

Prospective assessment of the diagnostic accuracy of multi-site photoplethysmography pulse measurements for diagnosis of peripheral artery disease in primary care

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4 Prospective assessment of the diagnostic accuracy of multi-site photoplethysmography pulse

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6 measurements for diagnosis of peripheral artery disease in primary care

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For Peer Review

Abstract

Peripheral arterial disease (PAD) is associated with cerebral and coronary artery disease. Symptomatic PAD affects about 5% of people over 55 years; many more have asymptomatic PAD. Early detection enables modification of arterial disease risk factors. Diagnostically, assessment of symptoms or signs can be unreliable; ankle brachial pressure index (ABPI) testing is time-consuming and few healthcare professionals are properly trained. This study assessed the diagnostic accuracy of multi-site photoplethysmography (MPPG), an alternative non-invasive test for PAD, in primary care.

PAD patients identified from general practice registers were age- and sex-matched with controls.

Participants were assessed using MPPG, ABPI and duplex ultrasound (DUS). Outcome measures were sensitivity and specificity of MPPG and ABPI (relative to DUS) and concordance.

MPPG test results were available in 249 of 298 eligible participants from 16 practices between May 2015 and November 2016. DUS detected PAD in 101/249 (40.6%). MPPG sensitivity was 79.8% (95% confidence interval [CI] 69.9-87.6%), with specificity 71.9% (95% CI 63.7-79.2%). ABPI sensitivity was 80.2% (95% CI 70.8-87.6%), with specificity 88.6% (95% CI 82-93.5%).

With comparable sensitivity to ABPI, MPPG is quick, automated and simpler to do than ABPI; it offers the potential for rapid and accessible PAD assessments in primary care.

Keywords

diagnosis, duplex ultrasound, peripheral arterial disease, photoplethysmography

Introduction

Peripheral arterial disease (PAD) is common in middle-aged and older patients. It is symptomatic in approximately 5% of those aged between 55 and 75 years¹ but many times more have asymptomatic PAD.^{2,3} It carries a poor prognosis once well established, via its association with cerebral and coronary artery disease.⁴ Its major risk factors are smoking, diabetes, hypertension and hyperlipidaemia. Classic symptoms include intermittent claudication (predictable, repeatable ischemic calf pain on exertion due to reduced tissue perfusion, relieved by rest).⁵ As it progresses patients may present with pain at rest, tissue gangrene or ulceration (critical limb ischemia) which has only a 50-60% 5-year survival.^{6,7} Claudication symptoms are highly specific but have a low sensitivity⁸ as PAD is often asymptomatic, even in patients with hemodynamically significant large vessel disease.⁹ There is also evidence that those with PAD are offered fewer risk reduction strategies in the United Kingdom National Health Service (NHS) than other groups of vascular patients.¹⁰ Since 2011, General Practitioner (GP) practices have been incentivized to create PAD registers to address risk factors in these patients. National Institute for Health and Care Excellence (NICE) guidance recommends less invasive treatments, focusing on need for diagnostics in primary care¹¹ and commissioning encourages adopting innovative diagnostic devices, especially if cost saving.¹²

Detecting PAD early gives the opportunity to control its vascular risk factors and reduce adverse cardiovascular events. NICE Guidelines¹¹ recommend diagnosis through symptoms and signs (S&S) and measurement of the ankle brachial pressure index (ABPI) in the first instance. However, S&S alone can have a poor diagnostic accuracy.¹³ Additionally, the ABPI test is time-consuming, requires an experienced operator, does not allow measurement of transient state¹⁴ and may produce false negatives in people with falsely elevated ankle pressure due to stiff arteries (e.g. in diabetic, renal and elderly patients).¹⁵ Furthermore, the amount of training healthcare professionals receive in ABPI measurement varies;¹⁶ this is a barrier to its widespread adoption. Consequently, diagnosis of PAD in primary care is often made via S&S alone, or by referral to secondary care if suspected. The Edinburgh Claudication

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3 Questionnaire (ECQ) is based on S&S, is known to have limitations in sensitivity and specificity¹⁷, and
4 evidence of its uptake in is lacking. There is a need for an accurate test for primary care use.¹⁸
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8 We have introduced multi-site photoplethysmography (MPPG) which uses low-level near-infrared light
9 non-invasively to detect the tissue blood volume pulse¹⁹ at multiple body sites, and have quantified the
10 levels of agreement between MPPG and ABI in a hospital setting for both sensitivity and specificity.¹⁹⁻²²
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14 We have now developed a portable device with novel probes, rapid operation and automated pulse
15 analysis, with potential to be less time consuming and require less training than ABPI in primary care.
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18 The aim of this study was to assess prospectively the diagnostic test accuracy, relative to duplex
19 ultrasound (DUS), of MPPG in a primary care setting with respect to the accuracy of ABPI, ECQ and
20 PAD registers.
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24 25 26 27 **Methods**

28 29 **Study design**

30 A prospective diagnostic accuracy study in a primary care setting (ISRCTN13301188²³). The index test
31 was the novel prototype MPPG device; the comparator test was ABPI; the reference test, to confirm the
32 presence or absence of PAD, was DUS.¹¹ This study compares the diagnostic performance of MPPG and
33 ABPI with DUS and measures the concordance of MPPG and ABPI. Diagnostic performances of ECQ²⁴
34 and GP PAD registers²⁵ for the same participants compared with DUS have already been reported.
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42 43 **Participants**

44 Participants were recruited from 16 practices in North East England between May 2015 and November
45 2016. PAD patients were identified from GP registers, and matched with controls by sex and age (within
46 5 years). The study protocol^{23,26} was approved by Newcastle & North Tyneside 1 Research Ethics
47 Committee (14/NE/1238); all participants provided written informed consent.
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Participants were required to be ≥ 45 years and excluded if: they were receiving renal support therapy; had significant limb tremor; had damaged skin at a PPG measurement site (great toe or index finger); were unable to tolerate ABPI; had toe or limb amputation.

Participants made two visits within 1 month. Visit 1 was for screening and enrolment by a Vascular Research Nurse who recorded sex, height, weight, demographics, past medical history (diabetes, hypertension, ischemic heart disease, stroke, transient ischemic attack and atrial fibrillation), smoking status and medications, and administered an ECQ. Visit 2 was for measurements by a Practice Nurse of MPPG, ABPI, heart rate and blood pressures (systolic, diastolic, mean arterial and pulse), and DUS of both legs by a Vascular Scientist. Practice Nurses were trained and assessed in MPPG and ABPI by a Vascular Research Nurse prior to the study.

The estimated sample size²⁷ was 250 participants (80% power, 5% significance level and equal numbers with and without PAD). A pre-test probability of .5 was representative of the target population: Bendermacher *et al*²⁸ reported PAD prevalence of 48.3% in patients visiting their GP with symptoms suggestive of intermittent claudication.

PAD assessments

Measurements were made in examination rooms (mean ambient temperature $22.9 \pm 1.4^\circ\text{C}$). Subjects lay supine for 10 min prior to ABPI and MPPG measurements with 5 min rest between. The order of these measurements was alternated and DUS was performed last with the Vascular Scientist blinded to earlier results. Practice nurses and Vascular Scientist were blinded to the referral details, but blinding to PAD status was impractical since PAD can result in observable changes to extremities. Besides any ongoing medication on and between visits there were no additional clinical interventions between the index and reference tests.

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2
3 *Reference test*

4 A duplex ultrasonography system (M-Turbo, Fujifilm Sonosite Inc., Bothell, WA, USA) was used on
5 both lower limbs to detect the presence of disease in the arterial lumen from groin to ankle, from images
6 and blood velocity waveforms. The Vascular Scientist used a 7-feature grading system²⁹, derived from
7 Thrush and Hartshorne,^{26,30} to classify patients as PAD+ (significant disease detected in either leg) or
8 PAD- (significant disease in neither).
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16 *Index test*

17 Bilateral pulses were measured with MPPG from the right and left great toe pads while the subject lay
18 comfortably supine and still. Prior to recording, the practice nurse checked signal quality and PPG gain
19 for each toe (Figure 1).
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24 Digitized signals were recorded at 500 Hz for 60 s. Individual pulses were extracted using R-wave gating
25 from the single-lead ECG, measured at the finger probes.³¹ Each pulse was normalized in time and
26 amplitude, checked for validity and clustered with other pulses of similar shape.³² The median pulse used
27 to calculate the Shape Index (SI)²¹ was based on the largest cluster; PPG signals with insufficient pulses
28 (≤ 15) in the largest cluster were considered inconclusive.
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35 The prospective cut-off threshold for SI was 0.71.²¹ If exceeded in either leg it was classed as test positive
36 for hemodynamically significant PAD (PAD+) and PAD- otherwise. If neither leg could be measured, or
37 if one leg was normal and the other could not be measured, the MPPG was recorded as “inconclusive”.
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43 *Comparator test*

44 ABPI was measured using a hand-held 8 MHz Doppler ultrasound probe, blood pressure cuffs of
45 appropriate size and a manual sphygmomanometer (Huntleigh Dopplex ABPI Kit, Huntleigh Healthcare
46 Ltd, Cardiff, UK). The cuff pressure was raised at least 30 mmHg supra-systolic until the pulse could no
47 longer be heard and then reduced, noting the pressure at pulse re-appearance. Right and left brachial
48 artery pressures, and both right and left foot pressures were measured. If a foot artery was incompressible
49 and the pulse still audible then a not recordable pressure was noted. Where measurements were available,
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3 the highest value from the foot was divided by the highest brachial pressure. A ratio of <0.9 for either leg
4 was considered as PAD+, consistent with guidelines¹¹ and our previous work.²¹ If neither leg could be
5 measured, or if one leg was normal and the other could not be measured, or both arms could not be
6 measured, then ABPI was recorded as “Inconclusive”. Measurements in either leg of >1.3 were
7 suggestive of the presence of calcification or incompressible arteries and these patients were assigned
8 ABPI “Inconclusive”.

16 **Data analysis**

18 *Summary statistics*

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20 Height and BMI were described as mean and standard deviation. Number (and %) were used for previous
21 medical history. Matching of the groups was checked with Chi-squared test of proportions for sex,
22 smoking status and previous medical history; Student’s t-test for age and BMI.

27 *Diagnostic test accuracy*

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29 Diagnostic performances were per-participant rather than per-leg as diagnostically it is the patient who
30 would have PAD. 3x3 contingency tables were formed from the binary PAD+ and PAD- outcomes plus
31 inconclusive tests. The proportion of test failures was summarized for the index and comparator tests.
32 Sensitivity (Se), specificity (Sp), positive (LR+) and negative (LR-) likelihood ratios and diagnostic odds
33 ratios (DOR) were calculated from conclusive tests. Differences between sensitivity and specificity for
34 MPPG vs ABPI were tested using a two sample test for equality of proportions with continuity
35 correction.³³ McNemar’s test was used for concordance of MPPG and ABPI. The significance level was
36 <0.05 .

47 *Analytical methods*

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49 Information from each clinical history sheet, ABPI report, duplex report and ECQ was collated in a
50 spreadsheet controlled by the Clinical Trial Manager. SIs were calculated from MPPG signals by JW
51 using Python.³⁴ Statistical analyses were by AJS using R³⁵ (v4.1.1) and package “mada”.³⁶ Analytical
52 code was incorporated into the manuscript using markdown.³⁷ Results were independently checked by IG

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3 and TAWB. Study reporting followed the STAndards for Reporting Diagnostic accuracy (STARD)
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5 statement.³⁸
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9 **Results**

10 **Participants**

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12 A sample of 125 PAD and 125 non-PAD patients were recruited as per protocol. Due to a protocol breach
13 where one of the sites reported ABPI measurements consistently in a non-standard fashion, and did not
14 adequately rest patients before performing the MPPG, these subjects were excluded and recruitment was
15 extended to include a further 48. In total 306 patients consented to recruitment; 8 withdrew after consent
16 and before DUS, leaving 298 eligible (149 PAD patients and 149 controls); 49 had no valid index test (48
17 at the excluded site and 1 with missing PPG data), leaving 249 available for analysis (125 PAD patients
18 and 124 controls), Figure 2. The baseline characteristics of participants are summarized in Table 1. There
19 is overall sex-matching of DUS PAD+ and PAD- groups, and age-matching to within 5 years.
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31 **Diagnostic accuracy**

32 The reference test was successful in all 249 participants, with 101 (40.6%) positive for PAD. The
33 prevalence was lower than the 50% intended because the GP PAD registers, on which allocation to PAD
34 or normal was based, were found to have sensitivity and specificity of <1 (Table 3).²⁵
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39 Systolic pressure was recorded in both arms in 248 patients; in 6 patients, pressure could not be measured
40 in the dorsalis pedis nor the posterior tibial artery in one or both feet. The left or right leg ABPI exceeded
41 1.3 in 17 patients and was inconclusive in 8.4%, Table 2a. There was evidence of terminal digit
42 preference (rounding of recorded values to the nearest 10): of 497 valid brachial artery pressure
43 measurements, 185 (37.2%) were zero; of 961 valid foot artery pressure measurements, 368 (38.3%) were
44 zero.
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MPPG was successful in 228 patients (Table 2b). The MPPG failure rate was 8.4%, due mainly to mis-setting of the manual gain controls and signal quality of the ECG sensor used on the trial device. There were no adverse events from performing the index, comparator or reference tests.

There was significant non-concordance between index and comparator tests ($p < 0.001$), Table 2c. The diagnostic performance of both tests compared with DUS is shown in Figure 3 and Table 3, with diagnostic accuracy of PAD registers and ECQ provided for reference. There was no difference in sensitivity between MPPG and ABPI (79.8 vs 80.2%; $p = 1$), but there was a significant difference in specificity (71.9 vs 88.6%; $p = 0.001$).

Discussion

PAD carries a poor prognosis once established, owing to its association with cerebral and coronary artery disease.⁴ However, if accurately identified, “at risk” patients can have optimal early risk factor treatment to reduce risk of disease progression, adverse cardiovascular events and mortality.³⁹ Ideally a test for PAD would be appropriate for use in primary care as in the majority of cases it can be managed without referral to secondary care, if a reliable diagnosis can be made.¹⁸

Measurement of ABPI, for confirmation of the presence of PAD, is currently recommended by guidelines worldwide. It usually takes 20 to 30 minutes, including a 10 minute period of supine rest and is suitable for use in primary care but has known disadvantages. Arterial calcification resulting in incompressible arteries, especially in diabetics, renal and older patients, can render the ABPI non-diagnostic.¹⁵

Additionally, resting ABPI may be less sensitive in milder PAD, either because an arterial stenosis is not hemodynamically significant or because collateral vessels are present. Most reports would consider a stenosis of $\geq 50\%$ as diagnostically positive for PAD, but such a stenosis would usually not be hemodynamically significant at rest. Diagnostic performance of ABPI may be improved by post-exercise testing, but this adds significant complexity, time and expense. In one study nearly half the patients referred for suspected arterial disease had normal resting ABPI.⁴⁰ These factors may be particularly

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3 important in some asymptomatic or minimally symptomatic PAD patients, and ABPI would fail to
4 identify them. Protocol variations,⁴¹ and inter-observer variability may also reduce its accuracy.
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6 Additionally, it may be less accurate when used by less skilled or occasional operators.⁴² In a recent
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8 retrospective study compared with DUS, ABPI was only moderately predictive, with sensitivity of 72.3%
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10 and specificity of 69.3%.⁴³ Especially in diabetics another approach has been to use toe pressure
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12 measurements, part of the widely used Wound, Ischemia and foot Infection (WIFI) scoring system⁴⁴, but
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14 their use is less suitable for use in primary care. However, measurement at the toe, as with toe pressures
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16 and the MPPG technique, may improve diagnostic accuracy by detecting more distal disease.⁴⁵
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21 ABPI testing is not universally used for PAD diagnosis and anecdotally the majority of patients referred
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23 to secondary care vascular units have not had an ABPI. Automated oscillometric ABPI devices, such as
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25 the MESI device (MESI Ltd., Ljubljana, Slovenia), are diagnostically equivalent to conventional ABPI
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27 but may be quicker to use, and are in principle less prone to operator variability.¹⁴ However there does not
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29 appear to be validation of their use against a reference standard.
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32 We have previously reported poor GP PAD Register accuracy²⁵ (sensitivity 86.1%, specificity 74.5%). It
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34 is highly likely that due to poor diagnostic accuracy in primary care, PAD patients are being missed,
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36 leading to lost opportunities for vital early management. We have also highlighted issues with using just
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38 symptoms for diagnosis such as the ECQ²⁴ (sensitivity 52.5%; specificity 87.1%).
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42 At least 50% of individuals with diagnostic ABPI in population surveys have no claudication symptoms
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44 and current guidelines are mainly focused on the management of symptomatic PAD. Furthermore, the
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46 QRISK2 score⁴⁷ was not improved by the addition of PAD but it is possible that MPPG offers predictive
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48 value in cardiovascular risk assessment, as a diagnosis of PAD in itself identifies high cardiovascular risk.
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51 We have previously reported a qualitative study which demonstrates that users perceived MPPG to be
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53 quicker and easier to use than ABPI,⁴⁸ and like ABPI it is safe. An updated version of the MPPG device
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3 includes automatic gain control, ECG with conventional electrodes and real-time pulse analysis;³² we
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5 expect these will reduce its test failure rate.
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8 Our study had limitations. Although a case-control approach was suitable for optimizing trial efficiency
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10 by artificially adjusting prevalence, there is a risk of the approach leading to spectrum bias by favoring
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12 the inclusion of those with established PAD, and who appear on a register, over those who have early
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14 stage or mild PAD. Secondly, although we excluded one site due to observed failure of measurement
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16 protocol, we cannot rule out the possibility of unobserved measurement protocol breaches at other sites.
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18 Thirdly, time constraints in the project required us to measure MPPG with a prototype device while
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20 designing a more ergonomic version in parallel, which limited our opportunity to compare aspects of
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22 human factors with ABPI.
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26 This was a prospective controlled trial to assess MPPG in a representative population. It had equivalent
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28 sensitivity to ABPI; specificities differed, but we found that ABPI was not always performed correctly,
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30 even in a trial setting. We have previously shown that healthcare professionals prefer MPPG to ABPI.⁴⁸
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32 We plan further developments to the MPPG technology, making it fully portable and plan further studies
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34 to investigate its economic case and its utility in subgroups, e.g. diabetes and AF. MPPG offers promise
35
36 the potential for rapid and accessible PAD assessments in primary care.
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49 are those of the author(s) and not necessarily those of the NHS, NIHR or the Department of Health and
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2
3 **Contributorship**

4 Study design: GS, AJS, JA, SW, SH; device design: JW, TAWB, JA, AJS; data collection: LW, TAWB,
5 GS, JW; writing: JA, GS, AJS; data analysis: JW, AJS; reviewing: SW, SH GS, JA, AJS. All authors
6 approved the final version of the paper.
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11
12 **Participating primary care practices**

13 Belford Medical Practice, Belford, Northumberland, UK; Denton Turret Medical Centre, Newcastle upon
14 Tyne, Tyne & Wear, UK; Guide Post Medical Group, Choppington, Northumberland, UK; Humshaugh &
15 Wark Medical Group, Hexham, Northumberland, UK; Marine Avenue Surgery, Whitley Bay, Tyne &
16 Wear, UK; Newburn Surgery, Newcastle upon Tyne, Tyne & Wear, UK; Northumberland Park Medical
17 Group, Shiremoor, Tyne & Wear, UK; Prudhoe Medical Group, Prudhoe, Northumberland, UK; Sele
18 Medical Practice, Hexham, Northumberland, UK; Station Medical Group, Blyth, Northumberland, UK;
19 Swarland Avenue Surgery, Benton, Newcastle upon Tyne, Tyne & Wear, UK; Throckley Primary Care
20 Centre, Newcastle upon Tyne, Tyne & Wear, UK; Village Green Surgery, Wallsend, Newcastle upon
21 Tyne, Tyne & Wear, UK; Village Surgery, Cramlington, Northumberland, UK; Walker Medical Group,
22 Walker, Newcastle upon Tyne, Tyne & Wear, UK; Waterloo Medical Group, Blyth, Northumberland,
23 UK.
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38 **Declaration of conflicting interests**

39 JA, TAWB and JW are authors of one published patent associated with the device. GS, AJS, LW, IG, SW
40 and SH declare that they have no conflict of interest.
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For Peer Review

Tables

Table 1:

Patient demographics, risk factors and comorbidities. PAD as assessed by DUS. Age and BMI (body mass index) are shown as mean (SD); smoking status and previous medical history of diabetes, ischemic heart disease (IHD), stroke transient ischemic attack (TIA) and atrial fibrillation (AF) are shown as number (%).

	All	PAD+	PAD-	P
Participants	249	101	148	-
Age (y)	71.9 (8.6)	73.3 (8.2)	70.8 (8.8)	0.024
Sex (M:F)	155:94	66:35	89:59	0.484
BMI (kg m ⁻²)	27.3 (4.6)	27.2 (5)	27.4 (4.4)	0.703
Smoking				<0.001
- never	70 (28.1)	13 (12.9)	57 (38.5)	-
- ex	127 (51)	61 (60.4)	66 (44.6)	-
- current	52 (20.9)	27 (26.7)	25 (16.9)	-
Diabetes	59 (23.7)	28 (27.7)	31 (20.9)	0.279
Hypertension	147 (59)	69 (68.3)	78 (52.7)	0.02
IHD	59 (23.7)	40 (39.6)	19 (12.8)	<0.001
Stroke	18 (7.2)	9 (8.9)	9 (6.1)	0.55
TIA	23 (9.2)	16 (15.8)	7 (4.7)	0.006
AF	20 (8)	7 (6.9)	13 (8.8)	0.771

Table 2:

Diagnostic cross-tabulations (numbers of participants) of ankle-brachial pressure index (ABPI), Table 2a, and multi-site photoplethysmography (MPPG), Table 2b, relative to duplex ultrasound (DUS). Pairwise comparison of MPPG and ABPI, Table 2c.

Table 2a

	DUS PAD+	DUS PAD-	DUS PAD Inconclusive	Total
ABPI PAD+	77	15	0	92
ABPI PAD-	19	117	0	136
ABPI PAD Inconclusive	5	16	0	21
Total	101	148	0	249

Table 2b

	DUS PAD+	DUS PAD-	DUS PAD Inconclusive	Total
MPPG PAD+	71	39	0	110
MPPG PAD-	18	100	0	118
MPPG PAD Inconclusive	12	9	0	21
Total	101	148	0	249

Table 2c

	ABPI PAD+	ABPI PAD-	ABPI PAD Inconclusive	Total
MPPG PAD+	68	36	6	110
MPPG PAD-	12	93	13	118
MPPG PAD Inconclusive	12	7	2	21
Total	92	136	21	249

Table 3:

Diagnostic accuracy for peripheral arterial disease (PAD) of primary care PAD registers,²⁵ ECQ,²⁴ ankle-brachial pressure index (ABPI) and multi-site photoplethysmography (MPPG) vs duplex ultrasound reference test. n: number of pairwise comparisons with conclusive index test and reference test; LR+: positive likelihood ratio; LR-: negative likelihood ratio; DOR: diagnostic odds ratio. Ranges in brackets are 95% confidence intervals.

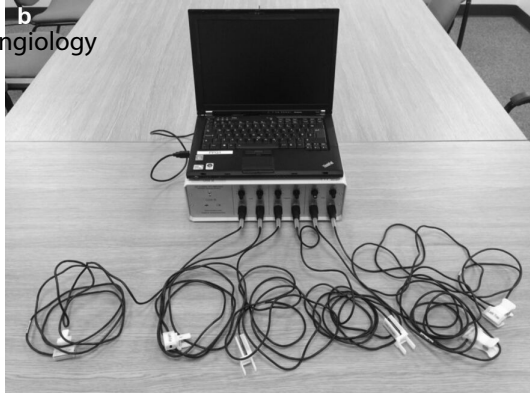
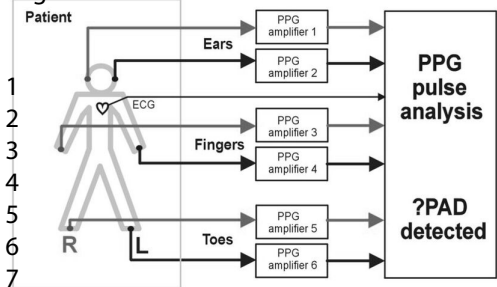
Test	n	Sensitivity (%)	Specificity (%)	LR+	LR-	DOR
Registers	250	86.1 (77.8-92.2)	74.5 (66.7-81.3)	3.4 (2.5-4.5)	0.19 (0.11-0.31)	18.2 (9.3-35.6)
ECQ	248	52.5 (42.3-62.5)	87.1 (80.6-92)	4.1 (2.6-6.4)	0.55 (0.44-0.68)	7.4 (4.0-13.8)
ABPI	228	80.2 (70.8-87.6)	88.6 (82-93.5)	7.1 (4.3-11.5)	0.22 (0.15-0.34)	31.6 (15.1-66.0)
MPPG	228	79.8 (69.9-87.6)	71.9 (63.7-79.2)	2.8 (2.1-3.8)	0.28 (0.18-0.43)	10.1 (5.4-19.1)

Figure legends

Figure 1. The multi site photoplethysmography (MPPG) device used in the study: (a) schematic diagram of signals and data flow; (b) signal processing unit and data collection computer; (c) finger probe capable of measuring photoplethysmogram (PPG) and electrocardiogram (ECG); (d) toe probe used for measuring PPG. In this study, PPG signals were measured at the toes and ECG from the finger probes.

Figure 2. Flow of participants through the study.³⁸ DNA: did not attend; PPG: photoplethysmography.

Figure 3. Diagnostic prospective performances of multi-site photoplethysmography (MPPG) and ankle-brachial pressure index (ABPI) in primary care with respect to the duplex ultrasound (DUS) reference test for peripheral arterial disease (PAD) detection. An ideal diagnostic test would be placed in the top left corner with sensitivity (Se; true positive rate) of 1, and a false positive rate (1-Sp) of 0. The Se and (1-Sp) show the comparable accuracy between PPG and ABPI. Also shown are the previously published diagnostic performance of the Edinburgh Claudication Questionnaire (ECQ)²⁴ and GP PAD registers²⁵ relative to DUS, also from the NOTEPAD trial.



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