Patients with symptomatic peripheral arterial disease (PAD) affecting the lower extremities are initially evaluated with an ankle-brachial index (ABI) and segmental pressure measurements. An ABI <0.90 diagnoses significant lower extremity PAD (>50% stenosis) with a sensitivity and specificity of 79% and 96%, respectively.1 An ABI between 0.90 and 1.0 is considered borderline. The localization of the stenosis can be inferred by an abnormal decrease (>20 mm Hg) in segmental lower extremity pressures. In the presence of calcified atherosclerosis, arteries may become stiff and noncompressible, which results in a falsely elevated ABI (often >1.3). For patients with suspected PAD and a normal ABI at rest, it is valuable to obtain postexercise ABI measurements, which if <0.85 are consistent with PAD and is an independent predictor of mortality.2 Imaging is then needed to confirm the location and degree of stenosis before revascularization or if the diagnosis of PAD is uncertain.

Characterization of PAD can be performed with noninvasive angiography using computed tomography (CTA) or magnetic resonance angiography (MRA), as well as with duplex ultrasonography (US), depending on patient specific characteristics (Table 1). Advances in both CTA and MRA provide clinicians with the opportunity to obtain a high resolution, 3-dimensional (3-D) road map of the peripheral arterial tree in patients, particularly when planning revascularization strategies. Invasive digital subtraction angiography (DSA) has been the accepted standard for evaluation of lower extremity atherosclerosis. Although DSA is a robust technique for diagnosing significant arterial stenosis or obstruction, it provides a 2-D view of the vessels, which may underestimate the degree of stenosis for tortuous vessels.3 Furthermore, there are inherent risks with arterial access, ionizing radiation, and the use of iodinated contrast media (CM).4

This review aims to deliver a comprehensive, yet concise review of noninvasive imaging modalities in the diagnosis of lower extremity PAD (defined as involving the aorta, iliacs, and infragenual arteries). Furthermore, we will integrate the available evidence and society guidelines, to provide an informed clinical perspective regarding the role of the imaging modalities in patient care. Briefly, future directions in computed tomography (CT) and magnetic resonance imaging (MRI) will be discussed as they pertain to clinical vascular medicine.

Computed Tomography Angiography

Background

Initially, CTA was limited by the use of single slice scanners that imaged a fraction of the arterial tree at a given time. With the advent of multidetector row CT, images of inflow and runoff vessels became possible using a single acquisition and CM injection. Multidetector row CT has progressed rapidly from 4-detector row scanners to 64-detector rows or more, resulting in increased speed of scanning and greater longitudinal field of view while maintaining near-isotropic imaging voxels. Minimum voxel dimension of 0.4 to 0.6 mm in the z-axis are currently achievable with 64-detector row scanners, optimizing visualization of smaller, distal arteries.

Image interpretation is aided by the use of advanced post-processing techniques. Volume rendered 3-D reconstruction of the arterial tree provides a global overview for the rapid identification of pathology. Maximum intensity projection (MIP) images provide similar views to traditional angiography and are useful for qualitatively assessing the degree of stenosis. The usefulness of both volume rendered and MIP are limited by obscuration of the vessels by bones. Thus, automated software techniques for bone removal have been implemented; however, even the best algorithms require some degree of manual correction. Either automated or interpreter generated centerlines in the vessel of interest can be placed to obtain curved planar reformations, which gives both longitudinal and cross-sectional views of the vessel, which are useful for quantitative measurements; however, this is done at the cost of distortion of nearby anatomic landmarks. Distortion-free detailed interrogation is performed with thin section multiplanar reformats, which can be oriented to any desired plane. Axial 2-D source data are used when other techniques are inconclusive.

Vessels with dense calcifications have high attenuation, which may lead to blooming artifact and resultant overestimation of stenosis. To minimize this, a window level of 200 Hounsfield units and width of 1000 Hounsfield units are recommended5 for image analysis. In the setting of heavily calcified vessels or metallic stents, image reconstruction using a sharp kernel (B46) can reduce blooming artifact,
although this results in increased background image noise. The true lumen in calcified arterial vessels is often best analyzed using a combination of reconstruction techniques and source images. Additionally, dual-energy CTA postprocessing to subtract voxels containing calcium in the vessel wall is a promising technique for evaluating calcified vessels.

### Technical Considerations for CTA Image Acquisition

Imaging of the lower extremity peripheral vasculature is performed from the aortic diaphragmatic hiatus through the toes, to evaluate the entire inflow and runoff (Figure 1). In the upper abdomen, visualization of the splanchnic and renal vasculature relies on good breath holding to prevent obscuration of the vessel by motion artifact. Respiration does not affect imaging beyond the pelvis.

CTA requires the use of iodinated CM for visualization of the vasculature. Injection rates vary depending on protocol, but typically are in the range of 4 to 6 mL/s delivered intravenously by a dual channel power injector. The amount of iodinated media will vary depending upon the patient and protocol used, with ≈100 to 120 mL used for an abdominal CTA with runoffs. However, this dose could be reduced to 80 mL in patients with a small body mass index. A saline chaser injected at the completion of the CM media injection results in greater enhancement of the vasculature and a reduction in the CM dose.

To maximize the arterial enhancement during the examination, both CM transit time and speed of acquisition need to be considered. CM transit time is the time from the beginning of CM injection to the arrival of CM in the territory of interest, and is derived by either real-time enhancement monitoring (bolus tracking) during the injection of full dose of CM or by a separate smaller test bolus performed before the exam. Historically, with slower scanners, the fastest acquisition speed was chosen and the duration of CM injection was set to the scan time with scan initiation determined by CM transit time. Because of the rapid acquisition of modern scanners, this approach results in under opacification of the peripheral vasculature as a result of insufficient time to fill the vascular tree. Adding 3 to 5 seconds to the CM transit time, reducing the pitch to a moderate value (typically around 0.9) and increasing the CM volume lengthens the scan duration allowing for better filling of the vasculature. However, pathology such as large aneurysms and high-grade stenosis can delay the transit of CM to the distal vasculature, resulting in scanning before its arrival. A second late scan of the calf should be preplanned in the event of inadequate pedal opacification.

A new strategy put forth by Fleischmann7 is to fix the duration of scanning the lower extremity vascular to 40 seconds by adjusting the pitch. The volume and rate of CM injection

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>CTA</td>
<td>Rapid acquisition&lt;br&gt;High spatial resolution&lt;br&gt;In-stent restenosis visualization better than MRA&lt;br&gt;Faster scan time than MRA</td>
<td>Heavily calcified vessels&lt;br&gt;Iodinated contrast&lt;br&gt;Ionizing radiation exposure</td>
</tr>
<tr>
<td>MRA</td>
<td>Both gadolinium enhanced and noncontrast approaches available&lt;br&gt;Neither iodinated contrast nor ionizing radiation are used</td>
<td>In-stent restenosis limited by metal artifact depending on stent type&lt;br&gt;Risk of NSF in patients with advanced renal disease who receive gadolinium</td>
</tr>
<tr>
<td>Duplex US</td>
<td>Easily accessible&lt;br&gt;Inexpensive&lt;br&gt;No radiation</td>
<td>Less accurate in aortoiliac region because of patient obesity or intestinal gas&lt;br&gt;Limited sensitivity for multilevel stenosis&lt;br&gt;Heavily calcified vessels</td>
</tr>
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</table>

CTA indicates computed tomography angiography; MRA, magnetic resonance angiography; US, ultrasonography; NSF, nephrogenic systemic fibrosis; and PAD, peripheral arterial disease.

<table>
<thead>
<tr>
<th>Table 1. Comparison Between CTA, MRA, and Duplex US for Diagnosis of PAD</th>
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<tr>
<td>Imaging Modality</td>
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</tr>
<tr>
<td>CTA</td>
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<tr>
<td>MRA</td>
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<tr>
<td>Duplex US</td>
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Figure 1. Computed tomography angiography of aortoiliac occlusive disease. Bone segmentation was achieved using automated algorithms with manual correction to produce full-volume maximum intensity projection (MIP) image after bone removal (A) and 3-dimensional volume rendered (VR) image with bones included at a partial transparency (B). Aortic occlusion is annotated on the MIP image by the asterisk directly inferior to the renal arteries. Occlusion of the bilateral common iliac arteries and stents, as well as the external iliac arteries, is also shown on both images. Reconstitution of runoff flow occurs at the superficial femoral arteries bilaterally. Collateral pathways are easily visualized on the VR images. The Arc of Riolan (arrow) supplies the inferior mesenteric artery (IMA) territory from the superior mesenteric artery. The superior rectal artery (arrowhead) supplies the internal iliac arteries (black arrows) from the IMA. The internal iliac artery collateralizes with the circumflex femoral arteries supplying the runoff vessels.
is based on weight and delivered as a bi-phasic injection to provide sustained opacification of the arterial system. Many patients with PAD undergo multiple imaging studies during their lifetime; thus, reducing exposure to radiation is paramount in this population. Reducing tube voltage results in better attenuation of CM because of the energy of the photons being closer to the k-edge of iodine, and reduction in effective dose to the patient. A decrease from 120 to 100 kVp results in a 34% reduction in radiation dose without affecting diagnostic image quality. More aggressive dose reduction from 100 to 80 kVp maintains diagnostic image quality with an additional 23% dose savings. However, in larger patients, lower kVp protocols are limited by noise. The newest current generation scanners offer an additional dose reduction of 50% while maintaining image quality because of advances in image processing.

Image domain-based iterative reconstruction algorithms, as compared with filtered back projection image reconstruction of prior generations scanners, reduce noise and maintain image sharpness through modeling techniques made possible by improvement in computer processing power. Alternatively, with a similar radiation dose, iterative reconstruction can be used to increase image sharpness without affecting noise levels, which preliminary studies suggest may improve visualization of the lumen of small stents or calcified vessels.

Magnetic Resonance Angiography

Currently, high performance MR scanners provide striking angiographic images without patient exposure to radiation or the complexity of removing overlying bone from 3-D reconstructed images. MRA can be performed using contrast-enhanced (CE-MRA) approach or noncontrast-enhanced, flow-sensitive techniques that take advantage of the difference in signal properties between static tissue and flowing blood. These noncontrast MRA techniques include time-of-flight (TOF) MRA, ECG-gated partial-Fourier fast spin echo (FSE), and steady-state free precession (SSFP). In addition, phase-contrast MRA shows arterial blood flow direction and velocity.

Contrast-Enhanced MRA

CE-MRA is the workhorse of clinical MRA because of the robustness of the technique (Figure 2). CE-MRA takes advantage of the increase in arterial signal after administration of intravenous paramagnetic gadolinium (Gd)-based contrast agents because of the shortening of T1 relaxation in blood. Fast T1-weighted gradient-echo sequences with low flip angles are used in combination with an intravenous bolus injection, allowing for rapid acquisition of 3-D volumes with high signal-to-noise ratio of vessel to background. Visualization of the vasculature is further enhanced by mask subtraction to remove the background signal, similar to DSA. MRA interpretation relies heavily on full-volume MIP images created from the subtracted datasets, which provide a global prospective. Detailed image analysis is done using subvolume MIPs and multilobar reformats.

In MR, images are derived from Fourier transformation of radiofrequency signals that are acquired during an imaging sequence. K-space is the raw image data as represented in frequency-time domain and is built up in a sequential, stepwise fashion. The data located at the center of k-space contribute most to the contrast agent within an image. Thus, for CE-MRA, acquisition of the center of k-space needs to occur during peak vessel enhancement. The timing of the scan initiation is determined from a test bolus or using bolus-tracking methods, similar to CTA.

There are 7 Gd-based contrast agents currently approved by the Food and Drug Administration in the United States, and 2 additional agents used in the European Union (Table 2). They are paramagnetic and classified on the basis of protein binding, linear or cyclic structure, and ionicity. In patients with normal renal function, the half-life of Gd-based contrast agents are ≈1.5 hours. All Gd-based contrast agents have been associated with the rare development of nephrogenic systemic fibrosis; however, the majority of cases involve the linear agents: Gadopentetate dimeglumine (Magnevist), Gadodiamide ( Omniscan), and Gadoversetamide (Optimark). The current recommendation is to avoid any Gd-based contrast agent in patients with a glomerular filtration rate <30 mL/min per 1.73 m² given risk of nephrogenic systemic fibrosis.

The older Gd-based contrast agents, move quickly from the vasculature to the interstitial space, which results in limited time for imaging with the maximal spatial resolution. However, a new blood pool contrast agent, gadofosveset trisodium, was recently approved by the Food and Drug Administration for 3-D MRA. This agent reversibly binds to albumin, increasing T1 relaxivity in a steady state, which lasts for about an hour. In a small study of 27 patients with 334 arterial segments, imaging with 0.03 mmol/kg of gadofosveset trisodium resulted in 100% agreement between degree of stenosis graded with steady-state MRA and DSA.

Multistation MRA can be performed to image the aorta and peripheral runoff arteries using the same bolus, typically ≈0.2 mmol/kg body weight, in a bolus-chase technique, wherein the aortoiliac, femoropopliteal, and tibial regions are sequentially imaged. Multistation MRA benefits from a bi-phasic injection protocol with a high initial rate of injection that is reduced for the lower stations, resulting in increased arterial opacification of the distal station. The routine use of parallel imaging, requiring phased array peripheral coils, has reduced typical breath holds requirements for the aortoiliac station from 15 to 20 seconds or less without significant loss of image quality.

Despite advances in acquisition speed, venous contamination of the tibial station can be problematic, particularly in the setting of critical limb ischemia, where there is a smaller time difference between arterial and venous enhancement. There are several options for addressing venous contamination, including thigh compression cuffs or a semicircular foam pillow behind the knee to impede lower extremity venous return. Another option is to image the calf vessels first with a separate contrast bolus (which eliminates the possibility of venous contamination). However, imaging the tibial station first using time-resolved MRA is the approach most commonly used in practice. Time-resolved MRA uses k-space undersampling
with view-sharing to acquire multiple 3-D MRA datasets rapidly every 1 to 2 seconds during the injection of a small amount of contrast agent. Ninety seconds of imaging from the start of injection is sufficient for the calf in most cases. This dataset is subtracted from a mask image and is presented as a cine of MIP images, replicating the appearance of DSA and thus allowing form separation of arterial and venous phases.

The use of higher field strength MRI, such as 3.0 Tesla offer a higher signal-to-noise ratio, potential for lower doses of Gd and improved spatial resolution compared with 1.5 Tesla. In a small study of MRA at 3 Tesla, there was excellent agreement between degree of stenosis seen with MRA and conventional angiography, and there was nearly isotropic submillimeter 3-D voxels.

**Noncontrast-Enhanced MRA**

Noncontrast-enhanced MRA (Figure 3) was initially described by Wedeen et al and further developed by Miyazaki et al. The first such technique was 2-D TOF, a gradient-echo technique that depends on flow-related enhancement. There are several challenges to 2-D TOF, including inadequate signal for vessels deep in the abdomen, flow-related artifacts seen in areas of stenosis, difficulty in obtaining perfectly perpendicular imaging planes, and a lengthy scan time. The diagnostic performance of CE-MRA is >2-D TOF. However, 2-D TOF is useful for evaluation of tibial and pedal arterial stenosis or occlusion, particularly if inadequately visualized by contrast angiography and is as accurate as DSA for these vessels.

There has been renewed interest in noncontrast-enhanced MRA given concerns of nephrogenic systemic fibrosis secondary to Gd in patients with advanced renal disease. There are several new techniques: (1) ECG-gated partial-Fourier FSE, (2) 3-D FSE technique with sampling perfection with application of optimized contrasts using different flip angle evolution (SPACE), (3) balanced SSFP with arterial spin labeling, and (4) quiescent-interval single shot MRA using 2-D SSFP.

ECG-gated 3-D FSE exploits the difference in arterial and venous flow velocities during the cardiac cycle. During diastole arteries have lower blood flow, resulting in high signal intensity on T2-W images, whereas in systole, the higher arterial blood flow leads to low signal intensity. Venous blood is bright throughout the cardiac cycle because of the relatively low resting flow. The MRA is then obtained by subtracting systolic from diastolic images. In a small study at 1.5 Tesla, ECG-gated 3-D FSE was compared against CE-MRA and found to have a sensitivity and specificity of 85% and 76%, respectively, with an overestimation of stenosis in 22%. The use of parallel imaging and higher field strength may improve acquisition time and image quality.

3-D FSE with SPACE uses a noncontrast, T1-W dark blood whole body technique with a high degree of reliability in normal volunteers. It has improved k-space sampling efficiency compared with traditional 3-D FSE. Additional studies are needed to evaluate the test characteristics of this technique in patients with PAD.

Balanced SSFP with arterial spin labeling results in bright blood images in a single acquisition by first using a nonselective tag pulse to invert the magnetization for the entire imaging plane. Then a spatially selective tagging pulse is applied upstream of the arteries of interest and the tagged blood flows into the desired imaging region. In vessels with slow blood flow, the time needed to replace the tagged blood in the imaging plane can approach the T1 recovery time of blood, whereby the tagging effect would be lost.

Quiescent-interval single shot MRA using a modified single shot 2-D balanced SSFP pulse sequence has been evaluated...
in a pilot study of normal volunteers and subjects with PAD and can accurately depict peripheral vascular stenosis compared with CE-MRA with a sensitivity and specificity of 87% and 95%, respectively. Quiescent-interval single shot MRA does not use subtractive nonenhanced MRA methods. The sequence requires little optimization for an individual patient, and the peripheral MRA can be performed in <10 minutes. A 2-center study compared CE-MRA and quiescent-interval single shot MRA in 53 patients with known or suspected PAD and found a sensitivity and specificity of 85% to 90% and 95% to 97%, respectively, for the detection of significant stenosis.

Phase-contrast MRI shows a change in intravascular signal as arterial blood flow velocity deviates from the expected velocity encoded into the pulse sequence. Phase-contrast MRI has a sensitivity and specificity >90% for detection of clinically relevant stenosis (>75%) compared with DSA. However, Phase-contrast MRI is typically used only as an adjunct for determining degree of stenosis because of the long image acquisition time.

**Duplex US**

Duplex US uses the combination of gray scale (B-mode) for vessel morphology and color pulsed wave Doppler techniques. It is safe, inexpensive, and can provide functional information about vessel stenosis. The primary criteria of intra-arterial peak systolic velocity (PSV) and ratio of PSV between the site of stenosis and adjacent normal vessel are used to gauge the degree of stenosis (Figure 4). A PSV ratio of >2.5 suggests a stenosis of 50% to 74% and if the end-diastolic velocity is >60 cm/s, this suggests a tighter stenosis, in the range of 75% to 99%. However, the most commonly used criteria is PSV ratio >2.0, along with PSV>200 cm/s, and aliasing and spectral broadening seen with color Doppler to diagnose a stenosis >50%. The addition of color flow imaging improves the diagnostic performance of duplex US for aortoiliac and femoropopliteal arteries. If no color Doppler signal is visible in the vessel, arterial occlusion is suggested (Figure 5). The evaluation of infrapopliteal vessels although feasible by US is time consuming and may be technically challenging. Thus, a complete evaluation of the native lower extremity arterial system may not be feasible in many patients.

For evaluation with duplex US, patient body habitus may limit evaluation of the aortoiliac vessels because of abdominal girth or intestinal gas. The quality of a duplex US can vary depending on the examiner’s experience, and there is only moderate interobserver agreement for duplex evaluation of the aortoiliac and femoropopliteal areas. In the presence of sequential stenosis, US is less sensitive for detection of further downstream lesions.

**Clinical Applications**

There are several important considerations when choosing a noninvasive imaging modality to characterize lower extremity PAD: (1) imaging time, (2) need for evaluation of nearby anatomy, such as renovascular disease, (3) whether the indication is for native vessel disease or follow-up after a

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**Table 2. GBCA Used in Contrast-Enhanced MRA**

<table>
<thead>
<tr>
<th>GBCA</th>
<th>Excretion</th>
<th>Protein Binding</th>
<th>Structure</th>
<th>Charge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine (Magnevist)</td>
<td>Kidneys</td>
<td>None</td>
<td>Linear</td>
<td>Ionic</td>
</tr>
<tr>
<td>Gadobenate disodium (Multihance)</td>
<td>Primarily kidneys (small amount in feces)</td>
<td>Weak binding</td>
<td>Linear</td>
<td>Ionic</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>Kidneys</td>
<td>None</td>
<td>Linear</td>
<td>Nonionic</td>
</tr>
<tr>
<td>Gadoversetamide (Optimark)</td>
<td>Kidneys</td>
<td>None</td>
<td>Linear</td>
<td>Nonionic</td>
</tr>
<tr>
<td>Gadoteridol (Prohance)</td>
<td>Kidneys</td>
<td>None</td>
<td>Cyclic</td>
<td>Nonionic</td>
</tr>
<tr>
<td>Gadoxetate disodium (Evist)</td>
<td>Kidney and feces (enters liver cells)</td>
<td>None</td>
<td>Linear</td>
<td>Ionic</td>
</tr>
<tr>
<td>Gadofosveset trisodium (Ablavar)</td>
<td>Kidneys</td>
<td>Strong-reversible binding</td>
<td>Linear</td>
<td>Ionic</td>
</tr>
</tbody>
</table>

MRA indicates magnetic resonance angiography; and GBCA, gadolinium-based contrast agent.
revascularization (bypass or stenting), and (4) patient specific factors, such as kidney disease, diabetes mellitus, or the presence of implantable metal devices. There are 3 sets of clinical guidelines which apply to the use of noninvasive imaging with lower extremity PAD: the European Society of Cardiology, American Heart Association/American College of Cardiology and Trans-Atlantic Inter-Society Consensus (TASC) II.

Rapid image acquisition is a strength of CTA. CTA studies can be performed with scan times <5 minutes compared with MRA (≈20–30 minutes) or duplex US (30–45 minutes). If both legs are evaluated by duplex US, the scan times are quite long (≈1 hour) and may hinder patient flow in the vascular laboratory.

Native Vessel Disease

The TASC II guidelines and European Society of Cardiology recommend obtaining a MRA, or CTA, or duplex US for imaging of native vessel disease, depending upon local availability, cost, and experience. American Heart Association/American College of Cardiology guidelines support the use of CTA and MRA in the diagnosis of the anatomic location and presence of significant stenosis in patients with native vessel lower extremity PAD. Imaging with either CTA or MRA is well suited for the diagnosis of patients with lower extremity PAD, who have suspected aortic aneurysm/dissection, renovascular disease, trauma, or acute limb ischemia.

When choosing an imaging modality for native vessel disease, clinicians should consider whether the patient has underlying renal insufficiency, diabetes mellitus, or implanted metal devices. For patients who have normal renal function and are not diabetic, initial evaluation with either CTA or MRA is reasonable based on their similar excellent diagnostic capabilities. Overall, duplex US is a less sensitive technique for imaging native vessel stenosis compared with CTA or MRA; however, the greatest limitation of duplex US is the time required for evaluation of 2 lower extremities. A brief review of the important recent trials supporting the recommendation for either CTA or MRA in the diagnosis of native vessel disease follows.

A recent systematic review of the diagnostic performance of CTA included 20 studies using DSA as the accepted standard. This analysis included studies which used 2 to 4 detector row CT scanners as well as the contemporary 16 to 64 detector rows. In this population of nearly 1000 patients, 68% had symptomatic PAD and sensitivity of CTA for stenosis >50% or occlusion was 95% (95% CI, 92%–97%) with a specificity of 96% (95% CI, 93%–97%). Regardless of the location, excellent test characteristics were seen in the aortoiliac (sensitivity 96%, specificity 98%), femoropopliteal (sensitivity 97%, specificity 94%), and tibial arteries (sensitivity 95%, specificity 91%). Traditionally, the diagnostic performance of CTA in tibial disease is lower compared with the aorta-iliac and femoral levels, particularly in the setting of heavily calcified vessels.

A more recent single-center study evaluated the diagnostic performance of 64-slice CTA compared with DSA for detection of stenosis >70% on a per segment basis. CTA had an accuracy of 98%, sensitivity of 99%, and specificity of 97%. Furthermore, this study compared the clinical decision making outcomes using the TASC II guidelines based on CTA and DSA findings, which were identical in all patients but one who developed critical limb ischemia following CTA.

A recent meta-analysis was performed of CE-MRA for determination of >50% stenosis or occlusion in patients with symptomatic PAD compared with DSA. The pooled sensitivity of MRA was excellent at 95% and specificity 96%. Another meta-analysis of CE-MRA for the diagnosis of PAD compared with DSA demonstrated multiple studies with sensitivities and specificities >95%. Revascularization plans based on MRA agreed with the independent DSA in 90% of cases. Furthermore, a strategy of preoperative planning with MRA instead of DSA was expected to result in a 31% cost savings, highlighting the important role of preoperative noninvasive imaging as a cost savings measure.

Duplex US for the detection of stenosis >50% or occlusion was evaluated in a meta-analysis of 16 studies, which found good sensitivity for aortoiliac lesions (86%) and femoropopliteal (80%) with an excellent specificity of 96% or greater for

Figure 4. Duplex ultrasonography showing in-stent restenosis of a right superficial femoral artery (SFA) stent (for reference, the proximal SFA velocity is 96 cm/s, giving a peak systolic velocity [PSV] ratio of 278/96 cm/s, or 2.9). EDV indicates end-diastolic velocity; and RI, resistance index.

Figure 5. Duplex ultrasonography showing an occluded superficial femoral artery (SFA) stent without any evidence of flow on color or pulsed wave Doppler.
both. In a single-center study, 152 patients with symptomatic PAD were evaluated with duplex US, MRA, and DSA. The diagnostic accuracy for hemodynamically significant stenosis involving the aorta, iliac, and superficial femoral arteries (SFA) was 89% for duplex US and 94% for MRA compared with DSA. On the basis of a meta-analysis, the pooled sensitivity of 88% for duplex US was significantly lower than MRA (99%) for the detection of PAD. However, their pooled specificities were similar (96% for MRA and 95% for duplex US). No significant difference was noted in the diagnosis of stenosis above or below the knee.

Given that clinicians have an option of MRA, CTA, or duplex US for the noninvasive imaging of lower extremity PAD, it is important to evaluate the results from clinical trials comparing these modalities with regards to clinical outcomes. The Diagnostic Imaging of Peripheral Arterial Disease (DIPAD) trial evaluated clinical confidence in treatment plans and cost in >500 patients imaged with a duplex US, or MRA at 1.5 Tesla, or 16-detector row CTA. After adjusting for baseline variables, clinical confidence was higher and less additional imaging was required with the initial use of either MRA or CTA compared with duplex US. Importantly, the total cost for CTA were significantly lower compared with MRA or duplex US (because of the need for additional imaging in the US group). A randomized controlled trial compared CE-MRA and CTA for the initial diagnostic imaging as well as total diagnostic costs. No difference was found in the number of patients who underwent additional vascular imaging within 60 days of their initial study. The total diagnostic cost per patient was higher for MRA because of the baseline higher cost.

Prior Bypass Graft
Either duplex US, or CTA, or MRA can be used to evaluate for graft patency after lower extremity bypass surgery. The American Heart Association/American College of Cardiology recommends a surveillance program for postoperative inframalleolar bypass grafts with duplex US at 3, 6, 12, and 24 months after surgery (class I, level of evidence [LOE] A). Duplex US is ideally suited for postsurgery arterial bypass surgery surveillance of femoral-popliteal or femoral-tibial/ pedal venous grafts. Asymptomatic vein graft stenosis can result in acute thrombosis and ultimately graft failure if not detected early. In one study, vein grafts which were revised on the basis of stenosis findings with duplex US, had a 1-year patency rate of 90% compared with those grafts which were not revised and which had a patency rate of only 66%. However, duplex US is not well established for evaluating long-term patency of angioplasty or femoral-popliteal bypass with a synthetic conduit (class IIb, level of evidence [LOE] B).

When duplex US was compared with 4-row CTA, there was excellent agreement for the diagnosis of graft stenosis, aneurysmal changes, and arteriovenous fistulas. There was also no difference between duplex US and CTA when compared with DSA. Compared with duplex US, CTA may be superior for the detection of clinically significant stenosis in PAD bypass grafts.

Stents
CTA is superior to MRA for evaluation of restenosis in metallic stents or stent grafts. There are varying types of metal vascular stents, which influence the ability of a MRA to determine the degree of in-stent restenosis reliably (Figure 6). The lumen within a steel stent may be completely obscured because of susceptibility artifact and radiofrequency shielding. Stents made with nitinol, cobalt, and platinum are less sensitive to these effects. Stents oriented with the long axis parallel to the B0 field of the scanner demonstrate better imaging characteristic compared with those oriented perpendicularly.

Li et al used 64-detector row CTA to determine in-stent restenosis in 41 patients compared with DSA. Of the 81 stents, 76% were considered to be assessable based on image quality; motion or metal artifact influenced the interpretability of the other stents. For the group of evaluable stents, there was excellent sensitivity (95%) and specificity (96%) for detection of in-stent stenosis. When comparing the total group of in-stent stenosis seen on DSA with all CTA images (evaluable and nonevaluable stents), there was a lower sensitivity of 86% and specificity of 72% for CTA detection of in-stent stenosis. Beam hardening artifact from stents still limits detection of in-stent restenosis with CTA. Future in vivo studies will be required to determine whether iterative reconstruction can improve visualization.

Duplex US can be used to determine areas of in-stent restenosis, particularly within the iliac, SFA, or popliteal arteries (Figures 4 and 5). To identify >80% stenosis of the SFA compared with DSA, a PSV >275 cm/s and velocity ratio (comparing the velocity within the stent to a diseased free area vessel proximal to the stent) of >3.5 has excellent specificity (94%) but only moderate sensitivity (74%). The limited sensitivity of duplex US for detection of significant stenosis results in CTA being the diagnostic modality of choice for in-stent restenosis unless there are concerns regarding the potential for renal failure with the iodinated CM.

Figure 6. Magnetic resonance angiography showing a clearly patent right superficial femoral artery stent (double arrows). This is a nitinol stent which does not have the metal dropout artifact on magnetic resonance imaging.
Special Populations

Patients with Diabetes
Patients with diabetes mellitus often have heavily calcified vessels, which presents a diagnostic challenge in terms of using duplex US or CTA. With duplex US, heavily calcified vessels may result in an obscured arterial lumen and inability to diagnose the degree of PAD reliably. CE-MRA is not subject to image artifact generated by heavily calcified vessels (Figure 7). Interobserver agreement for degree of stenosis or occlusion is higher with CE-MRA than CTA, in the presence of arterial calcifications.48 From our perspective, for patients with diabetes, MRA should be considered the test of choice because of calcified vessels and concomitant renal insufficiency.

Renal Failure
As discussed previously, because of concerns regarding nephrogenic systemic fibrosis, the current recommendation is to avoid gadolinium-based contrast agents14 in patients with advanced renal failure with an estimated glomerular filtration rate <30 mL/min per 1.73 m² unless the information provided by the CE-MRI is not obtainable by another means. Patients with any degree of renal insufficiency can be safely imaged with duplex US and noncontrast MRA. With CTA, iodinated CM has an associated risk of contrast-induced nephropathy defined as an increase in serum creatinine from baseline by >25% or >0.5 mg/dL within 3 days of contrast agent administration without other cause. Those at highest risk for contrast-induced nephropathy have baseline renal insufficiency, diabetes mellitus, concurrent nephrotoxic drug use, hypertension, congestive heart failure, and dehydration. Large doses of CM and high-osmolar CM may further increase the risk of contrast-induced nephropathy.49 The greatest risk seems to be in patients with pre-existing renal insufficiency, particularly those with diabetes mellitus, regardless of the osmolality of the contrast agent used.50 It is important to ensure adequate hydration and to minimize the total volume of CM used. In addition, patients with allergic reactions to iodinated CM need premedication with steroids and antihistamine before receiving it.

Implanted Metal Devices
For patients with implanted metal devices, it is important to determine compatibility with exposure to magnetic fields. Device information cards may have manufacturer information regarding safety testing with MRI. Publications are available which consolidate the available information regarding metal devices and MRI safety.51 Newer pacemakers are being developed that are MRI-compatible. Patients who are pacemaker-dependent or have certain types of brain aneurysm clips, neurostimulator devices, or retained ocular ferromagnetic foreign bodies are best imaged with another modality because of potential risk. In addition, even if an implanted medical device is considered compatible with the MRI environment, there may be significant susceptibility artifact generated during the scan.

Clinical Application Summary
Given the options available for multimodality imaging of lower extremity PAD, we present an overview on the basis of our perspective and review of the literature (Figure 8).

Future Directions
Atherosclerotic Plaque Characterization
The degree of atherosclerotic plaque can be inferred by the amount and degree of stenosis seen on noninvasive imaging. However, recent studies, especially with MRI, have sought to understand atherosclerotic plaque burden and component characterization of the lower extremities to predict plaque stability and response to drug therapy. The total plaque volume in the SFA can be reliably measured by MRI52 and was used in a clinical trial of lipid lowering therapy.53 Atherosclerotic plaque composition is linked with vulnerability and progression, therefore multicontrast MRI showing calcification and lipid rich necrotic core54 may be useful in clinical trials of PAD
Atherosclerotic plaque composition in the SFA can also be evaluated with 18F-fluoro-deoxy-glucose-positron emission tomography/CT (FDG-PET/CT),55 which identifies areas of inflammation (PET) and calcification (CT) and has excellent reproducibility in clinical trials. Complementary MRI and
FDG-PET/CT have been used to evaluate atherosclerosis in the SFA.\textsuperscript{56} FDG-PET/CT shows a higher vascular FDG uptake within lipid rich plaque visualized by MRI.\textsuperscript{56}

**Calf Muscle Metabolism and Perfusion**

Current research using CT, MRI, and US is aimed at simultaneous evaluation of lower extremity anatomy as well as physiology to better understand which treatment options are best for a given patient. A recent study using FDG-PET in patients with claudication found evidence of impaired calf muscle glucose uptake,\textsuperscript{57} which did not correlate with baseline blood glucose levels. Another method for noninvasive evaluation of skeletal muscle metabolism in PAD is 31-phosphorus magnetic resonance spectroscopy. PAD patients have delayed recovery of phosphocreatine energy stores after exercise,\textsuperscript{58} which does not correlate well with MRI measures of calf muscle perfusion, suggesting uncoupling of perfusion and energetics and indicating an intrinsic mitochondrial defect in calf skeletal muscle in PAD.\textsuperscript{59} Magnetic resonance spectroscopy used for evaluation of patients with PAD is currently limited to the research arena.

Calf muscle perfusion can be measured with CE-MRI first pass perfusion with Gd at peak exercise,\textsuperscript{60} with noncontrast-enhanced MRI using arterial spin labeling after exercise\textsuperscript{61} or hyperemia related to thigh cuff occlusion and release.\textsuperscript{62} Contrast US with microbubbles has also been used to evaluate lower extremity arterial perfusion reserve.\textsuperscript{63} These techniques may prove useful in development of novel angiogenic therapies for patients with PAD.

**Conclusions**

Noninvasive imaging for lower extremity PAD is indicated to identify the location and severity of arterial stenosis when considering possible intervention. The major guidelines (TASC II, European Society of Cardiology, and American College of Cardiology/American Heart Association) support the use of duplex US, CTA, or MRA depending upon patient specific factors, local expertise, and safety profile. Promising research studies are providing new insights into using noninvasive imaging for atherosclerotic plaque characterization and lower extremity physiology assessment.

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