**GAE: Ahmed Tawakol, MD**

**GEIC: Javed Butler, MD**

**Somatostatin Receptor PET/MR Imaging of Inflammation in Patients with Large Vessel Vasculitis and Atherosclerosis**

**Brief title:** **Inflammation Imaging in Arterial Disease**

Andrej Ćorović, MB BChir,a Christopher Wall, MB BChir,a Meritxell Nus, PhD,a Deepa Gopalan, MBBS,b,c Yuan Huang, PhD,d Maria Imaz, BS,a Michal Zulcinski, MS,e Marta Peverelli, MD,a,f Anna Uryga, PhD,a Jordi Lambert,a Dario Bressan, PhD,g Robert T. Maughan, PhD,f Charis Pericleous, PhD,f Suraiya Dubash, MD, PhD,h, i Natasha Jordan, MD,j David R. Jayne, MD, PhD,k Stephen P. Hoole, DM,l Patrick A. Calvert, MD, PhD,l Andrew F. Dean, MD,m Doris Rassl, MD,n Tara Barwick, MD,b,i Mark Iles, PhD,e Mattia Frontini, PhD,o Greg Hannon, PhD,g Roido Manavaki, PhD,p Tim D. Fryer, PhD,q Luigi Aloj, MD,p Martin J. Graves, PhD,p Fiona J. Gilbert, MD, PhD,p Marc R. Dweck, MD, PhD,r David E. Newby, MD, PhD,r Zahi A. Fayad, PhD,s Gary Reynolds, MD, PhD,t Ann W. Morgan, MD, PhD,e Eric O. Aboagye, MD, PhD,i Anthony P. Davenport, PhD,a Helle F. Jørgensen, PhD,a Ziad Mallat, MD, PhD,a Martin R. Bennett, MD, PhD,a James E. Peters, MD, PhD,u James H.F. Rudd, MD, PhD,a Justin C. Mason, MD, PhD,f Jason M. Tarkin, MBBS, PhD\*a,f

aSection of Cardiorespiratory Medicine, University of Cambridge, Cambridge, UK

bDepartment of Radiology, Imperial College Healthcare NHS Trust, London, UK

cDepartment of Radiology, Cambridge University Hospitals NHS Trust, Cambridge, UK

dEPSRC Centre for Mathematical Imaging in Healthcare, University of Cambridge, Cambridge, UK

eLeeds Institute of Cardiovascular & Metabolic Medicine, University of Leeds, Leeds, UK

fVascular Sciences, National Heart & Lung Institute, Imperial College London, London, UK

gCancer Research UK Cambridge Institute, Cambridge, UK

hDepartment of Oncology, University College London NHS Trust, London, UK

iDepartment of Surgery & Cancer, Imperial College London, London, UK

jDepartment of Rheumatology, Cambridge University Hospitals NHS Trust, Cambridge, UK

kDepartment of Medicine, University of Cambridge, Cambridge, UK

lDepartment of Cardiology, Royal Papworth Hospital NHS Trust, Cambridge, UK

mDepartment of Histopathology, Cambridge University Hospitals NHS Trust, Cambridge, UK

nDepartment of Histopathology, Royal Papworth Hospital NHS Trust, Cambridge, UK

oInstitute of Biomedical & Clinical Science, University of Exeter Medical School, Exeter, UK

pDepartment of Radiology, University of Cambridge, Cambridge, UK

qDepartment of Clinical Neurosciences, University of Cambridge, Cambridge, UK

rCentre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

sBioMedical Engineering & Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, USA

tDepartment of Rheumatology, University of Newcastle; Newcastle, UK

uCentre for Inflammatory Disease, Imperial College London; London, UK

**Sources of Funding:** This work was funded by grants to JMT from the Wellcome Trust [Clinical Research Career Development Fellowship 211100/Z/18/Z]; the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC); and the British Heart Foundation (BHF, Clinical Research Training Fellowship for AC [FS/CRTF/20/24035]). This work was additionally supported by the Cambridge BHF Centre of Research Excellence [18/1/34212] and the Cancer Research UK Cambridge Centre [A25177]. For the purpose of open access, the lead author has applied a CC BY public copyright licence to any Author Accepted Manuscript. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

**Competing interests**: none

**\*Address for correspondence:**

Dr Jason M Tarkin

Section of Cardiorespiratory Medicine, University of Cambridge

Heart & Lung Research Institute

Papworth Road

Cambridge Biomedical Campus

Cambridge, CB2 0BB, UK

Email: jt545@cam.ac.uk

Tel: +44(0)1223331504

**Tweet:** PET/MR imaging using somatostatin receptor radionuclide tracers holds major promise for diagnosis and therapeutic monitoring of large vessel vasculitis @jmtarkin @jhfrudd @mallat\_lab @hfj22 #MolecularImaging#thinkPET

**Acknowledgements:** We acknowledge support from the Wolfson Brain Imaging Centre PET/MRI team; the Invicro-London clinical imaging centre; GE Healthcare application support; and the UKGCA Consortium. MN, MI, JL, MF [FS/18/53/33863], APD [TG/18/4/33770], HJ, ZM, MRD, DEN, and MRB are supported by the BHF; MZ is supported by the European Union’s Horizon 2020 research and innovation programme [Marie Skłodowska-Curie grant agreement No. 813545]; DRJ, RM and MJG are supported by the NIHR Cambridge BRC; ZAF is supported by NIH/NHLBI [R01HL135878]; GR is supported by the Wellcome Trust; AWM is supported by the Medical Research Council (MRC, [MR/N011775/1]), the NIHR Leeds BRC, the NIHR Leeds Medtech and In Vitro Diagnostics Co-operative, and an NIHR Senior Investigator award; EOA acknowledges support from Imperial Experimental Cancer Research Centre and MRC [MR/J007986/1, MR/N020782/1]; JP is supported by a UK Research and Innovation Fellowship at Health Data Research UK [MR/S004068/2]; JHFR is part-supported by the NIHR Cambridge BRC, the BHF, the Higher Education Funding Council for England, the Engineering and Physical Sciences Research Council and the Wellcome Trust; DG, RMT, CP, TB, EOA, JEP and JCM acknowledge support from the NIHR Imperial BRC.

**ABSTRACT**

**Background:** Assessing inflammatory disease activity in large vessel vasculitis (LVV) can be challenging by conventional measures.

**Objective:** We aimed to investigate somatostatin receptor 2 (SST2) as a novel inflammation-specific molecular imaging target in LVV.

**Methods:** In a prospective, observational cohort study *in vivo* arterial SST2 expression was assessed by positron emission tomography/magnetic resonance imaging (PET/MRI) using 68Ga-DOTATATE and 18F-FET-βAG-TOCA. *Ex vivo* mapping of the imaging target was performed using immunofluorescence microscopy, imaging mass cytometry, and bulk, single-cell and single-nuclei RNA sequencing.

**Results:** Sixty-one participants (LVV, n=27; recent atherosclerotic myocardial infarction ≤2 weeks, n=25; control subjects with an oncological indication for imaging, n=9) were included. Index vessel SST2 maximum tissue-to-blood ratio (TBRmax) was 61.8% (p<0.0001) higher in active/grumbling LVV than inactive LVV, and 34.6% (p=0.0002) higher than myocardial infarction, with good diagnostic accuracy (AUC ≥0.86, p<0.001 for both). Arterial SST2 signal was not elevated in any of the control subjects. SST2 PET/MRI was generally consistent with 18F-FDG PET/CT imaging in LVV patients with contemporaneous clinical scans, but with very low background signal in the brain and heart allowing for unimpeded assessment of nearby coronary, myocardial, and intracranial artery involvement. Clinically effective treatment for LVV was associated with a 0.49 ±SEM 0.24 (p=0.04; 22.3%) reduction in SST2 TBRmax after 9.3 (SD 3.2) months. SST2 expression was localized to macrophages, pericytes, and perivascular adipocytes in vasculitis specimens, with specific receptor binding confirmed by autoradiography. *SSTR2*-expressing macrophages co-expressed pro-inflammatory markers.

**Conclusion:** SST2 PET/MRI holds major promise for diagnosis and therapeutic monitoring in LVV.

**CONDENSED ABSTRACT**

Assessing inflammatory disease activity in large vessel vasculitis (LVV) can be challenging by conventional measures. We investigated somatostatin receptor subtype 2 (SST2) as a novel inflammation-specific imaging target in LVV. In a prospective cohort study, SST2 positron emission tomography/magnetic resonance imaging (PET/MRI) differentiated active LVV from inactive LVV, and aortic inflammation due to recent atherosclerotic myocardial infarction. Repeat PET/MRI showed that the change in arterial signal was consistent with clinical response to LVV treatment. SST2expression was localized to macrophages, pericytes, and perivascular adipocytes in LVV specimens. SST2 PET imaging holds major promise for diagnosis and therapeutic monitoring in LVV.

**Key words:** Takayasu arteritis; Giant cell arteritis; Atherosclerosis; Inflammation; Molecular Imaging; Somatostatin Receptor

**Abbreviations:**

CRP: C-reactive protein

CT: Computed Tomography

GCA: Giant cell arteritis

FDG:Fluorodeoxyglucose

PET: Positron Emission Tomography

PGA: Physician’s Global Assessment

LVV: Large Vessel Vasculitis

MRI: Magnetic Resonance Imaging

MI: Myocardial Infarction

ROI: Region of Interest

SST2: Somatostatin receptor 2

TAK: Takayasu arteritis

TBR: Tissue-to-Blood Ratio

Clinical Trial: ClinicalTrials.gov: NCT04071691, NCT04073810

**INTRODUCTION**

Large vessel vasculitis (LVV) is a chronic relapsing and remitting systemic inflammatory disease, comprised of Giant cell arteritis (GCA) and Takayasu arteritis (TAK), which causes pan-arterial granulomatous infiltration of the aorta and its major branches. The initial clinical presentation of LVV is often confounded by non-specific constitutional symptoms that can lead to diagnostic uncertainty. However, dangerous clinical sequelae such as acute visual loss and myocardial infarction (MI) can occur in GCA and TAK, respectively.

While 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging has traditionally been used to assess for the presence and severity of LVV, limitations including a high false-positive rate among LVV patients in clinical remission have been highlighted in clinical practice guidelines.1 18F-FDG uptake related to chronic aortic inflammation in patients with atherosclerosis can also mimic LVV changes. Hence, although 18F-FDG PET is helpful for supporting an initial LVV diagnosis, it may be less useful for differentiating active arteritis from chronic vascular remodelling, or for identifying residual disease activity after treatment. As a glucose analogue, avid physiological 18F-FDG uptake in the brain and myocardium can also interfere with reliable assessment of temporal arteritis in GCA and coronary artery involvement in TAK.

We have previously demonstrated the ability of somatostatin receptor 2 (SST2) PET/ computed tomography (CT) to detect active inflammation in atherosclerosis using 68Ga-DOTATATE.2 *SSTR2* is expressed by inflammatory macrophages activated *in vitro*, and SST2 staining co-localises with CD68+ macrophages within inflamed carotid atherosclerotic plaques. Of the somatostatin receptor PET tracers used for clinical neuroendocrine tumour imaging, 68Ga-DOTATATE has the highest binding affinity for SST2. A novel 18F click-labelled octreotide radioligand called 18F-FET-βAG-TOCA has also shown high SST2 binding affinity and favourable tracer kinetics.3 In this proof-of-concept study, we tested the hypothesis that SST2 could be a useful imaging target for diagnosis and therapeutic monitoring of LVV using PET/magnetic resonance imaging (MRI) with 68Ga-DOTATATE and 18F-FET-βAG-TOCA.

**METHODS**

Research was conducted with the approval of local research ethics committees (19/EE/0043; 05/Q1108/28; 16/NE/0319), in accordance with the Declaration of Helsinki. The retention, storage and use of tissue sections and blood samples were subject to the UK Human Tissue Act 2004. See Supplemental material for extended methods.

**Clinical study.** In this prospective observational cohort study (NCT04071691), participants with LVV based on American College of Rheumatology diagnostic criteria were enrolled from two hospitals in the UK (Cambridge University Hospitals NHS Trust and Imperial College Healthcare NHS Trust). Patients were managed following standard clinical practice guidelines for LVV. Clinical LVV activity status was graded independent of the study findings by three experienced rheumatologists, as “active” (new diagnosis or acute flare); “grumbling” (low-grade residual arteritis); or “inactive” (disease in remission), according to the Physician’s Global Assessment (PGA). PGA is an overall assessment of LVV activity based on clinical symptoms, signs, and inflammatory blood markers. The Indian Takayasu Clinical Activity Score (ITAS) was additionally used for patients with TAK (Supplemental Figure 1). Participants with atherosclerotic MI within 2 weeks enrolled in a parallel PET/MRI study that is part of the same larger project (NCT04073810), and control subjects from a previous oncology study,3 were also included. Venous blood was collected at the time of imaging.

**Imaging.** SST2 imaging was performed using 68Ga-DOTATATE (in Cambridge) or 18F-FET-βAG-TOCA (in London) on an integrated PET/MRI scanner (SIGNA, GE Healthcare), with a target injected activity of 250 MBq, a 50-min circulation time, and 30-min acquisition per bed position. Two bed positions were used to image the thoracic aorta, and subsequently head and neck vessels in patients with LVV, while a single bed position focused on the heart/aorta was acquired in MI patients. PET images were reconstructed using iterative time-of-flight (Q.Clear b=350), and a free-breathing two-point DIXON MRI sequence for attenuation correction. 3T MRI included breath-held proton-density weighted, blood-suppressed single-shot fast-spin echo aortic imaging, 3D carotid time-of-flight MR angiography, T1-weighted 3D fast spin echo with fat-suppressed, and gadolinium contrast-enhanced MR angiography. Multibed whole body 18F-FET-βAG-TOCA PET/CT was performed as part of a separate oncology trial using a PET/CT scanner (Biograph, Siemens) with ordered-subsets expectation maximization reconstruction, as previously described.3

**Image analysis.** Arterial radioactivity concentration measured as standardized uptake value was derived from 2D regions of interest (ROIs) drawn around the outer vessel boundaries of the thoracic aorta, proximal aortic arch vessels, and carotid and vertebral arteries on consecutive co-registered PET/MRI slices, with readers blinded to clinical details using open-source medical imaging software (Horos, v3.3.6), and normalized by blood pool activity to generate mean (m) and most diseased segment (mds) maximum tissue-to-blood ratios (TBR). The mdswas defined as the highest arterial TBRmax slice, averaged with contiguous slices above and below. The index vessel was the artery with the highest mTBRmax. Intra- and interobserver repeatability of these methods have previously been demonstrated using 68Ga-DOTATATE.2

**RNA sequencing.** Bulk RNAseq data is from the UKGCA Consortium Study [NCT04102930], which is linked to the NIHR Rare Diseases BioResource. Single-cell and single-nuclei RNAseq were performed using Chromium (10x Genomics).

**Histology & autoradiography.** Arterial specimens were analysed using methods for immunofluorescence microscopy as previously described,4 with primary antibodies for SST2 and CD68. 68Ga-DOTATATE autoradiography was conducted using established methods.2 Imaging mass cytometry was performed in temporal artery sections using FITC-conjugated SST2 and a panel of 10 metal-conjugated antibodies.

**Statistical analysis.** Statistical analyses were performed using R (Version 4.0.2) and Prism (Version 9.1.0, GraphPad). Data are expressed as median (interquartile range [IQR]) or mean (standard deviation [SD]) as appropriate. Group comparisons were made using the Kruskal-Wallis test and Wilcoxon matched-pairs signed rank test. Receiver operator characteristic (ROC) analysis was used to assess diagnostic accuracy and identify optimal TBR thresholds based on the Youden Index. Linear mixed-effects models were used to account for hierarchical data structure and multiple observations within patients, with patient and vessel included as random effects, and tracer as a fixed effect. A random-effects regression model was used to assess ΔTBR at follow-up compared with baseline. Results of the regression models were reported as effect size ± standard error of the mean (SEM) or absolute change (95% confidence interval [CI]) for log-transformed data, as well as the percentage difference between groups. Potential confounding factors associated with mTBRmax (p ≤0.1) in univariable linear mixed-effects models were included in multivariable sensitivity analyses. A 2-sided p-value <0.05 was considered significant.

**RESULTS**

Sixty-one participants (LVV, n=27; recent myocardial infarction, n=25; control subjects, n=9; **Figure 1**) were included. Baseline clinical data are summarised in **Table 1**. Patients with MI were imaged a median 8 (IQR 6, 8) days after MI and had a median Troponin I of 25,000 (IQR 3491, 25,000) ng/L at the time of infarct. All but 2 patients with MI underwent percutaneous coronary intervention to the culprit lesion. The mean injected activity and uptake times were 222 (SD 20) MBq and 53 (SD 4) mins for 68Ga-DOTATATE, and 212 (SD 35) MBq and 56 (SD 6) mins for 18F-FET-βAG-TOCA at baseline.

**LVV clinical disease activity.** To test the accuracy of SST2 PET for inflammatory disease activity in LVV, 3,828 ROIs were analysed from 27 baseline PET/MRI scans. Both mTBRmax and mdsTBRmax differed among patients with clinically active, grumbling, and inactive LVV for the index vessels, thoracic aorta, and all vessels combined (p<0.005 for all; **Figure 2A, 2B, 2C, 2D** and Supplemental Table 1). Data for the two tracers were pooled as there was comparable image quality and ability to distinguish active/grumbling LVV from inactive LVV (Supplemental Figure 2). Aortic mTBRmax >1.8 and mdsTBRmax >2.4 demonstrated the best diagnostic accuracy for differentiating active/grumbling LVV from inactive LVV (area under curve [AUC] 0.89, p=0.0009 for both; **Figure 2E**). In the linear mixed effects model, individual baseline TBRmax values for index vessels were 61.8% (95% CI 31.5% to 99.0%, p<0.0001) higher in active/grumbling LVV than inactive LVV (Supplemental Table 2). For the thoracic aorta the difference was 26.6% (95% CI 12.6% to 42.3%, p<0.0001), and for all vessels 11.6% (95% CI 1.0% to 23.4%, p=0.03).

**LVV vs. atherosclerotic inflammation.** To determine the accuracy of SST2 PET for discriminating vasculitis from aortic inflammation due to atherosclerosis, 153 ROIs were analysed from the ascending aortas of 17 patients with active/grumbling LVV and 182 ROIs in the ascending aortas of 25 patients with recent MI. Focal 68Ga-DOTATATE signals relating to aortic atherosclerosis in MI patients were of much lower intensity than in LVV and appeared patchy rather than circumferential. Aortic SST2 PET mTBRmax was higher in patients with active/grumbling LVV than recent MI (p<0.0001; **Figure 3A, 3B, 3C**). When including only MI patients with aortic atherosclerosis visible on CT angiography (n=15 [60%]), and also when comparing descending aorta mTBRmax the difference remained (p<0.005 for both; Supplemental Figure 3). Aortic mTBRmax >1.6 had the best diagnostic accuracy for differentiating patients with active/grumbling LVV from recent MI (AUC 0.86, p<0.0001; **Figure 3D**). In the linear mixed effect model, individual TBRmax values were 34.6% (95% CI 15.1% to 57.6%, p=0.0002) higher in active/grumbling LVV than recent MI.

**Control subjects.** Unlike patients with active vasculitis, none of the control subjects had aortic 18F-FET-βAG-TOCA increased above background (Supplemental Figure 4).

**18F-FDG PET imaging.** 18F-FDG PET/CT imaging was performed for clinical care and was not part of the research protocol of this initial study. However, in cases where contemporaneous clinical 18F-FDG imaging was performed within 1 year of the baseline imaging (n=10; median scan-scan interval 127 [IQR 38, 245] days) and in another patient where the interscan interval was longer (15 months), where both the treatment and PGA score remained unchanged, there was remarkably good agreement observed for SST2 PET/MRI and 18F-FDG PET/CT in 9 (82%) scans (**Figures 2A, 2B, 2C, 3A, 4A, 5A, and 5B**; Supplemental Figure 5). In 2 of these patients 18F-FDG PET showed no arterial uptake despite a clinical suspicion of active disease, however SST2 revealed increased signal in the affected vertebral (Supplemental Figure 5B) and intracranial (**Figure 4C**) arteries.

**Patterns of LVV involvement*.*** Unlike 18F-FDG, background SST2 PET activity was very low in the brain and healthy myocardium allowing the potential for unimpeded assessment of nearby vessels. None of the patients in the study had symptoms of active temporal arteritis at the time of PET/MRI due to the need for urgent treatment. However, SST2 PET identified LVV disease activity in patients with coronary arteritis, sub-clinical myocarditis, and intracranial vasculitis (**Figure 4A, 4B, and 4C**). Other patients with GCA and polymyalgia rheumatica symptoms had glenohumeral joint tracer uptake (**Figure 4D**).

**Therapeutic monitoring.** Fifteen patients with LVV underwent repeat SST2 PET/MRI (scan-scan interval median 9.6 [IQR 5.5, 11.4] months; mean injected activities and uptake times at follow-up, 68Ga-DOTATATE: 162 [SD 44] MBq and 59 [SD 8] mins, 18F-FET-βAG-TOCA: 174 [SD 45] MBq and 67 [SD 4] mins). Further details are in Supplemental Table 3. Although it was intended to repeat imaging for all patients after 6 months, some scans were delayed during the COVID-19 pandemic, and 12 patients declined to attend for the second scan as they remained in isolation when public restrictions were lifted. Ten of the 15 LVV patients who did undergo repeat imaging had newly initiated or escalated treatment after their baseline scan, which was associated with clinical improvement based on the PGA score in 8 of these patients.

Patients with newly initiated or escalated treatment (n=10) had lower SST2 PET mTBRmax in the index vessel at follow-up than baseline (p=0.01; **Figure 5A and 5C**). When comparing individual TBRmax values in a linear random effects model, clinically effective treatment for LVV (defined as any improvement in PGA score) was associated with 0.49 ± SEM 0.24 (p=0.04; 22.3%) reduction in index vessels, 0.32 ± SEM 0.09 (p=0.0003; 14.5%) reduction in thoracic aorta, and 0.39 ± SEM 0.17 (p=0.02; 18.4%) reduction across all vessels.

**Effect of IL-6 receptor blocking.** In 6 patients treated with tocilizumab (a monoclonal antibody against the IL-6 receptor) as per standard clinical dosing for relapsing or refractory LVV, there was a trend towards reduction in the index vessel mTBRmax at follow-up (p=0.09; **Figure 5E**). In patients whose PGA score was improved by tocilizumab (n=5), there was a reduction in TBRmax at follow-up using a linear random effects model for the thoracic aorta (-0.29 ± SEM 0.11, p=0.009; 13.8%) and across all vessels (-0.36 ± SEM 0.18, p=0.04; 17.7%), but no change in the index vessels. In the 1 patient whose clinical symptoms failed to respond to tocilizumab, arterial SST2 PET signal remained elevated at follow-up despite a CRP of <1.0 mg/L.

**PET/MRI repeatability.** Scan-scan repeatability was also evaluated. Importantly, there was no difference in index vessel mTBRmax in the 5 patients with LVV whose treatment remained unchanged (scan-scan interval 9.2 [SD 3.8] months; **Figure 5B and 5D**). The single measure intraclass correlation coefficient, using a two-way mixed effects model with absolute agreement for index vessel mTBRmax values from baseline and follow-up scans in LVV patients with inactive disease and no change in treatment (n=4 patients), was 0.86 (95% CI 0.04 to 0.99). The mean bias of individual TBRmax values (n=47 ROIs) between scans for these patients was 0.16 (SD 0.32) on Bland-Altman analysis (Supplemental Figure 6).

**Systemic inflammatory markers.** In contrast to the PET imaging findings, there were no differences in any of the blood inflammatory markers tested between patients with active/grumbling LVV and inactive LVV. There were also no differences in these markers between patients with active/grumbling LVV and recent MI. However, after excluding the 4 patients whose baseline treatment included tocilizumab, there was a difference in C-reactive protein (CRP) between active/grumbling LVV vs. inactive LVV (p=0.02), and a trend toward difference in active/grumbling LVV vs. recent MI (p=0.08; Supplemental Figure 7A and 7B). The effects of new or escalated LVV treatments on CRP and other inflammatory markers were varied, with no difference at follow-up compared to baseline aside for tocilizumab (**Figure 5C and 5E**).Although there was a moderate correlation between aortic mdsTBRmax and CRP in patients with LVV (r=0.44 [95% CI 0.06 to 0.71], p=0.02; Supplemental Figure 7C), there were no other associations between PET activity and inflammatory markers. However, SST2 PET was strongly correlated with the ITAS-CRP score in patients with TAK (mTBRmax r=0.82 [95% CI 0.46 to 0.95], p=0.001; mdsTBRmax r=0.75 [95% CI 0.29 to 0.93], p=0.006; Supplemental Figure 7D).

**Comparison with MRI.** Aortic thickening assessed by MRI (>2.2 mm) occurred in 70% (19/27) of LVV patients. Aortic mTBRmax and mdsTBRmax were greater in LVV patients with aortic thickening than those without (p<0.005 for both; Supplemental Figure 8A). Aortic mTBRmax was also correlated with maximum wall thickness (r=0.68, p=0.002; Supplemental Figure 8B) in these patients.

**Multivariable regression analysis.** After adjusting for potential confounders with p≤0.1 in univariable analysis (Supplemental Table 4), the difference in TBRmax between active/grumbling LVV and inactive LVV became more pronounced across all vessels (18% [95% CI 5.8% to 31.5%], p=0.003). For the index vessel and aorta, the differences remained unchanged.

***Ex vivo* mapping of *SSTR2*.** Bulk RNAseq data from temporal artery biopsies of GCA patients diagnosed by American College of Rheumatology criteria (n=40; mean age 75 [range 60 to 92] years; 24 [60%] female) showed increased expression of *SSTR2* compared to other somatostatin receptors (**Figure 6A**). There was no association between *SSTR2* expression and steroid duration (median 6 [range 0 to 16] days). However, *SSTR2* was correlated with *CD68* at both the gene- (r=0.34, p=0.03) and transcript-level (range r=0.33 to r=40, p<0.05; Supplemental Table 5).

Single-cell RNAseq data (n=8; mean age 72 [range 64 to 84] years; 5 [63%] female; median steroid duration 10 [range 4 to 13] days) localized *SSTR2* expression to macrophages in temporal artery biopsies from 2 of 5 patients with confirmed GCA based on clinical and histological criteria (**Figure 6B**). These 2 patients had positive ultrasound findings for temporal arteritis and the highest CRP levels at presentation of the cohort. *SSTR2* was not detected in any of the 3 samples without clinical or histological features of GCA in the single-cell RNAseq dataset.

To further corroborate these findings, single-nuclei RNAseq was performed in temporal artery biopsies from patients with histologically proven GCA (n=2; **Figure 6C**) and a carotid endarterectomy specimen (n=1; **Figure 6D**). Patient details for these and other specimens are in Supplemental Table 6. UMAPs and numbers of nuclei for cell clusters are in Supplemental Figure 9 and Supplemental Table 7. Macrophages again emerged as the dominant *SSTR2*-expressing cell type in the carotid atherosclerotic plaque, while pericytes were also identified in temporal biopsies. *SSTR2* expression was not detected by single-nuclei RNAseq in a healthy aortic specimen (n=1; not shown).

Cell clusters in the single-cell and single-nuclei experiments were not directly comparable. However, *SSTR2*-expressing macrophages identified in temporal arteries expressed pro-inflammatory markers (S100A8 and S100A9; Supplemental Figure 10A). *SSTR2*-expressing macrophages in the carotid artery expressed markers of resident and/or alternatively activated macrophages (MERTK, SOD2, LGALS3), but also CXCL3 which is an inflammatory cytokine (Supplemental Figure 10C and 10D). Pericytes were not distinguished as a distinct population in the single-cell RNAseq dataset.

**SST2 receptor immunostaining.** Immunofluorescence microscopy was performed to verify the expression and cellular distribution of SST2 receptors within sections of the same artery biopsies analysed for single-nuclei RNAseq (n=2), as well as additional temporal artery samples (GCA, n=2; control artery with no abnormality, n=1) and an aortic LVV specimen (n=1). Histological findings were consistent with RNAseq data. There was specific co-staining of SST2 and the pan-macrophage marker CD68 within inflamed regions of temporal arteries (**Figure 7A and 7B**) and aortic tissue (Supplemental Figure 11), as well as SST2 staining of cells surrounding microvessels in the adventitia with the morphological appearance of pericytes (confirmed by αSMA/NG2 staining using imaging mass cytometry). There was minimal SST2 staining in the control artery (**Figure 7C**).

**Autoradiography.** Autoradiographic binding of 68Ga-DOTATATE to SST2 receptors was confirmed in temporal artery sections of patients with active GCA (n=2) and compared with control arteries from patients without vasculitis (n=2). There was higher specific binding of 68Ga-DOTATATE in the LVV specimens than non-diseased control arteries, and very low non-specific binding when blocked with an unlabelled cold competing compound (**Figure 7D**). Quantification of autoradiographic signal further confirmed these findings (**Figure 7E**).

**Imaging mass cytometry.** Imaging mass cytometry was used to further delineate patterns of cell-type specific SST2 expression in temporal artery biopsies (n=6). Within CD68+ regions, SST2 appeared more closely co-localised with the inflammatory macrophage marker CD80, than CD206, although there was overlap with both markers (**Figure 8A**). SST2 staining did not co-localise with CD31 in the endothelium or αSMA in the media of the main vessels. There was also no overlap with CD3+ nor CD4+ T lymphocytes. However, cellular localisation of SST2 did occur with pericytes identified by NG2+ and αSMA around neo-vessels in the adventitia (**Figure 8A and 8B**), as well as cells with the morphologic appearance of perivascular adipocytes. SST2 staining was not detected in the control artery and was low in perivascular tissue (**Figure 8C**). **DISCUSSION**

Here we show for the first time that SST2 receptors are expressed by inflammatory macrophages, as well as pericytes and perivascular adipocytes within inflamed arteries of patients with LVV and can be detected using PET/MRI (**Central Illustration**). By re-purposing existing PET tracers for this novel application, we describe a method that has the potential to be rapidly incorporated into clinical practice. Moreover, we tested both 68Ga-DOTATATE and a newer 18F-octreotide analogue that could further accelerate clinical translation by allowing easier transportation to hospitals without on-site cyclotron or gallium-68 generator facilities.

**The unmet need for an inflammation-specific PET tracer for LVV.** The EULAR (European Alliance of Associations for Rheumatology) future research agenda highlights the need to study PET ligands specifically targeted to immune cells.1While 18F-FDG PET is an important component of the diagnostic work-up of patients with suspected LVV, it may be less useful for tracking response to therapy or monitoring long-term disease activity. Numerous studies have reported a discordance between clinical response to treatment and 18F-FDG PET findings, with a high percentage of scans interpreted as active LVV despite patients achieving clinically-defined disease remission.5–8 Whether residual 18F-FDG activity in clinical remission patients is a marker of future relapse risk is unknown.5,9 However, a lack of association between 18F-FDG uptake and acute phase markers, arterial wall thickening, and late-gadolinium enhancement on MRI has also been reported.5,10,11 It remains unclear whether 18F-FDG uptake during clinical remission reflects subclinical vasculitis, chronic vascular remodelling, concomitant atherosclerosis, or another factor.

**Could SST2 PET/MRI be useful for assessing disease activity in LVV?** We found that SST2 PET/MRI could accurately differentiate patients with clinically active/grumbling LVV from inactive LVV, and aortic inflammation due to recent atherosclerotic MI. SST2 PET signal was also correlated with peri-aortic thickening on MRI, another important marker of disease activity. Aside from our previous case report,12 the only other publication about SST2 imaging in vasculitis evaluated somatostatin receptor scintigraphy for detecting pulmonary and nasopharyngeal involvement in ANCA-associated vasculitis.13 TBR values reported for atherosclerosis in our previous PET/CT study are not directly comparable to the present study due to differences in scanner type and image reconstruction.2

**Is there a role for therapeutic monitoring with SST2 PET?** Repeat scanning showed that SST2 PET/MRI was able to track the clinical response to LVV therapy (or lack thereof), indicating that it could provide a means of identifying refractory or residual arteritis after treatment.Importantly, there was good scan-scan repeatability of arterial TBR measurements. In contrast, the effect of treatment on CRP and other blood inflammatory markers was less consistent. Monitoring disease activity in patients treated with tocilizumab is another clinical need, as CRP is reduced directly by IL-6 inhibition and is therefore not useful for monitoring inflammation in the arterial wall. In a small, exploratory sub-group of patients treated with tocilizumab in this study, changes in arterial SST2 PET signals were again consistent with individual clinical responses to this therapy. A larger randomised clinical trial is needed to confirm if SST2 PET could be useful for on-treatment monitoring with tocilizumab or other agents.

**Target validation of SST2 in LVV.** Both *SSTR2* gene expression and the presence of SST2 receptors were confirmed in macrophages within temporal artery biopsies of patients with GCA using multiple methods. Although we did not formally quantify co-staining, the histological findings were nonetheless consistent and reproducible across multiple samples. These findings are also consistent with a previous study that showed SST2 staining in CD68+ macrophages in sarcoid granulomas and a temporal artery biopsy from one patient with GCA.14

We also found that in patients with LVV, SST2 PET signals could additionally originate from pericytes and adipocytes within inflamed peri-adventitial tissue. Somatostatin receptor expression has been identified in pericytes from patients with interstitial lung disease15 and retinal disease,16 and avid 68Ga-DOTATATE uptake has also been reported in a patient with a rare metastatic hemangiopericytoma.17 Although endothelial cell *SSTR2* expression has also been reported,18 data from large publicly available RNAseq databases show very low or no *SSTR2* expression in endothelial cells (e.g., European Blueprint Study [https://www.blueprint-epigenome.eu], Tabula sapiens human cell atlas [https://tabula-sapiens-portal.ds.czbiohub.org]), which is consistent with our findings*. SSTR2* expression in adipose tissue is corroborated by data from the Human Protein Atlas (https://www.proteinatlas.org).

**Study limitations.** As the first proof-of-concept study to evaluate SST2 in LVV, there are several limitations to acknowledge including a non-randomised observational study design, modest sample size, and lack of head-to-head comparison with 18F-FDG. Given the clinical importance of 18F-FDG PET imaging in LVV despite its known limitations, to identify an alternative imaging target with as much promise as SST2 represents a breakthrough. However, our study was not designed to directly evaluate SST2 PET against the current reference standard as it was first necessary to establish feasibility and to lay the translational groundwork. For grading of clinical LVV disease activity, PGA score was used as there are no other validated disease activity measures for both GCA and TAK.19 Images from a first-in-human oncology trial were used as controls for arterial 18F-FET-βAG-TOCA uptake as this is the only other study that has used this tracer. While semi-quantitative TBR metrics were used instead of visual assessment scores because of high physiological liver uptake precluding its use as a background reference, TBR is an established method for vascular imaging research. Lastly, the participant dropout rate prior to follow-up imaging was higher than expected because of the first wave of the COVID-19 pandemic.

**CONCLUSION**

Somatostatin receptor PET/MRI using re-purposed radioligands such as 68Ga-DOTATATE or 18F-FET-βAG-TOCA could offer a useful clinical adjunct for diagnosis and monitoring of disease activity and therapeutic efficacy in LVV.

**PERSPECTIVES**

**Competency in Patient Care and Procedural Skills:** While 18F-FDG PET can identify large vessel vasculitis (LVV), non-specific uptake may occur during clinical remission. Somatostatin receptor 2 (SST2) PET/MR is an alternative method for assessment of inflammatory disease activity in LVV.

**Translational outlook**: Further studies are needed to compare the sensitivity and specificity of these diagnostic modalities across the clinical spectrum of disease activity and responses to treatment.

**References**

1. Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77(5):636-643.

2. Tarkin JM, Joshi FR, Evans NR, et al. Detection of Atherosclerotic Inflammation by 68Ga-DOTATATE PET Compared to [18F]FDG PET Imaging. *J Am Coll Cardiol* 2017;69:1774–1791.

3. Dubash SR, Keat N, Mapelli P, et al. Clinical Translation of a Click-Labeled 18F-Octreotate Radioligand for Imaging Neuroendocrine Tumors. *J Nucl Med* 2016;57:1207–1213.

4. Bucerius J, Hyafil F, Verberne HJ, et al. Position paper of the Cardiovascular Committee of the European Association of Nuclear Medicine (EANM) on PET imaging of atherosclerosis. *Eur J Nucl Med Mol Imaging* 2016;43(4):780-92.

5. Nus M, Martínez-Poveda B, Cardiovascular DM, 2016. Endothelial Jag1-RBPJ signalling promotes inflammatory leucocyte recruitment and atherosclerosis. *Cardiovasc Res* 2016;112(2):568-580.

6. Grayson PC, Alehashemi S, Bagheri AA, et al. 18 F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. *Arthritis Rheumatol* 2018;70:439–449.

7. Banerjee S, Quinn KA, Gribbons KB, et al. Effect of Treatment on Imaging, Clinical, and Serologic Assessments of Disease Activity in Large-vessel Vasculitis. *J Rheumatol* 2020;47(1):99-107.

8. Peña DP, Rheumatol IM-RE, 2021. Evidence for uncoupling of clinical and 18-FDG activity of PET/CT scan improvement in tocilizumab-treated patients with large-vessel giant cell arteritis. *Clin Exp Rheumatol* 2021;39 Suppl 129(2):69-75.

9. Geest KSM, Treglia G, Glaudemans AWJM, et al. Diagnostic value of [18F]FDG-PET/CT for treatment monitoring in large vessel vasculitis: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2021;48(12):3886-3902.

10. Blockmans D, Ceuninck L de, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: A prospective study of 35 patients. *Arthritis Rheum* 2006;55(1):131-7.

11. Arnaud L, Haroche J, Malek Z, et al. Is 18F-fluorodeoxyglucose positron emission tomography scanning a reliable way to assess disease activity in takayasu arteritis? *Arthritis Rheum*; 2009;60(4):1193-200.

12. Incerti E, Tombetti E, Fallanca F, et al. 18F-FDG PET reveals unique features of large vessel inflammation in patients with Takayasu’s arteritis. *Eur J Nucl Med Mol Imaging* 2017;44(7):1109-1118.

13. Tarkin JM, Wall C, Gopalan D, et al. Novel Approach to Imaging Active Takayasu Arteritis Using Somatostatin Receptor Positron Emission Tomography/Magnetic Resonance Imaging. *Circ Cardiovascular Imaging* 2020;13(6):e010389.

14. Neumann I, Mirzaei S, Birck R, et al. Expression of somatostatin receptors in inflammatory lesions and diagnostic value of somatostatin receptor scintigraphy in patients with ANCA-associated small vessel vasculitis. *Rheumatology* 2004;43(2):195-201.

15. Bokum ten AM, Hofland LJ, de Jong G, et al. Immunohistochemical localization of somatostatin receptor sst2A in sarcoid granulomas. *Eur J Clin Invest* 1999;29(7):630-6.

16. Mayr CH, Simon LM, Leuschner G, et al. Integrative analysis of cell state changes in lung fibrosis with peripheral protein biomarkers. *EMBO Mol Med* 2021;13(4):e12871.

17. Beltramo E, Lopatina T, Mazzeo A, et al. Effects of the neuroprotective drugs somatostatin and brimonidine on retinal cell models of diabetic retinopathy. *Acta Diabetologica* 2016; 53(6):957-964.

18. Hung TJ, Macdonald W, Muir T, Celliers L, Al-Ogaili Z. 68Ga DOTATATE PET/CT of Non-FDG-Avid Pulmonary Metastatic Hemangiopericytoma. *Clin Nucl Med* 2016;41(10):779-80.

19. Adams RL, Adams IP, Lindow SW, Zhong W, Atkin SL. Somatostatin receptors 2 and 5 are preferentially expressed in proliferating endothelium. *Br J Cancer* 2005;92(8):1493-8.

20. Rimland CA, Quinn KA, Rosenblum JS, et al. Outcome Measures in Large Vessel Vasculitis: Relationship Between Patient-, Physician-, Imaging-, and Laboratory-Based Assessments. *Arthritis Care Res* 2020;72(9):1296-1304.

 **FIGURES**

**Figure 1** | **Patient cohorts and tissue samples.** Flowchart summarising the patient cohorts and arterial samples included in the study.Participants with active and inactive large vessel vasculitis (LVV) were enrolled from 2 hospital sites. Positron emission tomography/ magnetic resonance imaging (PET/MRI) scans from patients with LVV were compared to patients with recent myocardial infarction (MI) enrolled in a parallel study, and control subjects from a prior oncology trial. Sources of arterial samples and RNA sequencing data from patients with giant cell arteritis (GCA), carotid atherosclerosis, and non-diseased control arteries used to evaluate target expression of somatostatin receptor 2 (SST2) in LVV are as shown.

**Figure 2** | **Clinical LVV activity.** Aortic somatostatin receptor (SST2) positron emission tomography/ magnetic resonance imaging (PET/MRI) signals (white arrows) in Takayasu arteritis (TAK) patients grouped by clinical disease activity: (**A**) active disease (treatment naïve at baseline imaging) with arterial thickening (asterisk); (**B**) grumbling disease with left subclavian occlusion (asterisk) and brachiocephalic stenosis; (**C**) inactive disease with no aortic thickening. Contemporaneous 18F-fluorodeoxyglucose (FDG) PET images (black arrows). (**D**) Quantitative comparisons of mean (m) and most diseased segment (mds) SST2 PET maximum tissue-to-blood ratio (TBRmax); (**E**) Receiver operating characteristic analyses of SST2 PET mTBRmax and mdsTBRmax for differentiating active/grumbling from inactive large vessel vasculitis (LVV). *Image scale bars=SUV; panel D error bars=median (IQR)*

**Figure 3 | Vasculitis vs. atherosclerotic inflammation.** Aortic somatostatin receptor (SST2) positron emission tomography/ magnetic resonance imaging (PET/MRI) signals (white arrows) in patients with: (**A**) active giant cell arteritis (GCA; treatment naïve at baseline imaging) and aortic thickening (asterisk), and (**B**) recent myocardial infarction (MI) with aortic atherosclerosis (asterisk) and inferior infarction (arrowhead; N.B. infarct-related myocardial PET uptake). Contemporaneous 18F-flourodeoxyglucose (FDG) PET images in panel **A** showing aortic uptake (black arrows). (**C**) Quantitative comparison of aortic mean SST2 PET maximum tissue-to-blood ratio (TBRmax); (**D**) Receiver operating characteristic analysis of SST2 PET mTBRmax for differentiating active/grumbling from inactive large vessel vasculitis (LVV). *Image scale bars=SUV; panel C error bars=median (IQR)*

**Figure 4** | **Varied patterns of LVV involvement.** Somatostatin receptor (SST2) positron emission tomography/ magnetic resonance imaging (PET/MRI) signals (white arrows) in: (**A**) the aortic root and left main coronary artery with adjacent peri-aortic thickening (asterisk) and 18F-fluorodeoxyglucose (FDG) PET uptake (black arrow) in a patient with active Takayasu arteritis (TAK); (**B**) the basal inferolateral left ventricular myocardium in a patient with inactive TAK and sub-clinical myocarditis confirmed by mid-wall late gadolinium enhancement (asterisk) and increased T2-oedema signal (asterisk); (**C**) the thickened intracranial portion of the right internal carotid artery (asterisk) in a patient with TAK and previous stroke in whom 18F-FDG failed to detect this abnormality; and (**D**) the right glenohumeral joint in a patient with giant cell arteritis (GCA) and polymyalgia rheumatica symptoms. N.B. there is a reduction in PET signal intensity following immunosuppressive treatment in panels **C** and **D**. *Image scale bars=SUV*

**Figure 5** | **Repeat imaging.** Baseline and follow-up images from patients with (**A**) newly diagnosed active giant cell arteritis (GCA; treatment naïve at baseline imaging) and (**B**) active CGA who of their own volition remained off treatment during the study because of side effects from prednisolone and methotrexate (subsequently well-controlled with tocilizumab). Somatostatin receptor (SST2) positron emission tomography/ magnetic resonance imaging (PET/MRI) shows resolution in aortic inflammation (white arrows) after treatment, and no change with lack of treatment. Contemporaneous (pre-treatment) 18F-fluorodeoxyglucose (FDG) PET images showing similar aortic uptake (black arrows) to SST2 PET. Graphs showing changes in baseline vs. follow-up clinical disease activity grading, index vessel mean SST2 maximum tissue-to-blood ratio (TBRmax), C-reactive protein and erythrocyte sedimentation rate in patients with: (**C**) any escalation in treatment, (**D**) no treatment change, and **(E**) those who received tocilizumab as part of their therapy regime. N.B. patients in panel **E** are a sub-set of panel **C**. Further clinical data for each patient who underwent repeat imaging are in Supplemental Table 4. *Image scale bars=SUV*

**Figure 6 | RNA seq.** Plots of(**A**) bulk, (**B**) single-cell and (**C, D**) single-nuclei RNA sequencing data from temporal arteries and a carotid atherosclerotic specimen, showing *SSTR2* expression localized to populations of macrophages and pericytes. Gene-level expression data displayed as normalized counts per million (CPM) in panel **A** confirms *SSTR2* is the dominant somatostatin receptor subtype expressed in temporal arteritis. In panel **B**, labels 1 to 8 indicate data from individual patients.

**Figure 7** | **SST2 staining and autoradiography in temporal arteritis.** Histological images from (**A, B**) patients with temporal arteritis showing immunofluorescence somatostatin receptor 2 (SST2) co-staining in CD68+ macrophages (arrow), as well as cells with the morphological appearance of pericytes (arrowhead), with corresponding hematoxylin and eosin slides; (**C**) control artery shows no SST2 staining; (**D**) autoradiographic images and (**E**) quantitative autoradiographic data confirms higher specific binding of 68Ga-DOTATATE to SST2 receptors in temporal arteritis specimens than control arteries. For panels **A** and **B**, patients had received prednisolone 40 mg for 20 days and 10 days respectively prior to undergoing temporal artery biopsy.

**Figure 8 | Localisation of SST2 in temporal arteritis using imaging mass cytometry.** Histological images from patients with temporal arteritis performed using imaging mass cytometry showing co-staining of somatostatin receptor 2 (SST2) with: (**A, B**) clusters of macrophages (CD68+/CD80+/CD206+; arrows), pericytes (αSMA+/NG2+); dashed arrows) around neovessels in the peri-adventitia; and peri-adventitial cells with adipocyte morphology (asterisk), with related hematoxylin and eosin slides shown. In contrast, there is minimal SST2 staining in (**c**) the control artery and perivascular tissue. Sections in panel **a** are from the same patient as Figure 6B.

**Central Illustration |** **SST2 PET/MRI in LVV: *in vivo* imaging and *ex vivo* target mapping.** Patients with large vessel vasculitis (LVV) and recent atherosclerotic myocardial infarction (MI) underwent somatostatin receptor 2 (SST2) positron emission tomography/magnetic resonance imaging (PET/MRI) in a prospective observational cohort study. In parallel, *ex vivo* mapping of the imaging target was performed using RNA sequencing, histology, and autoradiography. Figure summarises the research methods and main study findings. Arterial SST2 signal (arrow) measured by maximum tissue-to-background ratio (TBRmax) using PET/MRI accurately differentiated patients with active/ grumbling LVV from inactive LVV and recent MI, as well as control subjects. There was also a strong correlation between SST2 mTBRmax and para-aortic thickening in LVV patients. SST2 expression was identified in macrophages (dashed arrow), pericytes, and perivascular adipocytes with arterial specimens from patients with LVV.

**Table 1 | Baseline clinical characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
|  | **Large vessel vasculitis** | **Myocardial Infarction** | **Control subjects** |
| **Participants (n)** | 27 | 25 | 9 |
| **Median age, years (IQR)** | 63 (49, 68) | 61 (54, 65) | 56 (47, 69) |
| **% female (n)** | 78 (21) | 20 (5) | 67 (6) |
| **Median BMI, kg/m2 (IQR)** | 27.9 (25.5, 30.3) | 28.7 (26.0, 32.9) | 26.3 (24.0, 30.4) |
| **LVV Diagnosis, % (n)** |  |  |  |
| GCA | 48 (13) | n/a | n/a |
| Takayasu arteritis | 48 (13†) | n/a | n/a |
| Unspecified LVV | 4 (1\*) | n/a | n/a |
| **LVV clinical disease activity status, n (%)** |  |  |  |
| Active | 11 (41) | n/a | n/a |
| Grumbling | 6 (22) | n/a | n/a |
| Inactive | 10 (37) | n/a | n/a |
| **Medical history, n (%)** |  |  |  |
| Hypertension | 14 (52) | 12 (48) | 3 (33) |
| Hypercholesterolaemia | 9 (33) | 13 (52) | 0 (0) |
| Diabetes mellitus | 3 (11) | 4 (16) | 1 (11) |
| Chronic kidney disease | 1 (4) | 0 (0) | 0 (0) |
| Atrial fibrillation | 2 (7) | 2 (8) | 0 (0) |
| Stable angina | 5 (19) | 1 (4) | 0 (0) |
| Myocardial infarction | 0 (0) | 25 (100) | 1 (11) |
| Coronary artery bypass grafting surgery | 1 (4) | 0 (0) | 0 (0) |
| Stroke or transient ischaemic attack | 1 (4) | 0 (0) | 0 (0) |
| Peripheral vascular disease | 2 (7) | 0 (0) | 0 (0) |
| Rheumatoid arthritis | 3 (11) | 0 (0) | 0 (0) |
| Psoriasis | 1 (4) | 0 (0) | 0 (0) |
| Systemic lupus erythematosus  | 0 | 1 (4) | 0 |
| **Current or past smoking habit, n (%)** | 8 (30) | 15 (60) | - |
| **Family history of early coronary heart disease, n (%)** | 2 (7) | 9 (26) | - |
| **Baseline Immunosuppression, n (%)** |  |  |  |
| Corticosteroid | 17 (63) | 1 (4) | 0 (0) |
| Methotrexate | 9 (33) | 0 (0) | 0 (0) |
| Azathioprine | 1 (4) | 0 (0) | 0 (0) |
| Cyclophosphamide | 1 (4) | 0 (0) | 0 (0) |
| Mycophenolate mofetil | 2 (7) | 0 (0) | 0 (0) |
| Tocilizumab | 4 (15) | 0 (0) | 0 (0) |
| **Statin therapy, n (%)** | 11 (41) | 25 (100) | 1 (11) |
| **Anti-hypertensive therapy, n (%)** | 13 (48) | 24 (96) | 7 (78) |
| **Baseline blood tests‡, median (IQR)** |  |  |  |
| High-sensitivity C-reactive protein (mg/L), NR <3.0 | 4.24 (0.76, 19.60) | 4.93 (3.01, 11.43) | - |
| High-sensitivity Troponin I (n/L), NR<40 | 4.20 (2.00, 6.60) | 206 (13.5, 1132) | - |
| Erythrocyte sedimentation rate (mm/hr), NR <35 | 16 (6, 41) | - | - |
| Interleukin-6 (pg/mL) | 25.08 (10.33, 71.55) | 57.32 (8.01, 121.2) | - |
| Pentraxin-3 (ng/mL) | 2.16 (1.13, 3.80) | 2.80 (1.10, 9.13) | - |
| Total cholesterol (mmol/L) | 4.50 (3.60, 5.30) | 3.60 (3.15, 4.30) | - |
| Mean triglycerides (mmol/L) | 1.30 (1.06, 1.94) | 1.25(1.00, 1.83) | - |
| Mean HDL cholesterol (mmol/L) | 1.27 (1.05, 1.79) | 0.94 (0.81, 1.09) | - |
| Mean LDL cholesterol (mmol/L) | 2.23 (1.77, 3.04) | 1.99 (1.51, 2.47) | - |

**\***The patient with unspecified large vessel vasculitis was a 55-year-old man with history of Sjögren’s disease and stroke in whom vasculitis was diagnosed based on constitutional symptoms, raised C-reactive protein, and classical imaging findings

**†**One patient with active Takayasu arteritis also had a non-ST segment elevation myocardial infarction secondary to atherosclerotic plaque rupture 5 days before baseline PET/MRI

‡Blood results shown are from the day of baseline PET/MRI