ORIGINAL ARTICLE

[^{68}Ga]Ga-NODAGA^{ZOL} uptake in atherosclerotic plaques correlates with the cardiovascular risk profile of patients.

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ABSTRACT:

Objectives: This study aimed to determine the correlation of [^{68}Ga]Ga NODAGA^{ZOL} uptake in atherosclerotic plaques and the cardiovascular risk profile of patients imaged with positron emission tomography(PET), wherein quantification of uptake was determined by atherosclerotic plaque maximum target-to-background ratio(TBRmax). We also correlated uptake with a history of cardiovascular events.

Methods: We included patients who underwent PET/CT imaging post-injection of [^{68}Ga] Ga-NODAGA^{ZOL}. We documented the number of atherosclerotic plaques found in the major arteries on CT and the cardiovascular risks in each patient. We quantified the intensity of tracer uptake in atherosclerotic plaque in the major arteries using the maximum standardized uptake value (SUVmax). The SUVmax of the most tracer-avid plaque was documented as representative of the individual arterial bed. We determined background vascular tracer activity using the mean standardized uptake value(SUVmean) obtained from the lumen of the superior vena cava. The maximum target to background ratio (TBRmax) was calculated as a ratio of the SUVmax to the SUVmean. The TBRmax was correlated to the number of atherogenic risk factors and history of cardiovascular events.

Results: Thirty-four patients(M: F 31:3; mean age±SD: 63±10.01 years) with ≥2 cardiovascular risk factors were included. Statistically significant correlation between TBRmax and the number of cardiovascular risk factors was noted in the right carotid($r=0.50;p<0.05$); left carotid($r=0.,649;p<0.05$); ascending aorta($r=0.375;p<0.05$); aortic arch($r=0.483;<0.05$); thoracic aorta($r=0.644;p<0.05$); left femoral($r=0.552;p<0.05$) and right femoral arteries($r=0.533;p<0.05$). TBRmax also demonstrated a positive correlation to history of cardiovascular event in the right

carotid(U=26.00;p<0.05); left carotid(U=11.00;p<0.05); ascending aorta(U=49.00;p<0.05); aortic arch(U=37.00;<0.05); thoracic aorta(U=16.00;p<0.05); left common iliac(U=49.500;p<0.05), right common iliac(U=43.00;p<0.05), left femoral(U=40.500;p<0.05) and right femoral(U=37.500;p<0.05).

Conclusion: In this cohort of patients, a positive correlation was noted between atherosclerotic plaque uptake of [^{68}Ga]Ga-NODAGA^{ZOL} and the number of atherogenic risk factors which translates to the risk of atherosclerosis and cardiovascular risk factors.

Key words: [^{68}Ga] Ga-NODAGA^{ZOL}, SUVmax, SUVmean, TBRmax, atherosclerotic plaque.

INTRODUCTION:

Worldwide, cardiovascular diseases are a major cause of morbidity and mortality, with their major driver being atherosclerosis.[1] Thus, the early identification of atherosclerosis can guide preventive care which includes lifestyle modifications and medical treatment (e.g., aspirin, antihypertensive therapy, lipid-lowering therapy) to prevent its clinical manifestations such as myocardial infarction, stroke, or peripheral artery disease**.**[2]

The exact cause of atherosclerosis is unknown. High levels of low-density cholesterol (LDLc) have been implicated, however for atherosclerosis to emerge there should be an interplay with multiple other risk factors.[3] Multiple risk factors for atherosclerosis have been proposed. In addition to the known traditional risk factors,

recent studies have also shown that there are other emerging risk factors which include high levels of C-reactive protein(CRP), triglycerides, sleep apnoea, emotional stress, sugar-sweetened beverage, air pollution and alcohol abuse[4-7].

Atherosclerosis is characterized by the accumulation of low-density lipoprotein cholesterol (LDLc) in the intima of vessels, causing an inflammatory lesion, called an atheroma. In patients with persistently elevated circulating levels of LDLc, atherosclerosis progresses over decades with enlargement of existing lesions and continued formation of new lesions.[8] Inflammation is a hallmark of atherosclerosis. Upon breaching of the vascular intimal integrity, there is an influx of LDLc and monocytes, which become macrophages. These macrophages oxidize LDLc to a toxic LDLc which is, in turn, toxic to the macrophages themselves. In early atheroma, there is little inflammation, and the macrophages die by apoptosis and are phagocytosed by adjacent cells to minimize inflammation. If the atheroma is large, the macrophages die by other processes which include necrosis. This becomes a nidus for dystrophic calcification.[9-10]

Zoledronate(ZOL) is a bisphosphonate that has been successfully complexed to Gallium-68 using NODAGA as the bifunctional chelator. Gallium-68 NODAGA-Zoledronate ([^{68}Ga] Ga-NODAGA^{ZOL}) targets calcium and hydroxyapatites which includes sites of dystrophic calcification.[11,12] Studies have shown uptake of [^{18}F]-Sodium fluoride ([^{18}F] NaF) in atherosclerotic plaques which has a similar tissue localization property as [^{68}Ga] Ga-NODAGA^{ZOL}.[13] [^{68}Ga]Ga-NODAGA^{ZOL} has also been demonstrated to localize in areas of dysregulated calcium homeostasis e.g., in acute myocardial infarction.[14,15]However, no study has evaluated the utility of [^{68}Ga]Ga-NODAGA^{ZOL} uptake in atherosclerotic plaques; and its correlation to

atherogenic risk factors and history of cardiovascular disease. The study aimed to evaluate how the [^{68}Ga]Ga-NODAGA^{ZOL} uptake based on PET semi-quantitative parameters correlates with cardiovascular risk factors and history of cardiovascular events.

MATERIALS AND METHODS:

Patients:

We retrospectively evaluated patients who had undergone PET/CT imaging with [^{68}Ga]Ga-NODAGA^{ZOL} as part of two past and ongoing prospective studies. The first compared [^{68}Ga]Ga-NODAGA^{ZOL} and [^{68}Ga]Ga-PSMA-11 in prostate cancer and the second ongoing coronary atherosclerosis study. [15,16] We accessed the medical records of all patients to extract information regarding their cardiovascular profile and medication use. All patients had given written informed consent, and the study was approved by the University of Pretoria Ethics Committee.

Thirty-four (34) patients were including 31 men were included. The mean age of the study population was 63 ± 10.01 years. All patients had at least two cardiovascular risk factors. The detailed description of the baseline characteristics of the study population is shown in table 1.

Table 1: Patient characteristics

Variable	Data
Patients(n)	34(100%)
Age(years)	
<65	19(55.9%)
≥65	15(44.1%)
Mean ± SD	63.00 ± 10.01
Range	34 – 81
Gender	
Male	31(91.2%)
Female	3(8.8%)
Atherogenic risk factors	
Dyslipidemia n(%)	11(32.4)
History of HIV infection n(%)	2(5.9%)
History of cardiovascular event	19(55.9%)
Diabetes Mellitus n(%)	9(26.5%)
Smoking n(%)	20(58.8%)
Systemic hypertension n(%)	21(61.8%)
Renal dysfunction n(%)	11(32.4%)
Total number of cardiovascular risk factors	
2	4(11.8%)
3	7(20.6%)
4	6(17.6%)
5	4(11.8%)
6	12(35.3%)
7	1(2.9%)
Cardiovascular drug use at the time of imaging	
Angiotensin converting enzyme inhibitors	10(29.4%)

Statins	**10(29.4%)**
Insulin	**4(11.8%)**
Oral anti-diabetic	**13(38.2%)**
Angiotensin receptor blockers	**2(5.8%)**
Beta blockers	**4(11.8%)**
Calcium channel blockers	**6(17.6%)**
Diuretics	**4(11.8%)**
Anticoagulation therapy	**10(29.4%)**

Tracer preparation, PET/CT acquisition and analysis:

[^{68}Ga] Ga-NODAGA^{ZOL} preparation:

[^{68}Ga]Ga was eluted from an 1850 MBq loaded ^{68}Ge/^{68}Ga generator (iThemba LABS, Somerset West, South Africa) using eluate fractionation and via Jelco 22G X 1″ polymer catheter (Smiths Medical, Croydon, South Africa) to obtain a metal-free radiogallium transfer. One millilitre of radiogallium was added to a kit vial containing 45 µg buffered NODAGA^{ZOL} at a pH of 3.5 to 4. The mixture was heated in a heating block at 90–95 °C for 10 min. Post labelling, instant thin-layer chromatography (ITLC) was performed to determine the radiochemical purity of the labelled product. A sample (5 µl) of [^{68}Ga]Ga-NODAGA^{ZOL} was spotted on ITLC strip (Merc kMillipore ITLC aluminium sheet with silica gel 60 Å, F254) and developed in a mobile phase solution (Acetyl Acetone + Acetonitrile + (0.6 M) HCL). The developed ITLC strip (radioactivity) was counted and recorded on radio-chromatogram ([Rf = 0.0–0.2 [^{68}Ga]Ga-NODAGA^{ZOL} (> 95%)}, Rf = 0.8–1.0 {free ^{68}Ga/ ^{68}Ga-colloids (<5%)}).

Image Acquisition:

No special patient preparation was obtained. PET/CT imaging was commenced at 60 min post intravenous injection of 0.054mCi/Kg (2MBq/kg) of [^{68}Ga]Ga-NODAGA^{ZOL} on a hybrid Biograph 40 True-point PET/CT scanner (Siemens Medical Solution, IL, USA). Image acquisition was from vertex to mid-thigh. The detailed imaging parameters are as we have previously reported. [17]

Image analysis:

PET/CT image interpretation/analysis was done on a dedicated PET/CT workstation equipped with a Syngo.via software (Siemens Medical Solution, IL, USA). Atherosclerotic plaques in the right carotid artery, left carotid artery, ascending aorta, arch of the aorta, thoracic aorta, abdominal aorta, right common iliac artery, left common iliac artery, right femoral artery and left femoral artery were determined on the CT images. The number of lesions per artery bed were counted. Patients were grouped based on the number of atherosclerotic plaques identified in their arterial beds of interest as no atherosclerotic plaque, ≤5, 6 to 10, and >10 atherosclerotic plaques in the arterial bed of interest. The frequencies in terms of proportion having the quantity of plaques of all the patients was expressed in absolute and in terms of percentages.

Volumes of interest (VOIs) were drawn in the respective lesions to determine the maximum standardized uptake value (SUVmax). The lesion demonstrating the highest SUVmax for that artery in each patient was taken as the reference. This was then followed by the determination of background activity (mean standardized uptake value (SUVmean)); derived by calculating the mean of three (3) regions of interest placed in the superior vena cava (the SUV of the blood pool). Lastly, the maximum

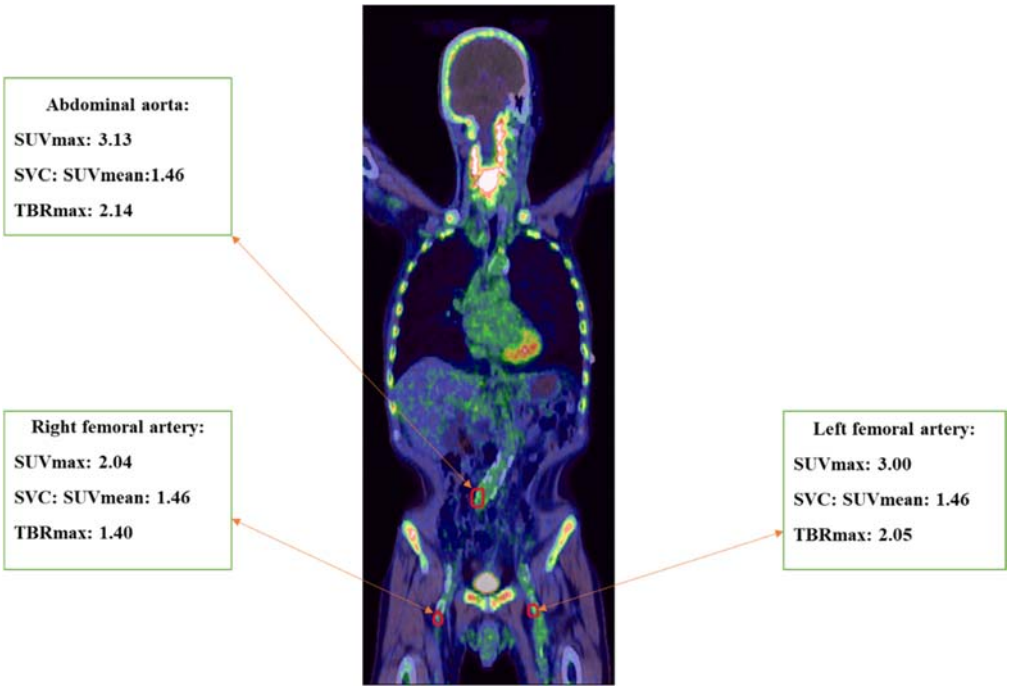

Fig 1: A 75-year-old male known with multiple cardiovascular risk factors (7) and a history of myocardial infarction. The abdominal aorta is noted to be skewed due to known vertebral scoliosis. Multiple atherosclerotic plaques are noted. The ones in the lower thoracic/upper lumbar region demonstrate minimal [^{68}Ga]Ga-NODAGA^{ZOL} uptake whereas those in the lower lumbar region are seen to demonstrate significant uptake: The representative plaque in the abdominal aorta; TBRmax: 2.14.

Also noted is uptake in multiple atherosclerotic plaques in the bilateral femoral arteries: representative TBRmax right-1.40 and left-2.05

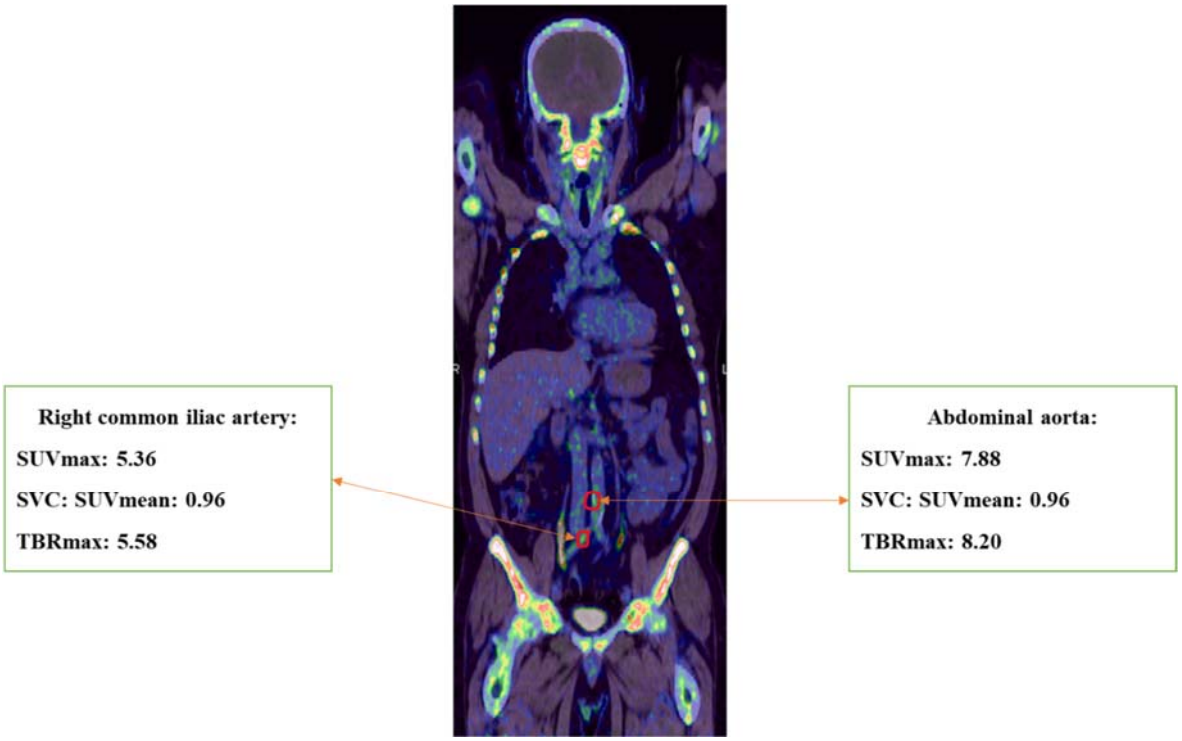

Fig 2: A 56-year-old male with 6 cardiovascular risk factors. Multiple atherosclerotic plaques are noted in both the abdominal aorta and the right common iliac demonstrating [^{68}Ga]Ga-NODAGA^{ZOL} uptake whereas those in the lower lumbar region are seen to demonstrate significant uptake: The representative plaques in the abdominal aorta; TBRmax: 8.20 and right common iliac TBRmax: 5.58

target to background ratio (TBRmax) was then calculated for each reference lesion in the respective artery for each patient as a ratio of SUVmax and SUVmean. Our change

of PET metrics used for quantifying radiotracer uptake is based on the recommendation of the Cardiovascular Committee of the European Association of Nuclear Medicine.[18]

Statistical analysis:

We performed descriptive statistics of baseline clinical and demographic information of patients. Categorical data are presented as frequencies while continuous variables are presented as mean ± standard deviation (SD) or as a median. We used Spearman correlation check for correlation between the TBRmax and the number of atherogenic/cardiovascular risk factors whereas Mann Whitney U test(U) was calculated to assess the correlation of TBRmax and the history of cardiovascular disease. Statistical significance was set at $p < 0.05$. We performed statistical analysis using IBM SPSS Statistics 21.0 (IBM Corp, Armonk, NY, USA).

RESULTS:

Frequency of atherosclerotic plaques

A total of 2678 atherosclerotic plaques were evaluated across all the major arterial beds of interest. Across all arterial beds of interest most patients had less than or equal to 5 atherosclerotic plaques, with the arch of the aorta dominant in that range;(76.5% of the total number of patients). The frequency distribution in the respective artery for the whole sample is shown in Table 2.

Table 2: Number of lesions in each artery

Number of lesions	Frequency	Percent (%)
Right carotid artery		
None	7	20.6
≤ 5	18	52.9
6 – 10	5	14.7
> 10	4	11.8
Left carotid artery		
None	9	26.5
≤ 5	18	52.9
6 – 10	5	14.7
> 10	2	5.9
Ascending aorta		
None	4	11.8
≤ 5	20	58.8
6 – 10	7	20.6
> 10	3	8.8
Arch of the aorta		
None	3	8.8
≤ 5	26	76.5
6 – 10	4	11.8
> 10	1	2.9
Descending thoracic aorta		
None	8	23.5
≤ 5	14	41.2
6 – 10	7	20.6
> 10	5	14.7
Abdominal aorta		

None	**3**	**8.8**
≤ 5	**7**	**20.6**
6 – 10	**5**	**14.7**
> 10	**19**	**55.9**
Right iliac artery		
None	**6**	**17.6**
≤ 5	**13**	**38.2**
6 – 10	**14**	**41.2**
> 10	**1**	**2.9**
Left iliac artery		
None	**5**	**14.7**
≤ 5	**9**	**25.5**
6 – 10	**6**	**17.6**
> 10	**14**	**41.2**
Right femoral artery		
None	**6**	**17.6**
≤ 5	**12**	**35.3**
6 – 10	**6**	**17.6**
> 10	**10**	**29.4**
Left femoral artery		
None	**6**	**17.6**
≤ 5	**10**	**29.4**
6 – 10	**11**	**32.4**
> 10	**7**	**20.6**

Correlation between uptake of [^{68}Ga]Ga-NODAGA^{ZOL} in atheromatous plague and cardiovascular risk factors.

We found a statistically significant correlation between TBRmax and the number of atherogenic risk factors in the following arteries: Right and left carotid arteries; ascending aorta, arch of the aorta, thoracic aorta; left femoral artery and right femoral artery. No statistically significant correlation was seen for the abdominal aorta and the bilateral iliac artery beds. (Table 3).

Table 3: Relationship between number of cardiovascular risk factors and TBRmax in the arteries.

	Number of cardiovascular risk factors	
TBRmax in the arteries	**r**	**p value**
Right carotid artery	**0.500**	**0.009**
Left carotid artery	**0.649**	**0.001**
Ascending aorta	**0.375**	**0.045**
Arch of the aorta	**0.483**	**0.007**
Descending thoracic aorta	**0.644**	**<0.001**
Abdominal aorta	**0.260**	**0.157**
Right iliac artery	**0.360**	**0.060**
Left iliac artery	**0.302**	**0.111**
Right femoral artery	**0.533**	**0.003**
Left femoral artery	**0.552**	**0.002**

r: Spearman correlation coefficient

Table 4: Relationship between history of cardiovascular events and TBRmax

	Yes	No	U	*p*-value
Variable	**Median (Range)**	**Median (Range)**		
Right carotid				
TBRmax	**2.57 (1.13 – 5.58)**	**1.41 (1.08 – 2.61)**	**26.000**	**0.006**
Left carotid				
TBRmax	**2.52 (1.17 – 3.53)**	**1.36 (1.16 – 1.85)**	**11.000**	**0.001**
Ascending aorta				
TBRmax	**2.51 (1.56 – 4.54)**	**2.02 (1.43 – 3.89)**	**49.000**	**0.019**
Arch of the aorta				
TBRmax	**2.46 (1.33 – 4.58)**	**1.73 (1.43 – 2.58)**	**37.000**	**0.003**
Descending thoracic aorta				
TBRmax	**2.80 (1.80 – 5.17)**	**1.87 (1.62 – 2.41)**	**16.000**	**0.001**
Abdominal aorta				
TBRmax	**3.26 (1.81 – 8.20)**	**2.44 (1.57 – 6.29)**	**69.000**	**0.068**
Right iliac artery				
TBRmax	**3.15 (1.99 – 6.96)**	**2.30 (1.64 – 8.29)**	**43.000**	**0.018**
Left iliac artery				
TBRmax	**3.39 (1.77 – 9.79)**	**2.16 (1.84 – 6.21)**	**49.500**	**0.026**
Right femoral artery				
TBRmax	**2.54 (1.00 – 5.56)**	**1.72 (1.00 – 2.00)**	**37.500**	**0.012**
Left femoral artery				
TBRmax	**2.09 (1.35 – 4.02)**	**1.58 (1.17 – 2.78)**	**40.500**	**0.018**
Average SUVmax/patient	**7.65 (0.80 – 30.60)**	**3.40 (0.10 – 26.80)**	**79.000**	**0.043**

U: Mann Whitney U test

Correlation between uptake of [^{68}Ga]Ga-NODAGA^{ZOL} in atheromatous plague and history of a cardiovascular event:

We also found a positive correlation between TBRmax and history of a cardiovascular event as follows: right and left carotid arteries; ascending aorta; the arch of the aorta; thoracic aorta; left common iliac artery; right common iliac artery; left femoral artery and right femoral artery. No statistically significant correlation was seen for the abdominal aorta. (Table 4)

Relationship between the number of cardiovascular risk factors, history of a cardiovascular event, and the number of atherosclerotic plaques in the arteries:

We found a positive correlation between the cardiovascular risk factors and the number of atherosclerotic plaques in the left carotid artery, aorta(arch, thoracic and abdominal) and bilateral iliac arteries. There was also a positive correlation between the number of risk factors and the overall number of atherosclerotic plaques in the studied vessels. There was however no correlation between the number of atherosclerotic plaques and the history of a cardiovascular event except for the abdominal aorta. (Table 5)

Table 5: Relationship between the number of cardiovascular risk factors, history of a cardiovascular event, and the number of atherosclerotic plaques in the arteries.

Number of atherosclerotic plaques in the arteries	Number of cardiovascular risk factors		Cardiovascular event	
	r	*p* value	r	*p* value
Right carotid artery	0.304	0.080	0.133	0.452
Left carotid artery	0.461	0.006	0.316	0.068
Ascending aorta	0.269	0.124	0.097	0.586
Arch of the aorta	0.480	0.004	0.273	0.119
Descending thoracic aorta	0.395	0.021	0.287	0.099
Abdominal aorta	0.582	0.000	0.411	0.016
Right iliac artery	0.410	0.016	0.214	0.223
Left iliac artery	0.426	0.012	0.247	0.160
Right femoral artery	0.117	0.508	0.000	0.999
Left femoral artery	0.166	0.347	-0.021	0.906
Composite total lesions	0.415	0.016	0.210	0.240

r: Spearman correlation coefficient

DISCUSSION:

In this retrospective study, we evaluated the relationship of [^{68}Ga]Ga-NODAGA^{ZOL} uptake in major vessel atherosclerotic plaques to atherogenic risk factors and history of cardiovascular disease. Uptake of [^{68}Ga]Ga-NODAGA^{ZOL} was based on

PET semi-quantification (TBRmax). We found that both the number of atherogenic risk factors and the history of cardiovascular disease had a positive correlation to the uptake of [^{68}Ga]Ga-NODAGA^{ZOL} in the arteries that were evaluated except for abdominal aorta and iliac arteries.

Atherosclerosis is the precursor of major cardiovascular-related events which have been implicated as the number one cause of morbidity and mortality related to non-communicable disease. The major components of atherosclerosis are inflammation; microcalcification and macrocalcification. Angiography has been the cornerstone of atherosclerosis assessment.[19] Molecular imaging complements morphological imaging by early detection of disease in the microscopic stages. Although clinical evaluation with the use of other risk calculators can determine the risk of disease, complementary information obtained from imaging can be of help in determining the course of the disease to assist in disease management and prevention of the associated complications.

Various molecular imaging probes have been used to image atherosclerosis targeting the inflammatory and dystrophic calcification components of the atherosclerotic plaques. In a review by Lawal et al, the clinical utility of [^{18}F]FDG PET/CT in assessing arterial inflammation as a risk for atherosclerotic disease among people living with HIV infection was emphasized. They also outlined potential newer probes that may quantify arterial inflammation in the HIV-infected population by targeting different proteins expressed on macrophages. [20] To image inflammation by targeting receptor expression (SSTR and CXCR4) by inflammatory cells [^{64}Cu]Cu-Dotatate and [^{68}Ga]Ga-Pentixafor had been used in vivo and in-vitro studies, whereas [^{18}F]FDG has been used to target the metabolic component of the inflammatory cells.

[21-23] [^{18}F]NaF has been used to target atherosclerotic plaque calcium due to its propensity to bind to calcium in addition to hydroxyapatites.[24-26] Investigators have also evaluated the relationship of tracer uptake to the atherogenic risk factors. Yun et al demonstrated a positive correlation of arterial FDG uptake with the atherogenic risk factors. They postulated that this may be used suggested a promising in the diagnosis of atherosclerosis and follow-up after treatment intervention.[27] Oliveira-Santos et al showed that in a high cardiovascular risk group, [^{18}F]-NaF atherosclerotic plaque uptake was related to the burden of cardiovascular risk factors.[28] Weiberg et al demonstrated a positive correlation of [^{68}Ga]Ga-Pentixafor uptake to cardiovascular risk factors. [29] Xing Li et al have compared [^{18}F]FDG and [^{68}Ga]Ga-Dotatate uptake; in addition, their respective relationships to individual atherogenic risk factors were evaluated. They concluded that in their series of patients there was a stronger association of increased [^{68}Ga]Ga-DOTATATE uptake with known risk factors of cardiovascular disease as compared to [^{18}F]FDG. [30] To our knowledge, no study has evaluated the uptake of [^{68}Ga]Ga-NODAGA^{ZOL} in atherosclerotic plaques including correlation to the atherogenic risk factors and history of cardiovascular disease. Unlike other studies which demonstrated correlation to individual atherogenic risk factors, in this study the correlation of [^{68}Ga]Ga-NODAGA^{ZOL} uptake was to the multiplicity of risk factors rather than an individual factor. This emphasizes/confirms that the aetiology of atherosclerosis is related to the multiple risk factors with their interplay involved in its progression. In simple terms these factors are synergistic.

[^{68}Ga]Ga-NODAGA^{ZOL} is a bisphosphonate that targets calcium and hydroxyapatites. [11-12] Studies have shown uptake [^{18}F] NaF in atherosclerotic plaques. [^{18}F] NaF has a similar tissue localization property as [^{68}Ga]Ga-NODAGA^{ZOL}

and [^{68}Ga]Ga-NODAGA^{ZOL} has also been demonstrated to localize in areas of dysregulated calcium homeostasis e.g., in acute myocardial infarction.[14,15] . [^{18}F]NaF uptake has been seen to be higher in microcalcification than macrocalcification thereby detecting early atherosclerosis than late with greater sensitivity as seen in a study by Hop H et al.[31]. In a study evaluating the prevalence and distribution of the atherosclerotic plaques in the abdominal aorta and its branches, Besser et al showed that the majority of atherosclerotic plaques in these were mostly calcified i.e. with macrocalcifications than mixed(with microcalcifications) which may explain what we see in this study whereby the abdominal aorta and iliac arteries do no show correlation with atherogenic risk factors due to preferential accumulation of [^{18}F]NaF to microcalcification which can be extrapolated to [^{68}Ga]Ga-NODAGA^{ZOL}, however further evaluation is advised.[32] We did not find correlation of history cardiovascular events with the number of atherosclerotic plaques except in the abdominal aorta. Studies have shown that the strongest predictors of cardiovascular events are the rate of development and the composition of the plaques [33,34]. The retrospective nature of the study deters us from knowing the exact composition of the plaques prior to the study. The correlation found in the abdominal aorta warrants further evaluation.

The correlation of [^{68}Ga]Ga-NODAGA^{ZOL} uptake to multiple risk factors emphasizes that a patient with multiple risk factors is more at risk of atherosclerosis than a patient with a single risk factor. To our knowledge as just mentioned this is a first study demonstrating that [^{68}Ga]Ga-NODAGA^{ZOL} uptake may be used in atherosclerotic plaque imaging also confirming that the aetiology of atherosclerosis is surely multifactorial not singular i.e. the risk factors are synergist in driving the pathogenesis of atherosclerosis. Our study had a large sample size to validate this. In a study by

Mamudu HM et al coronary artery calcium scores which communicates to the atherosclerotic plaque burden, was seen to significantly increase with the number of risk factors. This can also be postulated to our cohort of patients wherein we found a positive correlation of overall atherosclerotic burden to the number of risk factors.[35]

The limitations of the study include its retrospective design, the modest study population and the preponderance of male patients included in the study. However, this did not influence the results since the risk of cardiovascular disease levels out in both genders after the age of fifty years. In determining the correlation between [^{68}Ga]Ga-NODAGA^{ZOL} uptake in atheromatous plaques and the cardiovascular risk factors, we only considered the traditional cardiovascular risk factors. There are non-traditional/emerging risk factors that were not included in part of the risk factors considered. To get a good perspective of the correlation, a prospective study is warranted, to correlate with all the emerging and traditional risk factors including the validated risk calculator/scores. In addition, prospective longitudinal studies are needed to demonstrate the correlation between vascular/plaque uptake of [^{68}Ga]Ga-NODAGA^{ZOL} and the future risk of cardiovascular events.

CONCLUSION:

In this retrospective study, we found a strong association of [^{68}Ga]Ga-NODAGA^{ZOL} uptake with the number of atherogenic risk factors and history of cardiovascular disease. This confirms that atherosclerosis is a multi-factorial disease rather than a disease of singular aetiology and [^{68}Ga]Ga-NODAGA^{ZOL} may be useful in the quantification of atherosclerotic plaques.

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