

Summer 20 SCHOOL 25

A residential learning experience

14-15 February 2025

Novotel Geelong, VIC

Vascular assessment and the controversies – Challenges in Rheumatology

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The Clinical Scenario

62 year old female

Rheumatoid Arthritis

DD – 15 years

Long history of Raynauds – no previous ulceration

On initial visit patient complained of right forefoot pain

No lesions present

Blood Pressure 145/70 – Pulse Pressure of 75mmHg

All pulses were palpable, ABPIs R – 0.69 (monophasic), L – 0.97 (biphasic)

Symptoms consistent with rest pain & intermittent claudication - Referral to vascular team

2nd appt. patient presents with ischaemic clean open lesions to the apex R/1st toe

Extremely painful

Vascular team results: ABPI R – 0.37, L – 0.85

Chemical lumbar sympathectomy – no effect

Deterioration occurred

Above knee amputation discussed

The Clinical Scenario

- Case conference – Podiatrist, Rheumatologist and Vascular team
- Use of A-V Impulse System at home daily for 6 hours
- Forefoot off-loader
- Immediate improvement in pain, colour, temperature and wound status
- R/1st apical ulcer – demarcated and auto-amputated



- Questions – why were the results of the vascular assessment in clinic so different to those generated by the vascular team?
- What should the optimum vascular assessment be to detect Peripheral Arterial Disease (PAD) in those with RA?



Clinical Practice Guidelines



No recognition of PAD Risk for patients with inflammatory joint diseases

Recommendations: Diagnosis of peripheral arterial disease (PAD)

	Grade	Level of evidence
2.1. We recommend using the ABI as the first-line noninvasive test to establish a diagnosis of PAD in individuals with symptoms or signs suggestive of disease. When the ABI is borderline or normal (>0.9) and symptoms of claudication are suggestive, we recommend an exercise ABI.	1	A
2.2. We suggest against routine screening for lower extremity PAD in the absence of risk factors, history, signs, or symptoms of PAD.	2	C
2.3. For asymptomatic individuals who are at elevated risk, such as those aged >70, smokers, diabetic patients, those with an abnormal pulse examination, or other established cardiovascular disease, screening for lower extremity PAD is reasonable if used to improve risk stratification, preventive care, and medical management.	2	C
2.4. In symptomatic patients who are being considered for revascularization, we suggest using physiologic noninvasive studies, such as segmental pressures and pulse volume recordings, to aid in the quantification of arterial insufficiency and help localize the level of obstruction.	2	C
2.5. In symptomatic patients in whom revascularization treatment is being considered, we recommend anatomic imaging studies, such as arterial duplex ultrasound, CTA, MRA, and contrast arteriography.	1	B

ABI, Ankle-brachial index; CTA, computed tomography angiography; MRA, magnetic resonance angiography.

Accurate test available <i>Except in patients with small vessel disease & non compressible vessels</i>	⊕⊕⊕○ Moderate
Disease is sufficiently prevalent & has significant morbidity <i>Average 17% Lower risk populations 1-4% All-cause and CV mortality increase by 2-3 fold</i>	⊕⊕⊕○ Moderate
Screening leads to reduced morbidity & mortality <i>Minimal data on outcomes. FRS in 19% of men and 36% of women could be reclassified based on ABI</i>	⊕⊕○○ Low
Treatment of screening-detected individuals reduces morbidity or mortality <i>Minimal data</i>	⊕○○○ Very Low
Screening is not harmful and is cost effective <i>Minimal data. Harm & cost could be caused by downstream testing and treatment</i>	⊕⊕○○ Low

Most areas are weak/conditional recommendations based on low or moderate evidence

The current available evidence demonstrates that PAD is common in patients with multiple cardiovascular risk factors and is associated with significant morbidity and mortality, but it does not support the benefit of routine ABI screening.



Editor's Choice – 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

Inflammation is involved in atherosclerosis pathophysiology. Several markers of inflammation (e.g. high-sensitivity C-reactive protein, fibrinogen, interleukin 6) are associated with an increased risk of the presence, progression and complication of LEAD. Some autoimmune/inflammatory conditions are at increased risk for LEAD (e.g. systemic lupus erythematosus, rheumatoid arthritis).

1. Who should have an ABI measurement in clinical practice?

- Patients with clinical suspicion for LEAD:
 - Lower extremities pulse abolition and/or arterial bruit
 - Typical intermittent claudication or symptoms suggestive for LEAD
 - Non-healing lower extremity wound
- Patients at risk for LEAD because of the following clinical conditions:
 - Atherosclerotic diseases: CAD, any PADs
 - Other conditions: AAA, CKD, heart failure
- Asymptomatic individuals clinically-free but at-risk for LEAD:
 - Men and women aged >65 years
 - Men and women aged <65 years classified at high CV risk according the ESC Guidelines^a
 - Men and women aged >50 years with family history for LEAD

Recommendations	Class ^a	Level ^b
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD. ^{250,251}	I	C
In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated. ²⁵²	I	C

Clinical Practice Guidelines

NCGC National Clinical Guideline Centre

Lower limb peripheral arterial disease

Diagnosis and management

NICE Clinical Guideline 147

Methods, evidence and recommendations

August 2012

Peripheral arterial disease: diagnosis and management

Clinical guideline [CG147] Published: 08 August 2012 Last updated: 11 December 2020

Surveillance report 2017 – Peripheral arterial disease: diagnosis and management (2012) NICE guideline CG147

We found 54 new studies through surveillance of this guideline. Evidence that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated.

Diagnosis of peripheral arterial disease

- In people with suspected peripheral arterial disease (PAD), is ankle brachial pressure index (ABPI) as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, in determining the diagnosis and severity of PAD?

New evidence on diagnosis of PAD among people with diabetes suggests that other forms of assessment may be superior to ABPI for diagnosing PAD in patients with diabetes. Currently, the recommendation suggests the ABPI measurement as an assessment tool in people with suspected PAD. Topic experts agreed that the new evidence should be reviewed looking specifically at people with diabetes as the value of ABPI might differ in those with diabetes.

Decision: This review question should be updated, specifically for people with diabetes.

NICE (NICE, 2012). A minimum vascular assessment should include:

- 1. History of modifiable and non-modifiable risk factors
- 2. Palpation of foot pulses
- 3. Skin, temperature and other visible clinical features
- 4. Intermittent claudication and ischaemic rest pain identification
- 5. Differential diagnosis of common leg symptoms
- 6. Identification of arterial ulceration and severity
- 7. Identification of venous disease, oedema and lymphedema



Careful inspection of lower limbs, including feet (i.e. colour, presence of any cutaneous lesion). Findings suggestive of lower extremity arterial disease, including calf hair loss and muscle atrophy, should be noted

SVS Qualitative assessment of the extremity for signs of PAD includes the presence of weak or absent distal pulses, the absence of distal hair growth, evidence of dry skin secondary to apocrine gland dysfunction, and in the case of advanced PAD, nonhealing areas of skin breakdown.

Clinical Practice Guidelines – reliance on ABI

- A recent review has evaluated Clinical practice guidelines (2010 -2020). An exhaustive search was conducted through the major medical databases and websites of specialist international organisations of interest.
- The guidelines harmoniously adopted the Ankle-Brachial Index as the initial diagnostic investigation of choice. However, concerning further diagnostic investigations and imaging, we found several discrepancies among the recommendations in the absence of strong evidence¹
- Cochrane Review data from Crawford et al. screened over 17,000 citations (search up to 2013) to identify cross-sectional studies comparing ABI to either diagnostic angiography or arterial DUS as reference standards. Only a single eligible study was identified assessing 85 participants (158 legs evaluated by untrained personnel) with a reported sensitivity and specificity of ABI of 95 and 56% using dopplerometric ABI in patients with leg pain³
- Bunte et al. 2015 suggested that a significant proportion of patients (29%) with ischemic tissue loss may have an ABI reading within the normal range particularly when below-knee disease is present²
- Calculation of diagnostic efficacy identified that ABI had a diagnostic sensitivity for lower extremity arterial disease of 72.3% and specificity was 69.3% when correlated with arterial Duplex ultrasound (DUS). A total of 27.5% of those deemed to have a normal ABI had evidence of significant arterial disease⁴
- The current evidence base for screening for PAD is limited, with no direct evidence examining the effectiveness of ABI screening alone. Indirect evidence is scant and includes a single diagnostic accuracy study of the ABI in an unselected population showing poor sensitivity⁴

1. Uyagu OD et al. Quality assessment and comparative analysis on the recommendations of current guidelines on screening and diagnosis of peripheral arterial disease: a systematic review. *BMJ Open*. 2022 Sep 14;12(9):e061599. 2. Crawford F et al. Ankle brachial index for the diagnosis of lower limb peripheral arterial disease. *Cochrane Database Syst Rev*. 2016 Sep 14;9(9):CD010680. 3. Bunte et al. Validation of the relationship between ankle-brachial and toe-brachial indices and infragenicular arterial patency in critical limb ischemia. *Vasc Med*. 2015 Feb;20(1):23-9 4. Alagha et al. Diagnostic Performance of Ankle-Brachial Pressure Index in Lower Extremity Arterial Disease. *Surg J (N Y)*. 2021 Jul 19;7(3):e132-e137. 5. Guirguis-Blake et al. Screening for Peripheral Artery Disease Using the Ankle-Brachial Index: An Updated Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Jul. (Evidence Synthesis, No. 165.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK526319/>

RA and Vascular Disease


- RA is one of the most common of the chronic inflammatory autoimmune diseases and is recognized as an independent cardiovascular risk factor¹
- According to the 2021 ESC Guidelines on CVD prevention, RA is an independent cardiovascular risk factor, increasing the risk of developing acute sudden cardiovascular events by about 50%, even in the subclinical stages or in patients with early- stage RA and symptoms for less than one year²
- RA patients have more than twice the risk of developing MI compared to the general population, and it appears that RA patients run roughly the same risk of developing acute cardiovascular events as do patients with type 2 diabetes mellitus³
- The prevalence of PAD in people with RA is reportedly up to 2.4 times that of the general population, independent of other cardiovascular risk factors. PAD also presents at a younger age and demonstrates an accelerated rate of progression⁴
- Chronic inflammation, characterized by elevated levels of C-reactive protein and other biomarkers, has been shown to be associated with PAD with the highest two quartiles increasing the risk of PAD more than threefold, independently of all other risk factors

1. Popescu D et al. Cardiovascular Risk Assessment in Rheumatoid Arthritis: Accelerated Atherosclerosis, New Biomarkers, and the Effects of Biological Therapy. *Life (Basel)*. 2023 Jan 23;13(2):319. 2. Visseren et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* 2021, 42, 3227– 3337. 3. Houge IS, Hoff M, Thomas R, Videm V. Mortality is increased in patients with rheumatoid arthritis or diabetes compared to the general population - the Nord-Trøndelag Health Study. *Sci Rep.* 2020 Feb 27;10(1):3593. 4. et al. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation.* 1998 Feb 10;97(5):425-8. 5. Ridker et al. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA.* 2001 Jul 14;285(28):3109-17.

Application of PAD screening guidelines in RA?

NICE (NICE, 2012). A minimum vascular assessment should include:

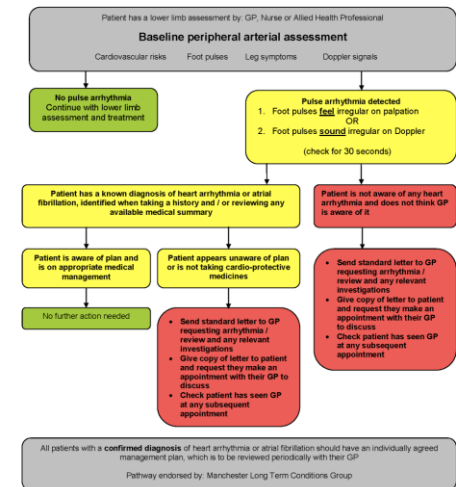
- 1. History of modifiable and non-modifiable risk factors
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- Pedal pulse palpation test was set to be positive for having PAD if one or more pulses were missing. Sensitivity was 71.7% and specificity was 72.3%¹.  Applicable in RA with pain, swelling, disease flare?
- A large cohort study has shown RA was associated with an increased incidence of atrial fibrillation (AF) which suggests that this arrhythmia is relevant in cardiovascular risk assessment of these patient. RA groups of patients had a significantly higher risk of AF (odds ratios 1.53)²
- Recent data show merit in podiatrists screening for AF, with one case of possible AF in every 22 people tested³ and 18% AF detection in community podiatry settings⁴

Should we use CW Doppler screening in all RA patients?



Atrial Fibrillation Early Detection Pathway (Podiatry)



1. Londero LS, Lindholt JS, Thomsen MD, Hoegh A. Pulse palpation is an effective method for population-based screening to exclude peripheral arterial disease. *J Vasc Surg.* 2016 May;63(5):1305-10.
2. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Svendsen JH, Torp-Pedersen C, Hansen PR. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ.* 2012 Mar 8;344:e1257.
3. Empowering podiatrists to perform pulse checks for opportunistic atrial fibrillation detection during annual diabetes foot checks. *Open Heart.* 2019 Feb 6;6(1):e000795.
4. <https://aftoolkit.co.uk/opportunistic-atrial-fibrillation-af-screening-in-a-podiatry-setting-torbay-devon/>

Application of PAD screening guidelines in RA?

NICE (NICE, 2012). A minimum vascular assessment should include:

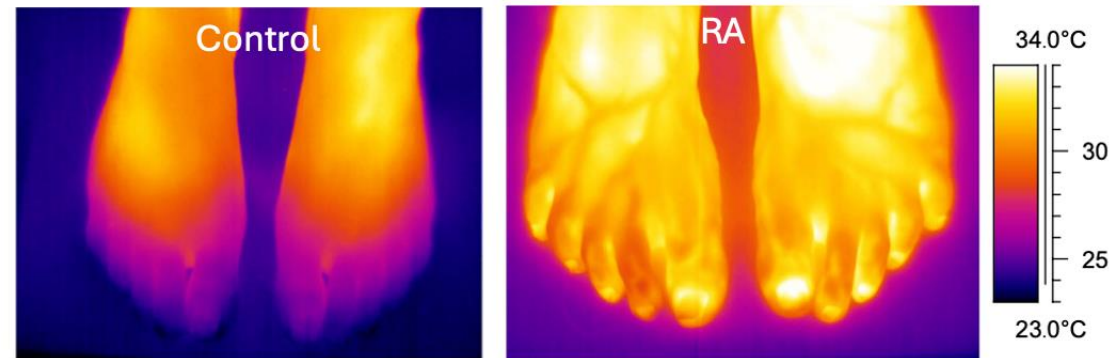
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Should we document/ consider overall disease activity and tender and swollen joint counts when assessing temperature gradients in RA ?

RA patients with confirmed absence of synovitis by clinical examination and musculoskeletal ultrasound have been shown to have a significant higher mean foot temperatures ($\sim 2^{\circ}\text{C}$) than the healthy subjects¹

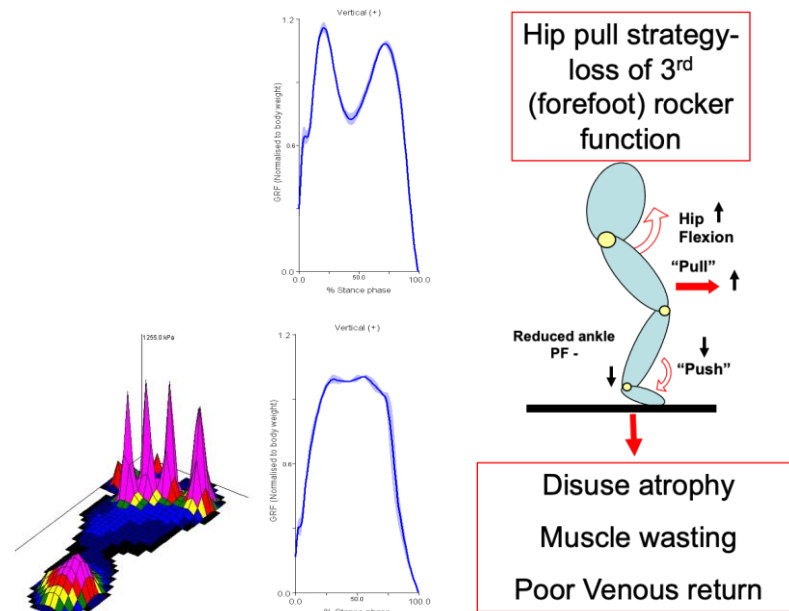
However, no significant differences between inflamed joint temperatures that were detected by ultrasonography and joint temperatures without inflammation²



Application of PAD screening guidelines in RA?

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1. Thurtle OA, Cawley MI. The frequency of leg ulceration in rheumatoid arthritis: a survey. *J Rheumatol.* 1983 Jun;10(3):507-9.
2. McRorie ER, Ruckley CV, Nuki G. The relevance of large-vessel vascular disease and restricted ankle movement to the aetiology of leg ulceration in rheumatoid arthritis. *Br J Rheumatol.* 1998 Dec;37(12):1295-8.
3. McRorie ER, Ruckley CV, Nuki G. The relevance of large-vessel vascular disease and restricted ankle movement to the aetiology of leg ulceration in rheumatoid arthritis. *Br J Rheumatol.* 1998 Dec;37(12):1295-8
4. Firth J, Hale C, Helliwell P, Hill J, Nelson EA. The prevalence of foot ulceration in patients with rheumatoid arthritis. *Arthritis Rheum.* 2008 Feb 15;59(2):200-5

Utility of the ABI for PAD detection in RA?

- A recent narrative review was undertaken exploring the association between PAD and RA as well as diagnostic options. A total of 44 studies were finally incorporated in the narrative review¹
- Main conclusions
 - The prevalence of arterial obstruction, diagnosed as $ABI < 0.9$, was 15-16% in several studies¹
 - Ankle-Brachial Index (ABI) < 0.9 might not be a sensitive tool for early PAD evaluation
 - People with RA often lead a sedentary lifestyle because of musculoskeletal impairment and do not complain of exercise-induced ischemic symptoms
- One study showed an Odds Ratio of 0.04 for prediction of foot ulceration but reported wide confidence intervals and high levels of missing data (11%) due to inability to perform ABI due to ankle oedema or the patient being unable to tolerate the measurement²
- In a cross-sectional study among the 931 RA patients' arteries, 7% had an ABI of 1.3 or higher and were considered incompressible, compared with 0.7% in the control group ($p < 0.001$)³
- Pulse pressure (difference between systolic and diastolic blood pressure) is used as a non-invasive marker of arterial stiffness. Increased pulse pressure, is thought to be associated with increased calcification in lower extremity vessels and linked with higher levels of procedural complications and mortality in patients who undergo tibial interventions for critical limb ischemia⁴

Evidence of calcification in RA

- Arterial calcification is an independent risk factor for cardiovascular and all-cause mortality.
- The processes are complex but are closely related to those involved in bone homeostasis, and it is relevant that calcification of the arterial wall and osteopenia often co-exist.
- RA has been associated with medial artery calcification formation. This is thought to occur secondary to chronic inflammation¹
- Tibial artery calcification is also a significant prognostic marker for PAD severity and worse limb-related outcomes²
- The medial arterial calcification (MAC) score is simple scoring system using foot x-rays to score infra-malleolar artery calcification. Higher pedal calcification scores were associated with an elevated risk of major amputation and was able to further stratify the risk of major amputation among high-risk patients with diabetes³
- Semiquantitative ultrasound scoring systems have been proposed (the presence of vessel wall calcifications and/or atherosclerotic plaques and flow velocity measurements) but the reliability and predictive properties are yet to be established.



Image taken from reference 1

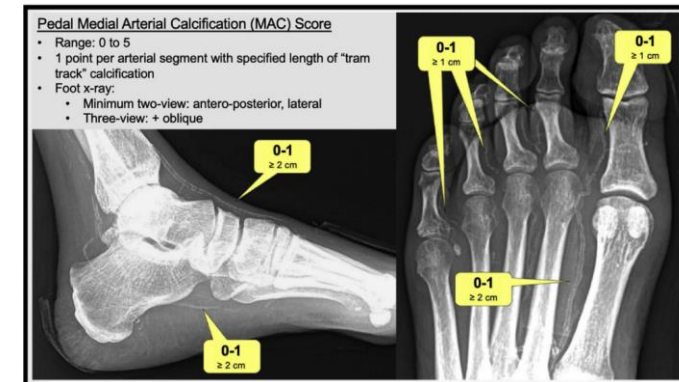


Image taken from reference 3

Should we carefully appraise standard foot x-rays for subtle evidence of calcification? What is the future role for point of care ultrasound imaging for vascular assessment?

Neurogenic or vascular claudication in RA?

- Up to 80% of the patients with RA can have some degree of cervical spinal involvement. Inflammatory synovitis in this region commonly progresses to bone erosion, ligamentous laxity, leading to late spinal instability¹
- Cervical lesions have been shown to be significantly associated with lumbar spinal lesions²
- The validity of symptom attributes in differentiating neurogenic from vascular claudication have been studied³
- The presence of symptoms that are triggered with standing, relieved with sitting, located above the knees and have a positive shopping cart sign represent strong evidence that a patient has intermittent neurogenic claudication rather than vascular claudication.

Symptoms of Lumbar Spinal Stenosis (Elevator Syndrome)



- Standing provokes symptoms
- Pain/weakness in the legs

- Patients lean forward while walking to relieve symptoms

- Sitting or bending forward relieves symptoms

The Clinical Scenario



- Questions – why were the results of the vascular assessment in clinic so different to those generated by the vascular team? **Calcification**
- What should the optimum vascular assessment be to detect Peripheral Arterial Disease (PAD) in those with RA? **Lack of evidence**



? Use of Pulse pressure for impression of arterial stiffness



? Appraise standard foot x-rays for subtle evidence of calcification



Atrial fibrillation screening



? Role of venous refill times for venous assessment



? Future role of POCUS and AI



Thank you for your attention

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