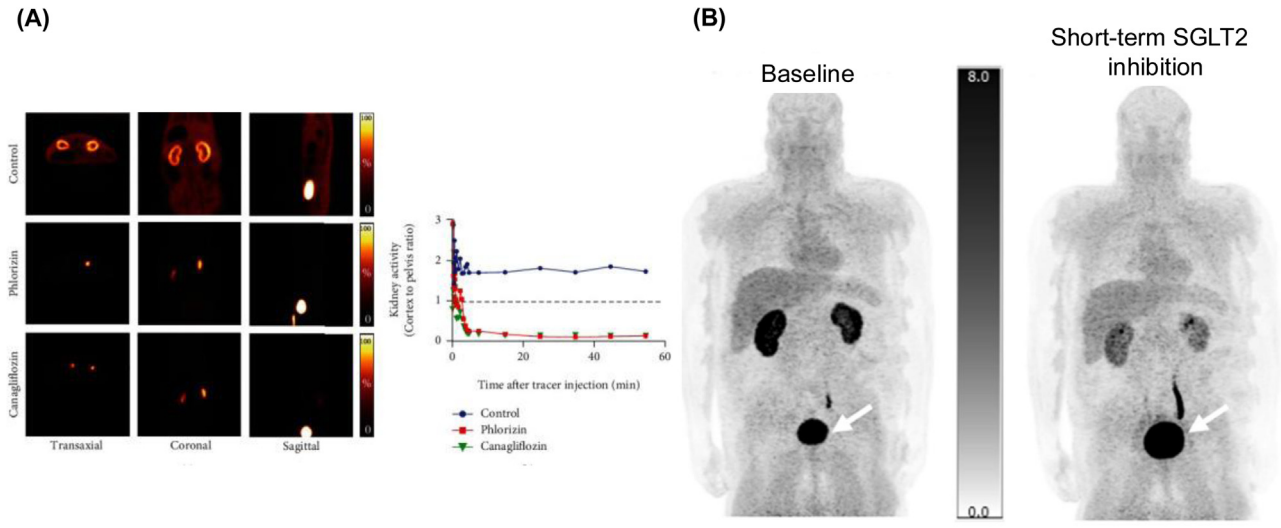


**Figure 5** Renal sodium glucose cotransporter (SGLT)-targeting [$^{18}$F]Me-4FDG PET in a translational setting. Uptake in the kidneys was increased in controls (upper row), while in SGLT-inhibited animals (middle and lower rows), radiotracer accumulation was by far lower relative to the pelvis and bladder (*left*). Those findings were also corroborated by time-activity curves, with cortex-to-pelvis ratios revealing lower [$^{18}$F]Me-4FDG uptake in kidneys in SGLT-inhibited rats (using phlorizin and canagliflozin, *right*). Reproduced from *Matsusaka* et al. (30), Vivo Functional Assessment of Sodium-Glucose Cotransporters (SGLTs) Using [$^{18}$F]Me4FDG PET in Rats. Mol Imaging. 2022;2022:4635171. Licensed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

delaying the onset of CKD.[28] The EMPA-KIDNEY trial reported on a delayed progression of CKD or lower rates of cardiovascular-related death in the empagliflozin group relative to placebo.[5] That is in line with findings of the previously published DAPA-CKD trial reporting on a significant reduction of renal or cardiovascular death in CKD patients with or without diabetes treated with dapagliflozin[29] The recently introduced PET radiotracer alpha-methyl-4-deoxy-4-[$^{18}$F]fluoro-D-glucopyranoside ([$^{18}$F]Me-4FDG) allows for precise assessment of SGLT activity, as it is taken up by SGLT but not glucose transporters (unlike [$^{18}$F]FDG).[30] The easy labeling process for [$^{18}$F]Me-4FDG, which avoids extensive purification steps and uses a simple two-step synthesis, is similar to the well-established automated production of [$^{18}$F]FDG.[30] [$^{18}$F]Me-4FDG has already been evaluated in a preclinical scenario. After SGLT inhibition in rats, reabsorption of the radiotracer in the renal cortex was substantially reduced relative to untreated controls, thereby confirming high specificity of [$^{18}$F]Me-4FDG for imaging SGLT in the kidneys (Fig. 5).[30] Of note, this radiotracer has also been applied to humans in a translational setting. In a dosimetry study, effective dose was low ($0.013 \pm 0.003$ mSv/MBq).[31] Moreover, a recent prospective study enrolling type 2 diabetes subjects scheduled for [$^{18}$F]Me-4FDG PET at baseline and two weeks after SGLT2 inhibition revealed enhanced renal excretion of the PET agent and urine glucose, while only [$^{18}$F]Me-4FDG provided robust predictive potential for HbA1c response to SGLT2 inhibition.[32] As such, future studies may also investigate whether [$^{18}$F]Me-4FDG provides improved glycemic control by employing image-based therapeutic guidance.[30] For instance, SGLT inhibition could then be initiated based pretherapeutic PET studies or drug doses could be optimized based on the PET signal strength.[1]

## Conclusions

Multiple novel radiotracers for renal radionuclide imaging have recently been introduced, including PET agents targeting AT1R ([$^{18}$F]DR29), NET ([$^{18}$F]AF78), or SGLT ([$^{18}$F]Me-4FDG). Further developments include introduction of PET agents assessing GFR, along with split renal function ([$^{18}$F]FDS). All of those radiotracers inherit advantages of F-18 radiochemistry, which allows for high clinical throughput and potentially improved diagnostic read-out. Of note, recent major clinical trials applying SGLT inhibiting drugs have reported on an improved outcome on both renal and cardiovascular endpoints. Thus, future studies may apply those novel radiotracers in a cardiorenal theranostic setting, e.g., by dosage optimization based on PET signal strength or to determine high-risk individuals prior to therapy onset. Further, with the combined information from multiple radiotracers, it may be possible to leverage artificial intelligence/machine learning to maximize the development of predictive biomarkers.

## Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the author(s) used Google-Assisted AI for language editing and research. After using this tool/service, the authors reviewed and edited the content

as needed and takes full responsibility for the content of the publication.

## Declaration of competing interest

RAW has received speaker honoraria from Novartis/AAA and PentixaPharm and reports advisory board work for Novartis/AAA and Bayer. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Takahiro Higuchi:** Conceptualization, Funding acquisition, Supervision, Validation, Visualization, Writing – review & editing. **Xinyu Chen:** Visualization, Writing – original draft. **Sophie C. Siegmund:** Writing – review & editing. **Konrad Klimek:** Writing – review & editing. **Daniel Gröner:** Writing – review & editing. **Steven P. Rowe:** Writing – review & editing. **Michael Fischereder:** Writing – review & editing. **Rudolf A. Werner:** Conceptualization, Project administration, Supervision, Writing – original draft.

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