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The future of imaging in CVD intervention trials: 2017 and beyond

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Abstract

Purpose of Review—As our understanding of cardiovascular disease has advanced over the past decades, multiple novel treatment strategies have been developed with the hope of reducing the global morbidity and mortality associated with this condition. Large-scale trials to test such novel therapies using clinical end-points are expensive, leading to interest in phase 2 clinical trials with imaging-derived outcome measures.

Recent Findings—Non-invasive imaging techniques that assess changes in both atherosclerotic disease burden and plaque composition in response to therapy are well established. With the advent of molecular techniques and hybrid imaging, we now have the ability to assess disease activity alongside these standard anatomic assessments. This multi-faceted approach has the potential to provide a more comprehensive assessment of the actions and efficacy of novel therapies in the carotids, aorta, and coronary arteries.

Summary—This review will examine how advanced non-invasive imaging strategies have been used to investigate drug efficacy in intervention trials to date, and crucially how these approaches are set to evolve and play a central role in developing the next generation of atherosclerotic medication.

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Conflicts of Interest

None

Figure 1 Reproduced from Noguchi et al. Effect of Intensive Statin Therapy on Coronary High-Intensity Plaques Detected by Noncontrast T1-Weighted Imaging: The AQUAMARINE Pilot Study. *Journal of the American College of Cardiology*; 2015 Jul 21;66(3):245–56. **Figure 6. PMR Regression With Statin Treatment and Figure 7. PMR Progression in the Control Group** Figure 2 A–D Reproduced from Tang et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *JACC*, 2009;53(22):2039–50. **Figure 2. Example of a high dose patient.**

Figure 2 E–H Reproduced from Tahara N et al. Simvastatin Attenuates Plaque Inflammation: Evaluation by Fluorodeoxyglucose Positron Emission Tomography. *Journal of the American College of Cardiology*; 2006 Nov 7;48(9):1825–31. **Figure 2. Effects of simvastatin on 18FDG uptake in atherosclerotic plaque inflammation.**

Keywords

Cardiovascular disease; hybrid imaging; novel therapies; drug efficacy; atherosclerosis; molecular imaging

INTRODUCTION

Recent advances in cardiovascular imaging have equipped researchers and clinicians with the ability to investigate many distinct features of the atherosclerotic disease process. In particular, we now have the capacity to quantify disease burden, to detect adverse plaque characteristics and, most recently, to assess disease activity. Measuring the impact of novel drug therapies on each of these key features can provide early insights in to their likely clinical safety and efficacy. Whilst initially confined to the carotid and aorta, the evolution of sophisticated imaging techniques has recently extended advanced imaging to the coronary arteries.

Approval of novel drugs generally requires demonstration of an improvement in hard clinical outcomes within large phase III randomized controlled trials. However, such studies demand large patient numbers and long follow-up periods to demonstrate a clinical effect. They are therefore extremely expensive. This, coupled with the recent failure of several novel drugs to demonstrate benefit, has led to growing interest in intermediate clinical studies, which may help screen therapies most likely to be effective or ineffective. Furthermore, early indications of some potential drug toxicity are of paramount importance before the initiation of phase 3 studies involving large populations of patients. Non-invasive imaging has an important role to play in both these respects, allowing direct visualisation of the atherosclerotic disease process, and an appreciation of how this changes in response to therapy. Moreover, the development of hybrid scanners provides the opportunity to investigate simultaneously multiple different aspects of the disease process, providing greater insight in to the action of novel therapies.

In this review, we will first briefly discuss the advantages of non-invasive compared to invasive imaging, before providing an overview of established non-invasive techniques, which facilitate the assessment of carotid plaque burden and characteristics. Finally, we will discuss novel strategies that can provide similar anatomical assessments in the coronary arteries, while incorporating advanced molecular assessments of disease activity. Ultimately, we believe that a hybrid non-invasive imaging approach will emerge as the most effective and comprehensive assessment of drug action, safety (hint) and efficacy.

Invasive versus non-invasive imaging in intervention trials

Some of the earliest studies examining the effects of medication on atherosclerotic plaque were performed using invasive imaging. In particular, intravascular ultrasound was used to quantify the effect of lipid lowering and antihypertensive therapy on plaque burden.^{1,2} Intravascular ultrasound provides high spatial-resolution images of the arterial wall, enabling an accurate assessment of luminal dimensions, atheroma volume and plaque burden which can then be used to quantify therapeutic efficacy. This has provided evidence of the

incremental benefit of intensive versus moderate lipid lowering³, and documented the effects of alternative therapies on atheroma progression.⁴⁻⁶ More sophisticated invasive approaches have also been adopted in phase two studies, including the use of optical coherence tomography to assess the effect of drugs on fibrous cap thickness and near infrared spectroscopy to assess the lipid core burden index.^{7,8}

Whilst invasive imaging offers unparalleled spatial resolution, its widespread use in research is limited by a small, yet significant, risk of complications. Furthermore, intravascular imaging can be time consuming and depends on the ability to safely pass the imaging catheter down the coronary lumen. Thus, serial invasive imaging studies often do not incorporate the entire coronary vasculature and are instead limited to specific coronary territories free from critical stenoses.

Non-invasive imaging, on the other hand, provides the opportunity to safely perform serial imaging of the entire vascular bed with a very low or absent risk of serious complication. Multiple different non-invasive techniques are available, each providing distinct information and possessing unique advantages and disadvantages. (Table 1)

CAROTID IMAGING

Most data from non-invasive cardiovascular intervention trials has been derived from the study of the carotid arteries. Indeed, the large calibre and stationary nature of the carotid vessels means they are particularly well suited for non-invasive imaging. Furthermore, histological validation can be obtained from carotid endarterectomy specimens. For this reason, many trials investigating the treatment of atherosclerosis have studied carotid atheroma as a surrogate marker of coronary disease. Indeed, whilst the majority of cardiovascular-related deaths occur as a direct consequence of coronary atherosclerosis, the systemic nature of this disease means that the assessments of atheroma burden and disease are of relevance to the vascular tree as a whole.⁹

Carotid Ultrasound

Carotid ultrasound is a simple and accessible screening tool that informs about plaque burden using measurements of the intimal medial thickness or total atheroma volume. Recent data have confirmed the important prognostic information provided by carotid plaque burden; highlighting the equivalent risk prediction provided by this method when compared directly with coronary CT calcium scoring.¹⁰ Carotid intimal thickness has been utilized as a surrogate measure of atherosclerotic disease burden in trials assessing the impact of lipid lowering therapy on cardiovascular disease.^{11,12} Given the low cost, safety and accessibility of carotid ultrasound, it is very attractive as a screening tool for large populations of patients in the community. However, it lacks accuracy compared to more sophisticated techniques, thus its use in future studies to assess the efficacy of novel drugs may be limited.

Magnetic Resonance of the Carotid Arteries

Magnetic Resonance is an attractive modality for cardiovascular intervention trials due to its ability to perform serial imaging to track the effect of therapies across multiple vascular territories without the risks associated with radiation exposure.¹³ High spatial-resolution

imaging of the carotid vessels is readily feasible, with accurate, reproducible measurements of carotid plaque thickness, volume and area derived from black-blood imaging sequences.

In common with ultrasound, these measures of carotid plaque burden predict major adverse cardiovascular outcomes^{14,15} and have already been used in several studies to investigate the time course of atherosclerotic regression in response to lipid lowering therapy.^{16–18} Furthermore, MR plaque burden measurements have been utilised in trials comparing different doses of lipid lowering therapy, highlighting the increased efficacy of aggressive versus conservative lipid lowering in plaque regression.^{19–21} The excellent reproducibility of plaque burden measurements within the carotid arteries means that positive drug effects can be appreciated despite small subject numbers, making this technique an attractive end point for clinical trials from a cost effectiveness perspective.^{20,21}

In addition to quantification of plaque burden, high spatial-resolution multi-contrast MR imaging provides detailed information regarding plaque composition based upon the distinct paramagnetic properties of different tissue types. It is well recognised that atherosclerotic plaques which are prone to rupture exhibit distinct characteristics including a large lipid necrotic core, thin fibrous cap, angiogenesis and microcalcification.²² MRI can detect many of these features of vulnerability in the carotid arteries (Figure 1), providing an opportunity to investigate changes in plaque composition and therefore to investigate the plaque stabilising effects of therapies.

Previous intervention trials have quantified the lipid burden and necrotic core of carotid plaque and demonstrated both a reduction in lipid content and increase in fibrous tissue following intensive lipid-lowering therapy.^{18,24,25} Longitudinal scanning has enabled appreciation of the time course of this effect, highlighting that the depletion of plaque lipid occurs in advance of a reduction in total plaque volume.^{18,24,25} This suggests that MRI-derived measures of lipid core may be more sensitive to treatment effects than plaque burden measurements and therefore of added value in future cardiovascular intervention trials.

In addition to quantifying the lipid core, MR can be used to identify intra-plaque haemorrhage and endothelial thrombus associated with plaque rupture or erosion. In the presence of acute thrombus or haemorrhage, the formation of methaemoglobin leads to profound T1 shortening and results in high intensity signals on T1 weighted imaging sequences. This has been well demonstrated in the carotid arteries of patients who have suffered a recent stroke^{26,27}, and is associated with a 6-fold increase in future cerebrovascular events.²⁸ Whether this high-risk plaque-imaging characteristic within the carotids is modifiable with therapy remains to be established. Like carotid imaging, aortic imaging with MRI is well established and feasible.

CORONARY IMAGING

The majority of adverse cardiovascular events arise in the coronary arteries. Direct imaging of this vascular bed therefore remains desirable even despite the systemic nature of atherosclerosis. However, imaging of the coronaries is more complex than the carotids due to the small calibre, tortuosity and complex motion of these vessels. Nonetheless, rapid

advances in spatial-resolution and image quality continue to address these challenges, making it likely that non-invasive coronary imaging will be used increasingly in future intervention trials.

Computed Tomography Calcium Scoring

Coronary artery calcification is pathognomonic of coronary artery disease and the burden of calcification as measured by CT calcium scoring has been shown to correlate with cardiovascular risk.^{29–32} On this basis, coronary artery calcium scoring has been used as an end point in numerous trials investigating the effect of lipid lowering therapy. However, findings from these studies have been inconsistent, with some suggesting statins halt the progression of CT calcium scores whilst others have indicated the exact opposite.^{33–36} In a recent meta-analysis of 8 intravascular imaging studies, aggressive statin therapy appeared overall to be associated with progression of coronary artery calcification, despite a reduction in soft plaque and total atheroma volume.³⁷

If coronary calcium scores predict adverse events, why do statins increase this score despite their well-established clinical benefits? On an individual plaque basis, the heavily calcified plaques quantified by CT are generally stable and it is the mixed or non-calcified plaques that are more prone to rupture. Whilst the CT calcium score does not directly assess the plaques that will themselves rupture, it does provide a surrogate measure of the total plaque burden. The higher the calcium score the higher the plaque burden (including non-calcific plaque) and therefore the higher the risk of events. However, it is also likely that in the context of drug therapy increases in CT calcium may relate to a plaque stabilisation effect and be associated with a reduced future risk of events. This important discrepancy highlights the difficulty in interpreting changes in the CT calcium score in clinical trials. More advanced imaging that directly visualises the non-calcified or mixed atherosclerotic plaques prone to rupture and precipitate events is being developed.

Computed Tomography Coronary Angiography

Computed tomography coronary angiography (CTCA) enables accurate non-invasive visualisation of individual coronary plaques and their morphological characteristics. Importantly, it is able to visualise and quantify non-calcific plaque, providing key prognostic information. Whilst this approach was previously hampered by difficulties in contouring the vessel and plaque boundaries, automatic post-processing methods appear set to markedly simplify this process.^{38,39} CTCA also holds the ability to identify specific high-risk plaque characteristics including necrotic core, spotty calcification and positive remodelling. Identification of these characteristics provides yet further prognostic information⁴⁰ and may be modulated by lipid lowering therapy.⁴¹ CTCA therefore appears set to play a major role in future clinical trials providing a direct assessment of the total plaque volume, non-calcified plaque volume and adverse coronary plaque characteristics in a single scan.⁴² Changes in these key parameters are likely to provide important insight as to the clinical efficacy of novel agents.

Magnetic Resonance Imaging of the Coronary Arteries

As imaging capabilities evolve, coronary magnetic resonance imaging is gaining interest as an effective non-invasive imaging strategy to monitor the effects of therapeutic interventions on atherosclerosis. Recent advances in whole heart self-navigated coronary angiography techniques, combined with higher field strengths, novel contrast agents, sophisticated software for motion correction and rapid image acquisition, mean there is hope that MR may become an even more effective tool for coronary imaging in future intervention trials.⁴³

Currently, one of the most promising MR techniques for coronary plaque imaging is the use of non-contrast T1-weighted imaging to identify methaemoglobin related to intracoronary thrombosis or intraplaque haemorrhage.⁴⁴ This T1-weighted MR imaging approach provides important prognostic information and, in an observational study, was used alongside CTCA to investigate the effect of intensive lipid lowering therapy on coronary plaque progression. The results demonstrated that pitavastatin treatment was associated with a significant reduction in plaque signal intensity (18.9% reduction; $p < 0.001$), a change which correlated with percentage reduction in total atheroma volume and high risk plaque features as assessed by CTA.²³

MOLECULAR IMAGING

Molecular imaging provides the opportunity to study many different aspects of disease activity, providing the ability to quantify early biological changes prior to the appearance of structural changes on anatomical imaging modalities (Figure 2).⁴⁵

Positron Emission Tomography

Positron emission tomography is an effective non-invasive imaging modality capable of monitoring disease activity at the molecular level through the detection of specific biological processes within tissues. The high sensitivity of PET imaging enables the detection of small metabolic changes potentially before any morphological changes become evident⁴⁸, an advantage which can lead to early indications of therapeutic safety and efficacy. Numerous tracers, both novel and established, targeting specific characteristics of high-risk atherosclerosis have already been investigated in pre-clinical or clinical studies.

FDG-PET—The most established and widely used PET tracer is ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG), a glucose analogue, which enters glucose-utilising cells and is unable to proceed through the glycolytic pathway, accumulating in proportion to cellular glycolysis. Whilst not entirely specific to inflammatory cells, use of this tracer exploits the increased metabolic activity of macrophages in comparison to surrounding cells. ¹⁸F-FDG uptake, therefore, may be used as a surrogate for inflammation, providing an assessment of inflammatory plaque activity across multiple vascular beds.⁴⁹ Given the central role that inflammation plays in the progression of atherosclerosis and the precipitation of acute plaque rupture it remains a key target for novel therapies. Indeed, this is the current subject of the Cardiovascular Inflammation Reduction Trial (CIRT) – Imaging Study (PI Zahi Fayad; NCT02576067).

Histologically, the ¹⁸F-FDG signal corresponds to macrophage density⁵⁰, and multiple studies have proven its utility for detecting inflamed, potentially high-risk atherosclerotic

disease in the carotids and large vessels.^{50,51} Data has established that ^{18}F -FDG uptake within the carotids and large vessels improves prediction of cardiovascular risk⁵², identifies the culprit lesion following transient ischaemic attacks, and predicts recurrence of stroke.^{53,54} The high inter-observer reproducibility and low short-term inter-scan variability in FDG-PET measurements within the carotid arteries means that therapeutic drug effects can be demonstrated with relatively small number of patients, and despite only small changes in SUV or TBR measurements.⁴⁸ Indeed, reduction in the vascular ^{18}F -FDG signal has been demonstrated just four weeks following the commencement of statin therapy.⁵⁵ These advantageous imaging characteristics have already been exploited in a number of phase II cardiovascular intervention trials, summarized in Table 2, with the FDG PET demonstrating good agreement with the results of larger phase III trials examining clinical endpoints. (Table 2) FDG-PET is therefore increasingly being used in clinical trials.^{49,62,63}

Whilst promising for the study of inflammation and atherosclerosis within the large vessels and the systemic effects of anti-inflammatory agents, direct quantification of coronary arterial ^{18}F -FDG uptake has been more challenging. Glucose is also the predominant energy source of the myocardium, leading to a frequent observation of intense physiological uptake in the left ventricle, obscuring activity in the coronary vessels. Even despite dietary restriction that switches myocardial metabolism from glucose to free-fatty acid, coronary arterial uptake is unclear in over half of coronary territories.⁶⁴ This has encouraged a search for more specific PET tracers to detect inflammation and alternative high-risk atherosclerotic disease processes including angiogenesis, hypoxia, and microcalcification. (Table 3)

^{18}F -Sodium Fluoride—One alternative PET ligand which holds promise in future cardiovascular intervention trials is ^{18}F -sodium fluoride (^{18}F -NaF), a well-established bone tracer which binds selectively to hydroxyapatite, detecting regions of calcification activity within the vasculature.^{70,71} Histological studies have confirmed its sensitivity and specificity for regions of newly developing microcalcification, a feature closely associated with unstable or vulnerable atherosclerosis.^{72,73} This radiotracer has been found to identify the culprit coronary vessel in over 90% of patients following myocardial infarction and, in patients with stable coronary artery disease, localises to high-risk features on intravascular ultrasound and CT including positive remodelling, microcalcification and necrotic core.⁶⁴

PET-CT imaging with ^{18}F -NaF has already been adopted as an exploratory end point in randomised trials, investigating the potential role of anti-calcific therapy in halting the progression of aortic stenosis (NCT02132026). The adverse impact of calcification in aortic stenosis is clear. In atherosclerosis, further work is required to establish whether the ^{18}F -fluoride signal reduces with therapy and whether this is associated with an improvement in clinical outcomes. Nonetheless, this tracer has demonstrated the feasibility of using PET to measure disease activity in the coronary arteries.

Molecular Magnetic Resonance

Magnetic Resonance also holds the ability to quantify disease activity at the molecular level and a number of targeted MR contrast agents have been investigated in pre-clinical and clinical studies. These include agents targeting elastin in the arterial wall⁷⁴ and fibrin within

thrombus.⁷⁵ Perhaps the most advanced and promising of these techniques is the use of ultrasmall superparamagnetic particles of iron oxide (USPIO). Following their circulation within the blood pool, USPIOs are phagocytosed by inflammatory cells. Their pronounced T2/T2* shortening effect leads to focal regions of hypo-intensity on T2 weighted MR sequences, which may be used to identify regions of inflammation. In the carotid arteries, USPIO accumulation occurs in the majority of ruptured or high-risk plaques, and corresponds to areas of macrophage accumulation.⁷⁶ Similarly USPIO-enhanced MR has been used to identify focal regions of inflammation within abdominal aortic aneurysms and appears to identify patients with more rapidly expanding aneurysms.⁷⁷

USPIO-enhanced MR has already been used in intervention studies assessing the effects of existing anti-inflammatory therapies on carotid atherosclerosis. The ATHEROMA study randomised patients with carotid disease and USPIO accumulation to low or high-dose atorvastatin and demonstrated a significant reduction in USPIO accumulation in those treated with high-dose statin following three months of therapy.⁴⁶

FUTURE STRATEGIES-HYBRID IMAGING

The development of hybrid imaging strategies provides the opportunity to investigate each of the above features in a single scan, thereby providing a multi-parametric assessment of the atherosclerotic disease process and in depth assessments of the efficacy of novel treatments. The increasing availability of PET/CT and, more recently, PET/MR imaging systems enables direct visualisation of key pathological process and the accurate coregistration of biological activity to anatomical images during a single scan. Intervention trials have already utilised PET/CT systems to investigate treatment efficacy.^{55,58} It appears likely that, with greater availability, PET/MR will adopt a central role in the investigation of novel therapies, especially given the lower radiation burden and comprehensive imaging assessment offered by these scans.

Indeed, we believe that in the near future carotid FDG-PET/MR will become the predominant imaging techniques used to assess drug efficacy in clinical trials. Not only does it offer the assessment of disease activity provided by PET, but also accurate measurement of plaque burden and composition provided by the MR. The effects of drug therapy on multiple different aspects of the atherosclerotic disease process will therefore be available from a single low-radiation imaging technique. Moreover, the excellent reproducibility of both MR and PET scanning means that relatively few patients would be required to detect even small therapeutic effects. Multiple time point studies may also be possible at acceptable radiation exposures.

Beyond the next few years, there is hope that coronary PET/CT imaging may reach the forefront of cardiovascular intervention trials, allowing direct assessments of drug efficacy in the coronary vasculature; where the majority of cardiac events arise. This will require continued development of post-processing software and sophisticated motion correction techniques to overcome the challenges faced in coronary arterial PET. However, the development and validation of specific PET tracers for inflammation, microcalcification and other high-risk disease processes appears set to provide detailed assessments of coronary

disease activity. These will complement measures of plaque burden and plaque morphology available on CTCA again providing multi-parametric atherosclerotic plaque characterization.

Conclusion

In conclusion, rapid advances in imaging technology have provided the ability to directly visualise, quantify and monitor the effect of therapeutic interventions on atheroma burden, plaque composition and disease activity within the vasculature. With an expanding catalogue of novel therapies targeting multiple different aspects of the atherosclerotic disease process, early indicators of therapeutic efficacy and safety are of critical importance prior to the initiation of phase III outcome studies. Non-invasive imaging modalities have already played a valuable role in our understanding of drug effects and with the advent of hybrid imaging offer comprehensive multi-parametric assessments of drug efficacy. These approaches are likely to play an expanding role in the testing and development of novel atherosclerotic therapies.

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Key Points

- Non-invasive imaging has greatly contributed to our understanding how anti-atherosclerotic therapies work, providing direct visualisation of plaque burden, plaque morphology and atherosclerotic disease.
- Continued advances in imaging technology, particularly with the evolution of hybrid imaging, now allow assessment of each of these parameters in a single scan. Moreover, techniques to measure each of these features in the coronary arteries are developing rapidly.
- In the future studies, hybrid imaging is likely to adopt a central role both in the carotid arteries using FDG-PET/MR and PET/CT with novel radiotracers in the coronary arteries.
- Non-invasive imaging is likely to play a central role in the future the development and approval of novel therapies directed against atherosclerosis.

Figure 1. The impact of therapy on plaque composition

Patient treated with statins. T1 weighted MRI sequences demonstrate a high-intensity plaque (HIP) with a PMR of 1.68 in the proximal segment of the left anterior descending artery (LAD) at baseline (A, yellow dotted circle). This HIP corresponds to the low-density coronary plaque with positive remodeling in the proximal portion of the LAD on CTA (B). Cross-sectional CTA images of this HIP lesion show positive remodeling with low attenuation plaque (LAP) (a, b, c). After 12 months of intensive statin treatment, PMR decreased to 1.08 (C, yellow dotted circle). CTA at follow-up shows a decrease in LAP volume (D, d, e, f).

Patient not treated with statins. Noncontrast T1-weighted imaging at baseline does not show any HIPs. The PMR was 0.92 in a lesion in the proximal segment of the right coronary artery (E, yellow dotted circle), which corresponds to a minor coronary plaque on CTA (F, a, b, c). However, after 12 months, a representative HIP was observed at the same lesion in the right coronary artery (G, yellow dotted circle), accompanied by an increase in the PMR to 1.35. CTA shows significant progression of coronary plaque morphology (H, d, e, f).

PMR: Plaque to Myocardium Ratio

Figure reproduced from Noguchi et al. J Am Coll of Cardiol. 2015;66(3):245–56.²³

Figure 2. The effect of therapy on disease activity

T₂*-weighted imaging of a left common carotid artery before and after ultrasmall superparamagnetic iron oxide (USPIO) infusion at 0 (**A and B**), and 12 weeks (**C and D**).

(**B**) USPIO uptake can clearly be seen in the plaque at baseline (**yellow arrowhead**).

(**C**) Pre-USPIO imaging remains very similar at 12 weeks (**red arrowhead**).

(**D**) Signal enhancement post-USPIO can be seen with no evidence of signal voids (**blue arrowheads**) (indicating minimal USPIO uptake and a lack of activated macrophages).

Effects of simvastatin on ¹⁸F-FDG uptake in atherosclerotic plaque inflammation (**E–H**).

FDG-PET images and fused PET/CT image demonstrate FDG signal in the aortic arch and carotid arteries (**E and F**). Repeat imaging following simvastatin reveals attenuation of FDG signal (**G and H**)

Figures A–D reproduced from Tang *et al* J Am Coll Cardiol, 2009; 53(22):2039–2050.⁴⁶

Figures E–H reproduced from Tahara N *et al*. J Am Coll Cardiol 2006;48(9):1825–31.⁴⁷

Table 1

Advantages and disadvantages of currently available imaging modalities.

Modality	Advantages for intervention trials	Disadvantages for intervention trials
Carotid Ultrasound	Easy and quick to perform Accessible Inexpensive Screening in the community	May not identify early therapeutic effects of therapy. Limited accuracy Surrogate measure for the presence and severity of coronary artery disease
CT calcium scoring	Reproducible measure of plaque burden. Score correlates with cardiovascular outcomes.	Does not quantify non-calcified plaque Difficulty in result interpretation
Computed Tomography Coronary Angiography	Can quantify non-calcified plaque and measure total plaque burden Detects adverse plaque characteristics	Artefact created by coronary calcification. Inferior soft tissue contrast. Exposure to ionising radiation.
Magnetic Resonance Imaging	Superior soft tissue contrast. Radiation free. Opportunity for repeated imaging. Multi-parametric imaging to detect plaque burden, plaque characteristics and disease activity	Coronary imaging remains challenging Prolonged scanning times. Contraindications to scanning.
Positron Emission Tomography	High sensitivity. Potential to monitor multiple pathophysiological processes. Can detect early changes in disease activity.	Exposure to ionising radiation. Limited specific tracers approved for human use.

Table 2

Cardiovascular Intervention trials using FDG-PET.

Author and Year	Number of subjects	Therapy	Vascular bed	Duration of treatment	Summary of Findings
Tahara et al, 2006 ⁴⁷	43	Simvastatin 5–20mg vs dietary modification.	Carotid arteries and thoracic aorta	3 months	Significant reduction in plaque 18FDG uptake in treated group
Tawakol et al, 2013 ⁵⁵	83	Atorvastatin 10mg vs Atorvastatin 80mg	Carotid arteries and thoracic aorta	12 weeks	Reductions in TBR 4 weeks following commencement of treatment in both groups. Additional relative reduction in high dose atorvastatin (10.6% [2.2–18.3%]; p=0.01) at 12 weeks.
Mizoguchi et al, 2011 ⁵⁶	56	Pioglitazone 15–30mg vs glimepiride 0.5–4.0mg	Carotid arteries and ascending aorta	4 months	Reduction in plaque TBR in pioglitazone group (p<0.01) vs non-significant increase in glimepiride group.
Tawakol et al, 2014 ⁵⁷	83	Rilapladib (Lp-PLA ₂ inhibitor) 250mg vs placebo	Carotid arteries and ascending aorta (vessel with highest TBR analysed as index vessel)	84 days	No significant difference in TBR between treatment groups (VTBR 0.05 (0.06 to 0.16; p=0.372)
Elkhawad et al, 2012 ⁵⁸	99	Losmapimod (p38 mitogen-activated protein kinase inhibitor) 7.5mg vs 15mg vs placebo	Carotid arteries and aorta (artery with highest TBR analysed as index vessel)	84 days	No significant difference in TBR across whole vessel between each treatment group. However, reduced FDG uptake observed in most active segment in treated group.
Fayad et al, 2011 ⁵⁹	130	Dalcetrapib 600mg (CETP inhibitor) vs placebo	Carotid arteries and ascending thoracic aorta	24 months	7% reduction in most diseased segment TBR in dalcetrapib group, but no difference in index vessel TBR between groups.
Potter et al, 2009 ⁶⁰	30	B-vitamin therapy vs placebo	Carotid arteries, thoracic and abdominal aorta, femoral arteries	4 years	No reduction in arterial wall inflammation despite a reduction in circulating homocysteine
Maki-Petaja KM et al, 2012 ⁶¹	17	Anti-TNF alpha therapy	Aorta	8 weeks	Reduction in aortic inflammation and stiffness

Table 3

PET tracers currently under investigation for use in atherosclerosis.

PET tracer	Imaging target/process	Vessels targeted	Evidence to date and ongoing trials
18F-Fluoride	Microcalcification: hydroxyapatite	Coronary	Uptake in over 90% culprit coronary plaques following MI ⁶⁴ PREFFIR trial ongoing to investigate whether 18F fluoride uptake can predict future cardiac events (NCT02278211)
18F-FDG	Inflammation: macrophage glucose utilisation	Carotid Aorta	Strong correlation between FDG uptake and macrophage staining in carotid plaque ($r = 0.85$; $p < 0.0001$) ⁵¹ CIRT (NCT02576067) trial ongoing and will use FDG-PET to measure changes in plaque activity in response to methotrexate therapy.
68Ga-DOTATATE	Inflammation: SST receptor Macrophages	Coronary Aorta Carotid	Uptake correlates with history of CV events and presence of calcified plaque ⁶⁵ and can detect culprit lesions post ACS with a sensitivity of 88% and specificity of 78%. ⁶⁶ VISION study ongoing to assess relationship between PET signal and carotid artery inflammation (NCT02021188)
18F-Choline	Inflammation: macrophage choline metabolism	Aorta Carotids	ParisK study ongoing in order to assess relationship between 18F-choline uptake and carotid artery inflammation using PET/CT and MRI (NCT01899014)
18F-FMISO	Hypoxia	Aorta	Strong accumulation in atherosclerotic rabbit aortas and uptake increases with progression of atherosclerosis. ⁶⁷
68Ga-NOTA-RGD	Neoangiogenesis: $\alpha_v\beta_3$ Integrin	Aorta Carotid	Increased uptake in stenotic carotid arteries which correlated with $\alpha_v\beta_3$ integrin expression, though in small patient numbers. ⁶⁸
11C-PK11195	Inflammation : translocator protein expressed by activated macrophages	Carotid	Increased uptake in symptomatic vs asymptomatic carotid stenosis. PPV of 100% for detecting symptomatic plaque when PET signal combined with CT attenuation. ⁶⁹