$^{64}$Cu-DOTATATE for non-invasive assessment of atherosclerosis in large arteries and its correlation with risk factors: head-to-head comparison with $^{68}$Ga-DOTATOC in 60 patients

Running title: $^{64}$Cu-DOTATATE and Atherosclerosis

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Abstract

**Background:** The somatostatin receptor subtype 2 (SSTR2) is expressed on macrophages, an abundant cell type in the atherosclerotic plaque. Visualization of SSTR2, for oncological purposes, is frequently made using the 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA)-derived somatostatin analogues DOTA-Tyr3-octreotide (DOTATOC) or DOTA-Tyr3-octreotate (DOTATATE) for positron emission tomography (PET). We aimed to compare the uptake of the PET-tracers $^{68}$Ga-DOTATOC and $^{64}$Cu-DOTATATE in large arteries, in assessment of atherosclerosis by non-invasive imaging technique, combining PET and CT. Further, the correlation of uptake and cardiovascular risk factors was investigated.

**Methods:** Sixty consecutive patients with neuroendocrine tumors underwent both $^{68}$Ga-DOTATOC and $^{64}$Cu-DOTATATE PET/CT-scans, in random order. For each scan, the maximum and mean standardized uptake values (SUV) were calculated in five arterial segments, respectively. In addition, blood-pool corrected target-to-background ratio (TBR) was calculated. Uptake of the tracers was correlated with cardiovascular risk factors collected from medical records.

**Results:** We found detectable uptake of both tracers in all arterial segments studied. Uptake of $^{64}$Cu-DOTATATE was significantly higher than $^{68}$Ga-DOTATOC in the vascular regions both when calculated as maximum and mean uptake. There was a significant association between Framingham risk score and the overall maximum uptake of $^{64}$Cu-DOTATATE using SUV ($r=0.4; p=0.004$) as well as TBR ($r=0.3; p=0.04$), while no
association was found with $^{68}$Ga-DOTATOC. The association of Framingham risk score and maximum SUV of $^{64}$Cu-DOTATATE was found driven by BMI, smoking and diabetes ($p<0.001$, $p=0.032$, $p=0.025$, respectively).

Conclusions: In a series of oncologic patients, vascular uptake of $^{68}$Ga-DOTATOC and $^{64}$Cu-DOTATATE was found, with highest uptake of the latter. Uptake of $^{64}$Cu-DOTATATE, but not of $^{68}$Ga-DOTATOC, was correlated with cardiovascular risk factors, suggesting a potential role for $^{64}$Cu-DOTATATE in assessment of atherosclerosis.

Keywords:

PET/CT, atherosclerosis, molecular imaging, somatostatin receptor, macrophages.
Introduction

Atherosclerosis is a systemic condition that can evolve to manifest cardiovascular disease, with potential fatal stroke or myocardial infarction as result. Even though atherosclerosis is defined as a systemic condition, it consists of localized progressive plaques that can give rise to symptoms or proceed in a silent asymptomatic stage (1). Standard diagnosing of atherosclerosis include physical exam, diagnostic tests as blood tests, ECG, ankle/brachial index, ultrasound and invasive tests as angiography, intra-vascular coronary ultrasound and angioscopy (2,3). The examinations all vary in sensitivity, specificity, reproducibility and availability. With emerging research identifying and unravelling cellular and molecular mechanisms of the changes in the progressive atherosclerotic plaque, new doors in diagnosing both clinical and subclinical stages of the disease have opened. Further, findings of molecular targets and cellular markers that are involved in the disease have led to development of new and non-invasive diagnostic techniques.

One particular target is the macrophage which is an abundant cell type in the plaque and highly active in inflammation, a key-process in progressive atherosclerosis. It migrates into the arterial intima as a monocyte where it matures to become a phagocytic macrophage. Various processes and cellular targets involved with the presence of this cell type have been investigated and identified as targets for positron emission tomography (PET), with expression of the somatostatin receptor, a G
protein-coupled seven transmembrane protein, being one of them. Five human somatostatin receptors have been identified and in atherosclerotic plaques the somatostatin receptor 2 (SSTR2) is the most frequent (4-6). The somatostatin analogues DOTA-Tyr3-octreotide (DOTATOC) and DOTA-Tyr3-octreotate (DOTATATE) bind to somatostatin receptors, with highest affinity for the SSTR2. Hence, they might be potential tracers for molecular imaging of atherosclerosis (7,8). A recent prospective study in patients with symptomatic carotid stenosis has indicated that uptake of $^{64}$Cu-DOTATATE in a marker of activated macrophages within the plaque (9).

In our study, DOTATOC was labeled with the radionuclide $^{68}$Ga and DOTATATE with $^{64}$Cu. $^{68}$Ga is produced by a $^{68}$Ge/$^{68}$Ga generator that can last up to 9-12 months because of the $^{68}$Ge half-life of approximately 270 days. $^{68}$Ga has a physical half-life of 68 minutes, which is compatible with the kinetics of most peptides. This makes $^{68}$Ga a favorable positron emitter, independent of an on-site cyclotron and with fast target localization and blood clearance, with mainly excretion through the kidneys. $^{64}$Cu, on the other hand, is generated on a cyclotron and has a half-life of 12.7 hours. The long half-life of $^{64}$Cu allows for early as well as late PET-scans, even the day after injection. It has a substantially shorter positron range than $^{68}$Ga, 1 vs 4 mm, rendering it a much better spatial resolution, but it has a lower positron abundance (10-14).
The objective of this study was to evaluate the use of two somatostatin receptor-binding PET tracers in assessment of the large arteries. The uptake of the tracers was compared in various vascular regions and the correlation with known cardiovascular risk factors was investigated, to support the hypothesis that vascular lesions containing macrophages are present in individuals with a recognized risk for atherosclerosis.
Methods

Study design and patient selection

We performed the analysis on scans from an on-going clinical trial comparing $^{68}$Ga-DOTATOC and $^{64}$Cu-DOTATATE PET/CT in patients with neuroendocrine tumors. All patients (n=60) included in the original trial were included in the present sub-study. The original inclusion criterion was: verified neuroendocrine tumor with clinical indication for $^{111}$In-octreotide single photon emission tomography (SPECT)/CT. Exclusion criteria were age below 18, pregnancy/lactation, performance status 0-2, and chemotherapy or radiation therapy in the previous 5 weeks.

The study protocol complied with the Declaration of Helsinki (version 2013) and was approved by the Regional Scientific Ethical Committee. Written informed consent was obtained from all participants (protocol number H-D-2008-045).

For this sub-study, the patients were reviewed regarding the two PET/CT-scans and known cardiovascular risk factors were collected retrospectively from their medical records. The investigated cardiovascular risk factors include age, gender, BMI, smoking habits, diabetes, arterial hypertension defined by ongoing treatment, and hypercholesterolemia defined as ongoing treatment hereof. Because of few available cholesterol-levels, the Framingham risk score was calculated by use of BMI, according with Framingham Heart Study (15).
Imaging procedures and analysis

All patients underwent hybrid PET/CT-scans with $^{68}$Ga-DOTATOC and $^{64}$Cu-DOTATATE, in random order as soon as possible but with maximum 60 days in between. Each patient had the two examinations performed on the same hybrid PET/CT scanner (Siemens Biograph mCT64, Siemens, Berlin, Germany). For the $^{68}$Ga-DOTATOC-scan, 150 MBq was injected intravenously and, after 45 minutes, whole-body PET was performed in direct connection with a whole-body CT-scan (120 kV, effective mAs 40) for attenuation correction of the PET and anatomical localization of the vessels. Likewise, the PET/CT-scan after intravenous injection of 200 MBq of $^{64}$Cu-DOTATATE was performed, 60 minutes following the injection. The PET scans were acquired in three-dimensional list mode for 3 min per bed position. The PET reconstruction settings were CT based attenuation correction, resolution-recovery (point spread function, TrueX) and time-of-flight (3 iterations, 21 subsets, zoom 1.0). A 2 mm full width at half maximum Gaussian filter was the applied to all images post-reconstruction.

Anatomical co-registration of CT and PET was carefully checked before assessment of vascular tracer uptake. Uptake was determined in five distinct vascular segments (the aortic arch; the descending thoracic aorta; the proximal and distal abdominal aorta; and the common iliac arteries). For analysis, three dimensional (3D) regions of interest (ROIs) were drawn manually slice by slice on both scans in these particular
regions using Inveon Research Workplace (version 4.1, Siemens, Erlangen, Germany),

avoiding adjacent hot spots arisen from lymph nodal metastases etc. The mean and

maximal standardized uptake value ($\text{SUV}_{\text{mean}}$ and $\text{SUV}_{\text{max}}$, respectively) that correct for

injected dose, patient weight and time to acquisition were calculated for each 3D ROI

(figure 1). In addition, each patient had “whole artery $\text{SUV}_{\text{mean}}$” and “whole artery

$\text{SUV}_{\text{max}}$” calculated as the average of the 5 SUVs in each patient. Target-to-background

ratio (TBR) was determined by dividing SUV of the vascular segment with $\text{SUV}_{\text{mean}}$

from at least four 3D ROIs placed in the superior vena cava (representing the mean

evolution).

The coronary artery calcium score was assessed using Syngo.via version VB 10A

(Siemens Healthcare, Erlangen, Germany) and the Agatston equivalent method with

an attenuation threshold of 130 Hounsfield units.

Statistical analysis

Statistical analyses were made using IBM SPSS statistics (version 22, New York, USA).

The analysis and comparison of the uptake of the two tracers was made using the

Bland-Altman method. According to this method, the mean difference between

measurements is defined as “bias” and represents the systemic error in

measurements. The statistical significance of the bias was assessed using the t-test.

The 95% limits of agreement were defined as mean difference ±1.96 times the

standard deviation. All limits of agreement were calculated assuming normal
distribution of the differences. The associations between tracer uptake and cardiovascular risk factors were investigated using Spearman correlation and subsequent multiple regression with stepwise backward elimination to find potential predictors.
Results

Patient population

All 60 patients participating in the original study were also included in the present sub-study. The baseline characteristics including cardiovascular risk factors are shown in table 1. Framingham risk score describing the 10-year risk for cardiovascular disease, as calculated from BMI, showed 22% of patients with <10% risk (n=13), 17% with 10-20% risk (n=10), 20% with 20-30% risk (n=12), 27% with >30% risk (n=16). For 15% of the patients (n=9) it was not possible to calculate the risk, due to missing data. Forty-five % (n=27) had a coronary calcium score of zero, whereas 15% (n=9) had a score above 400.

PET/CT with $^{64}$Cu-DOTATATE and $^{68}$Ga-DOTATOC

The comparison of the uptake of the two tracers (figure 2a) showed, on Bland-Altman plot, that $^{64}$Cu-DOTATATE had a significantly higher uptake value than $^{68}$Ga-DOTATOC when calculated as whole artery SUV$_{\text{max}}$, p<0.001. The 95% limits of agreement were from -2.3 to 5.7. The uptake of $^{64}$Cu-DOTATATE was also significantly higher measured as whole artery SUV$_{\text{mean}}$, p<0.001, with 95% limits of agreement from -0.5 to 1.1 (Figure 2b). Representative images of high focal and low diffuse uptake of the two tracers are shown in figure 3. Also, venous SUV was higher with $^{64}$Cu-DOTATATE as compared to $^{68}$Ga-DOTATOC and the numeric difference between arterial and venous uptake was highest with $^{64}$Cu-DOTATATE (figure 4).
The mean difference between uptake of the tracers (SUV) was also calculated in the five regions respectively, with significant results in all five artery segments, showing higher uptake of $^{64}$Cu-DOTATATE, as seen in table 2.

**Correlation with risk factors**

The association between tracer uptake and risk factors was investigated using both $\text{SUV}_{\text{mean}}$ and $\text{SUV}_{\text{max}}$ in the five artery segments, for both tracers. We found an overall significant association between maximum $^{64}$Cu-DOTATATE uptake (whole artery $\text{SUV}_{\text{max}}$) and Framingham risk score ($r=0.4; \ p=0.004$, figure 5a), whereas maximum $^{68}$Ga-DOTATOC (whole artery $\text{SUV}_{\text{max}}$) did not correlate to Framingham risk score ($p=0.3$, figure 5b). Whole artery $\text{SUV}_{\text{mean}}$ did not correlate with Framingham risk score, neither with $^{64}$Cu-DOTATATE ($r=0.1; \ p=0.4$) nor with $^{68}$Ga-DOTATOC ($r=-0.3; \ p=0.1$).

Similar results were found when using TBR rather than SUV, but with a lower correlation between maximum $^{64}$Cu-DOTATATE uptake (whole artery $\text{TBR}_{\text{max}}$) and Framingham risk score ($r=0.3; \ p=0.04$), and no correlation between Framingham risk score and $^{68}$Ga-DOTATOC uptake.

The association between maximum $^{64}$Cu-DOTATATE uptake and Framingham risk score was consistently found in three of the five vascular regions (descending thoracic aorta, proximal part of the abdominal aorta and in the iliac arteries), whereas $^{68}$Ga-DOTATOC was only inversely correlated with Framingham risk score in one region (distal part of the abdominal aorta), Table 3.
Multiple regression including gender, age, BMI, diabetes, smoking, systolic blood pressure, coronary calcium score, and treatment for hypertension and treatment for hypercholesterolemia, showed that BMI, smoking, diabetes and coronary calcium score were independent predictors of SUV$_{max}$ with $^{64}$Cu-DOTATATE (p<0.001; p=0.01; p=0.005; p=0.03, respectively).

**Discussion**

We present here the first comparison of arterial uptake of $^{64}$Cu-DOTATATE with $^{68}$Ga-DOTATOC in a population unselected for cardiovascular risk profile using hybrid PET/CT. We found a higher uptake of $^{64}$Cu-DOTATATE and wide limits of agreement for maximum uptake (SUV$_{max}$) of the two tracers. In addition, we found results in support of an association between $^{64}$Cu-DOTATATE and cardiovascular risk factors suggesting this radiotracer as a potential non-invasive biomarker of cardiovascular risk. This result supports our recent finding in patients with severe carotid stenosis. Where $^{64}$Cu-DOTATATE uptake in excised carotid plaques were associated with the gene expression of a marker of alternatively activated macrophages (9). Together, it therefore may seem that $^{64}$Cu-DOTATATE may be valuable in imaging of atherosclerosis both in patients with and without known atherosclerotic cardiovascular disease.

The use of PET-technique to visualize atherosclerosis was initiated by the finding that patients scanned after injection of fluorodeoxyglucose (FDG), labelled with the
radionuclide $^{18}$F, for tumor visualization, also showed arterial uptake of the tracer (16). The first clinical study with PET-imaging of atherosclerosis, published in 2002(17), was consequently performed using $^{18}$F-FDG, which is a marker for uptake of glucose and hereby metabolism in tissue. The uptake of FDG has later been shown to correlate significantly with plaque macrophage content, with other circulating inflammatory biomarkers (18-21) and known cardiovascular risk factors (6,22). Therefore, hope has risen that FDG might be used to evaluate therapeutic intervention (23). Following the optimistic results that PET-scans with $^{18}$F-FDG have given, additional and more specific tracers have been developed, e.g. tracers targeting macrophages. Whilst $^{18}$F-FDG visualizes the metabolism of the cell and therefore the physiological state of inflammation that a given cell in an atherosclerotic plaque is in, targeting a macrophage-expressed receptor could be a more specific tracer.

The aim of this study was to compare the uptake of two somatostatin receptor-binding PET-tracers in large arteries, and evaluate the use of them in PET/CT in assessment of atherosclerosis. These tracers have earlier been used and compared in connection with cancer diagnostics, primarily neuroendocrine tumors (24-26). Furthermore, $^{68}$Ga-DOTATATE has previously been assessed in relation to inflammation in aorta and compared to $^{18}$F-FDG (27). There are to our knowledge no studies that have compared the uptake of DOTATOC and DOTATATE in aorta in addition to their possible role for risk evaluation.
Both DOTATOC and DOTATATE are somatostatin analogues conjugated with the chelator 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraaceticacid (abbreviated DOTA), which hereafter are labeled with radiopharmaceuticals to be visualized on PET-scan. The difference between the peptides is a replacement of octreotide C-terminal threoninol (DOTATOC) to the natural amino acid threonine which produces octreotate (DOTATATE). When the peptides are labeled with $^{67}$Ga, they both bind to the SSTR2 with exceptional affinity, however highest for DOTATATE (7). Based on this, and other previous studies (7,14,28,29) we would expect an uptake of both tracers in regions with plaque formations and furthermore that the, in our case, $^{64}$Cu-labeled DOTATATE would show higher focal uptake in aorta than $^{68}$Ga-DOTATOC.

We found a consistent difference between uptake of the tracers calculated as $\text{SUV}_{\text{max}}$, $\text{SUV}_{\text{mean}}$, $\text{TBR}_{\text{max}}$, and $\text{TBR}_{\text{mean}}$ in all tested vascular regions. All SUV results show highest uptake of $^{64}$Cu-DOTATATE. This was not unexpected, since $^{64}$Cu has shorter positron range ($\sim$1 mm) compared to that of $^{68}$Ga ($\sim$4 mm). $^{64}$Cu is thus less sensitive to both spillover and partial volume loss. In concordance with this we found especially $\text{SUV}_{\text{max}}$ to have wide limits of agreements when comparing $^{64}$Cu-DOTATATE with $^{68}$Ga-DOTATOC. The difference in affinity between the tracers is also consistent with the higher SUV of DOTATATE than DOTATOC in the vascular regions. It should be acknowledged that a higher PET-signal is preferable when assessing plaques, because of their small dimensions.
We also investigated association between the uptake of tracer and classic cardiovascular risk factors. A positive correlation reinforces the theory that individuals with a certain behavior and phenotype, known to have higher risk of developing atherosclerosis also would have high tracer uptake (30).

The results showed an association between Framingham risk score and overall maximum $^{64}$Cu-DOTATATE uptake whereas overall $^{68}$Ga-DOTATOC uptake was not associated to the risk score. This is important methodological information since studies of atherosclerosis using $^{68}$Ga-labeled somatostatin-receptor tracers may overlook true differences. Previous studies have shown a high congruence between $^{68}$Ga-DOTATATE and $^{68}$Ga-DOTATOC binding (24,31). Therefore, it is our hypothesis that the difference in both measured vessel-wall uptake (figure 2) and Framingham risk correlation (figure 5) is primarily caused by the difference in radiotracer emission energy between $^{64}$Cu and $^{68}$Ga and thus related to the spatial resolution of the examination rather than a physiological difference in tracer binding. Still, other studies have shown correlation between DOTATATE labeled with $^{68}$Ga and risk factors (6,8,27). However, more atherosclerotic vessels in these studies may be the cause hereof.

As expected, we only found an association between Framingham risk score and $\text{SUV}_{\text{max}}$, whereas $\text{SUV}_{\text{mean}}$ did not correlate. This is in concordance with previous studies (6,8,27) and further supports the hypothesis that vascular $^{64}$Cu-DOTATATE
uptake is heterogeneous and could serve as a marker of more advanced and potentially more vulnerable lesions. Similarly, we have previously found heterogeneous uptake of FDG in atherosclerotic carotid plaques (18).

A limitation of the study is the lack of histological samples to validate that the uptake of tracer is actually from vascular lesions and to what cell type the tracer is binding. Therefore, prospective studies are warranted with other (non-oncological) and larger patient groups to further validate the clinical use of PET/CT with somatostatin receptor-binding tracers in assessment of atherosclerosis (8).

**Conclusion**

In this study of two somatostatin receptor-binding tracers for PET/CT, we found a higher vascular uptake of the $^{64}$Cu-labeled DOTATATE than $^{68}$Ga-DOTATOC. Furthermore, results showed a significant correlation of Framingham risk score with uptake of $^{64}$Cu-DOTATATE, which was driven by smoking, BMI and diabetes. No such correlation was found with $^{68}$Ga-DOTATOC. We suggest that $^{64}$Cu-DOTATATE seems suitable for assessment of atherosclerosis even in the subclinical stages, but prospective studies to further validate this are required.
**Acknowledgments**: The staff in the PET center is thanked for their skillful assistance.

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**Disclosures**: none
References


FIGURE 1. Method for vascular tracer uptake quantification. Example from distal abdominal aorta: 1. The outer vessel wall is manually delineated on all consecutive axial slices. 2. The imaging software fuses these consecutive ROIs into a single 3D volume of interest (VOI) covering the distal abdominal aorta. 3. A single SUV_mean and SUV_max is recorded for each VOI.
FIGURE 2. Comparison of $^{68}$Ga-DOTATOC and $^{64}$Cu-DOTATATE uptake in the large arteries. Bland-Altman plots of difference with identity line shown dashed and the mean difference with 95% limits of agreement shown in horizontal colored lines. The top line show comparison of maximum (A) standardized uptake value (SUV) and (B) mean SUV. Likewise, the bottom line show comparison of (C) maximum target to background (TBR) and (D) mean TBR.
FIGURE 3. Examples of PET/CT fusion showing uptake of $^{64}$Cu-DOTATATE (A and C) and $^{68}$Ga-DOTATOC (B and C). The patient in the top panel is a 67 years old man with a FRS of 30. The images show high focal uptake in the thoracic aorta on the $^{64}$Cu-DOTATATE PET (A), whereas the same location on the $^{68}$Ga-DOTATOC PET is more blurred (B). The patient in the lower panel is a 31 years old woman with a FRS of 2. The images show lower and more diffuse uptake with both tracers.
FIGURE 4. Standardized uptake values of $^{68}$Ga-DOTATOC and $^{64}$Cu-DOTATATE in the arteries (blue) and the superior cava vein (black). The data are paired, and each patient is represented with a dot in each of the four categories. The median uptake is shown in bold lines.
FIGURE 5. Correlation between Framingham Risk Score and (A) whole artery $^{68}$Ga-DOTATOC uptake and (B) whole artery $^{64}$Cu-DOTATATE uptake.
TABLE 1. Baseline Characteristics

<table>
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<th>Value</th>
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<tr>
<td>Age (mean, range)</td>
<td>61 (31-81)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>36/24</td>
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<tr>
<td>History of CAD (%)</td>
<td>7 (4/60)</td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>17 (10/60)</td>
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<tr>
<td>Hyperlipidemia (%)</td>
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<td>Hypertension* (%)</td>
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<tr>
<td>Smokers (%) (current/ex)</td>
<td>28/22 (17/60, 13/60)</td>
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<tr>
<td>ASA-treatment (%)</td>
<td>17 (10/60)</td>
</tr>
<tr>
<td>BMI (mean, range)</td>
<td>25.7 (17-38)</td>
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<tr>
<td>Coronary calcium score (mean, range)</td>
<td>227 (0-3356)</td>
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*Defined as ongoing treatment for hypertension.
TABLE 2. Mean difference between $^{64}$Cu-DOTATATE and $^{68}$Ga-DOTATOC uptake in each region

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<thead>
<tr>
<th>Region</th>
<th>SUV$_{\text{mean}}$ Mean</th>
<th>p</th>
<th>SUV$_{\text{max}}$ Mean</th>
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<td></td>
<td>difference*</td>
<td></td>
<td>difference*</td>
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<tr>
<td>Aortic arch</td>
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<td>0.007</td>
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<td>2.2</td>
<td>&lt;0.001</td>
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<tr>
<td>Proximal abdominal aorta</td>
<td>0.3</td>
<td>&lt;0.001</td>
<td>1.1</td>
<td>0.04</td>
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<tr>
<td>Distal abdominal aorta</td>
<td>0.2</td>
<td>&lt;0.001</td>
<td>1.6</td>
<td>0.003</td>
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<tr>
<td>Iliac arteries</td>
<td>0.2</td>
<td>&lt;0.001</td>
<td>1.4</td>
<td>&lt;0.001</td>
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</table>

* $^{64}$Cu-DOTATATE uptake minus $^{68}$Ga-DOTATOC uptake
TABLE 3. Correlations between Framingham risk score and maximum tracer uptake in 5 regions

<table>
<thead>
<tr>
<th>Region</th>
<th>$^{64}$Cu-DOTATAE Spearman’s rho</th>
<th>$^{64}$Cu-DOTATAE p</th>
<th>$^{68}$Ga-DOTATOC Spearman’s rho</th>
<th>$^{68}$Ga-DOTATOC p</th>
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<tr>
<td>Aortic arch</td>
<td>0.30</td>
<td>0.36</td>
<td>0.03</td>
<td>0.8</td>
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<td>0.23</td>
<td>0.1</td>
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<td>0.013</td>
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<td>Iliac arteries</td>
<td>0.37</td>
<td>0.008</td>
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