PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Ankle-Brachial Index determination and peripheral arterial disease diagnosis by an oscillometric blood pressure device in primary care: validation and diagnostic accuracy study
AUTHORS	Nelson, Mark ; Quinn, Stephen; Winzenberg, Tamia; Howes, Faline; Shiel, Louise; Reid, Christopher

VERSION 1 - REVIEW

REVIEWER	Jesper Mehlsen, MD, Director of Research Coordinating Research Centre Frederiksberg University Hospital Denmark I have no competing interests
REVIEW RETURNED	24-Jul-2012

THE STUDY	The study bears a very close resemblance to a study published by our group investigating the usefulness of the oscillometric technique in general practise including 1,258 patients. The results obtained in the current manuscript are in accordance with ours (Mehlsen et al Clin Physiol Funct Imaging (2008) 28, pp426–429)
RESULTS & CONCLUSIONS	The conclusion could (should) have put more emphasis on the positive aspects of the fact that the oscillometric technique is not reliable in diagnosing but rather in ruling out PAD. Excluding those without PAD by the simple test will eventually increase the prevalence of disease in the remaining group thus improving the prediction by the following more elaborate diagnostic test. Thus the oscillomtric technique is valid for screening in population with a low prevalence of PAD

REVIEWER	Marc De Buyzere Research Coordinator Dept Cardiology Ghent University Hospital Ghent, Belgium
REVIEW RETURNED	26-Jul-2012

THE STUDY	Summary In the ABIDING Study (about 250 subjects from the REACH Registry) the authors compared agreement of two strategies to measure ABI and diagnose PAD: the conventional strategy (Doppler, mercury sphygmomanometer, research nurse) versus a pragmatic strategy (oscillometric BP device, practice nurse). Based on a cut-off of 0.90 for the conventional strategy prevalence of PAD

	was 22% in the study. Subjects fulfilled inclusion criteria of the REACH registry: > 45 years and known CVD or at least 3 risk factors. Correlation between the two methods was acceptable (although less than expected) but Bland-Altman agreement was poor. Sensitivity of the pragmatic method versus the conventional method taken as gold standard was poor (62%) but specificity (92%) and negative predictive value (90%) were high. The authors concluded that the pragmatic strategy showed poor agreement with the conventional strategy and had a poor sensitivity to detect ABI < 0.90 (conventional cut-off). The pragmatic strategy to measure ABI by oscillometric sphygmomanometers should not be recommended to diagnose PAD but may be useful to exclude the condition. Comments General Since the publication of the proof-of-concept paper by Benchimol et al (Angiology 2004) that an automated BP device can be used to reliably measure ABI the topic has been extensively studied. According to the authors most papers are from specialized units and there are only a few papers on oscillometric devices in the setting of primary care. Some evaluation for the office practice of the automated oscillometric determination of ABI has been described (Beckman et al, Hypertension 2006; Raines et al, Vasc Endovasc Surg 2004). Thus a validation study in primary care of the pragmatic strategy (Doppler, mercury sphygmomanometer, research nurse) versus the conventional strategy might be in place. The authors have a clear message that in primary care the pragmatic strategy lacks sensitivity to diagnose ABI <0.90. The pragmatic strategy diagnosed 48 PAD cases including 16 misclassifications and 20 subjects out of the 194 subjects declared PAD-free by the pragmatic strategy showed PAD by the conventional strategy. However it is clear that the authors have neglected part of recent publications on automated oscillometric devices to “screen” for ABI in large cohorts. For instance in the Czech-post MONICA population study (Wohlfart et al, Int Angiol 2011) the BOSO automatic oscillometric ABI device was not interchangeable for standard Doppler ABI and showed a sensitivity of 77%. In a smaller study (Aboyans et al, Int J Clin Pract 2008) automatic oscillometric devices were not recommended as reliable methods for ABI measurement. It is a major shortcoming that the authors did not discuss their own results and more importantly their own interpretation versus existing overall data (specialized and primary care settings). Verberk et al. recently published a meta-analysis (Hypertens Res 2012) on 25 studies with automated oscillometric determination of the ankle-brachial index. Overall, the pooled correlation coefficient between the oscillometric and Doppler ABI was 0.71. The average sensitivity and specificity of the oscillometric ABI estimation in PAD diagnosis were 69 and 96% respectively (with Doppler ABI taken as the reference). These authors concluded (with rather comparable figures as obtained by Nelson et al) that an automated ABI measurement obtained by oscillometric blood pressure monitors is a reliable and practical alternative to the conventional Doppler measurement for the detection of PAD. It is a completely different conclusion and point of view. It needs discussion.
RESULTS & CONCLUSIONS	Summary In the ABIDING Study (about 250 subjects from the REACH

	Registry) the authors compared agreement of two strategies to measure ABI and diagnose PAD: the conventional strategy (Doppler, mercury sphygmomanometer, research nurse) versus a pragmatic strategy (oscillometric BP device, practice nurse). Based on a cut-off of 0.90 for the conventional strategy prevalence of PAD was 22% in the study. Subjects fulfilled inclusion criteria of the REACH registry: > 45 years and known CVD or at least 3 risk factors. Correlation between the two methods was acceptable (although less than expected) but Bland-Altman agreement was poor. Sensitivity of the pragmatic method versus the conventional method taken as gold standard was poor (62%) but specificity (92%) and negative predictive value (90%) were high. The authors concluded that the pragmatic strategy showed poor agreement with the conventional strategy and had a poor sensitivity to detect ABI < 0.90 (conventional cut-off). The pragmatic strategy to measure ABI by oscillometric sphygmomanometers should not be recommended to diagnose PAD but may be useful to exclude the condition. Comments General Since the publication of the proof-of-concept paper by Benchimol et al (Angiology 2004) that an automated BP device can be used to reliably measure ABI the topic has been extensively studied. According to the authors most papers are from specialized units and there are only a few papers on oscillometric devices in the setting of primary care. Some evaluation for the office practice of the automated oscillometric determination of ABI has been described (Beckman et al, Hypertension 2006; Raines et al, Vasc Endovasc Surg 2004). Thus a validation study in primary care of the pragmatic strategy (Doppler, mercury sphygmomanometer, research nurse) versus the conventional strategy might be in place. The authors have a clear message that in primary care the pragmatic strategy lacks sensitivity to diagnose ABI <0.90. The pragmatic strategy diagnosed 48 PAD cases including 16 misclassifications and 20 subjects out of the 194 subjects declared PAD-free by the pragmatic strategy showed PAD by the conventional strategy. However it is clear that the authors have neglected part of recent publications on automated oscillometric devices to “screen” for ABI in large cohorts. For instance in the Czech-post MONICA population study (Wohlfart et al, Int Angiol 2011) the BOSO automatic oscillometric ABI device was not interchangeable for standard Doppler ABI and showed a sensitivity of 77%. In a smaller study (Aboyans et al, Int J Clin Pract 2008) automatic oscillometric devices were not recommended as reliable methods for ABI measurement. It is a major shortcoming that the authors did not discuss their own results and more importantly their own interpretation versus existing overall data (specialized and primary care settings). Verberk et al. recently published a meta-analysis (Hypertens Res 2012) on 25 studies with automated oscillometric determination of the ankle-brachial index. Overall, the pooled correlation coefficient between the oscillometric and Doppler ABI was 0.71. The average sensitivity and specificity of the oscillometric ABI estimation in PAD diagnosis were 69 and 96% respectively (with Doppler ABI taken as the reference). These authors concluded (with rather comparable figures as obtained by Nelson et al) that an automated ABI measurement obtained by oscillometric blood pressure monitors is a reliable and practical alternative to the conventional Doppler

	measurement for the detection of PAD. It is a completely different conclusion and point of view. It needs discussion.
GENERAL COMMENTS	Specific comments 1. The cross-sectional nature of the study is a study limitation. The authors start from the basic assumption that the cut-off for the pragmatic strategy should also be 0.90. Are they confident that there is no need for a more in-depth evaluation to see whether oscillometric determination of ankle and brachial pressure will lead to the same cut-off of 0.90 as for the conventional strategy? 2. Has the OMRON HEM-907 device sufficiently been validated for the measurement of ankle BP? 3. In the conventional strategy a research nurse measured ABI; in the pragmatic strategy a practice nurse measured ABI (no randomization). Did it influence (bias) the results? 4. In the statistical analysis it seemed to have been assumed (as in many other related papers) that conventional ABI is the gold standard for PAD. By definition cut-off of <0.90 obtained from "conventional" methods means PAD. Table 2 has been constructed starting from that point of view. Is the conventional strategy the gold standard or is it a conceivable proxy for the gold standard? Would it be possible to comment on that? 5. Table 1. Statistical comparison between included (n =242) and excluded (n = 8) might be obsolete as even average SBP values of 142 and 154 mmHg will not be significant. The Reviewer suggests removing it from the manuscript. Do the authors have information on 312 excluded subjects from Table 1? 6. Of interest, many subjects showed an ABI > 1.2. Did the authors expect it?

VERSION 1 – AUTHOR RESPONSE

Reviewer: Jesper Mehlsen
The study bears a very close resemblance to a study published by our group investigating the usefulness of the oscillometric technique in general practise including 1,258 patients. The results obtained in the current manuscript are in accordance with ours (Mehlsen et al Clin Physiol Funct Imaging (2008) 28, pp426–429)

We have included this in our discussion (see page 13) but this study has a significant limitation. The study enrolled 1258 consecutive general practice patients for an oscillometric determination of ABI with those with an ABI <0.9 referred for a Doppler measure in a vascular unit. Hence all 'negatives' including false negatives did not have a gold standard measure.

The conclusion could (should) have put more emphasis on the positive aspects of the fact that the oscillometric technique is not reliable in diagnosing but rather in ruling out PAD. Excluding those without PAD by the simple test will eventually increase the prevalence of disease in the remaining group thus improving the prediction by the following more elaborate diagnostic test. Thus the oscillometric technique is valid for screening in population with a low prevalence of PAD

This goes to the use of a test as a screening tool or a diagnostic test. This is differentiated by clinical symptoms. We have added more information on symptomatic versus asymptomatic individuals because the test performance did not improve in the former.
"Test performance for the asymptomatic subgroup on ECQ (N = 183 PAD 18%) sensitivity 54% (95% CI 37-69%) specificity 93% (89-97%) and symptomatic (N = 18 PAD 61%) sensitivity 9% (2-41%)

specificity 57% (18-90%).” Page 11.

The conclusion could (should) have put more emphasis on the positive aspects of the fact that the oscillometric technique is not reliable in diagnosing but rather in ruling out PAD. Excluding those without PAD by the simple test will eventually increase the prevalence of disease in the remaining group thus improving the prediction by the following more elaborate diagnostic test. Thus the oscillometric technique is valid for screening in population >with a low prevalence of PAD.

It's true that the NPV was 90%, and on the surface appears to be able to rule out the disease, but it missed ~40% of the PAD population hence our recommendations.

The authors start from the basic assumption that the cut-off for the pragmatic strategy should also be 0.90. Are they confident that there is no need for a more in-depth evaluation to see whether oscillometric determination of ankle and brachial pressure will lead to >the same cut-off of 0.90 as for the conventional strategy?

The mean (95% CI) for difference between pragmatic and conventional readings was -0.004 (-0.0296, 0.0223) indicating no systematic bias. The following sensitivity analyses indicate that a higher cut point is marginally better for sensitivity, but the improvement is not worth the confusion it may cause and the compromise in specificity which is paramount if the test is used for screening (see table following).

Cut off	Sensitivity	Specificity	PPV	NPV
0.85	0.54	0.95	0.76	0.88
0.86	0.54	0.95	0.74	0.88
0.87	0.56	0.95	0.74	0.89
0.88	0.58	0.94	0.71	0.89
0.89	0.62	0.93	0.71	0.9
0.9	0.62	0.92	0.67	0.9
0.91	0.65	0.91	0.65	0.91
0.92	0.67	0.9	0.65	0.91
0.93	0.69	0.89	0.63	0.91
0.94	0.71	0.88	0.62	0.92
0.95	0.71	0.86	0.58	0.92

Reviewer: Marc De Buyzere
However it is clear that the authors have neglected part of recent publications on automated oscillometric devices to “screen” for ABI in large cohorts. For instance in the Czech-post MONICA population study (Wohlfart et al, Int Angiol 2011) the BOSO automatic oscillometric ABI device was not interchangeable for standard Doppler ABI and showed a sensitivity of 77%. In a smaller study (Aboyans et al, Int J Clin Pract 20085) automatic oscillometric devices were not recommended as reliable methods for ABI measurement.

The Wohlfart post MONICA study (ditto Raines et al) utilised specialised ABI oscillometric equipment which introduces the similar barriers to its use as the conventional method, i.e. cost of specialised equipment and training. Aboyans et al was a small (N = 54) referred primary care population for suspected PAD with testing in a specialist centre.

It is a major shortcoming that the authors did not discuss their own results and more importantly their own interpretation versus existing overall data (specialized and primary care settings).

Discussion of our results has been expanded. We chose only testing in the primary care setting and not to review specialised clinics.

Verberk et al. recently published a meta-analysis (Hypertens Res 20126) on 25 studies with automated oscillometric determination of the ankle-brachial index. Overall, the pooled correlation coefficient between the oscillometric and Doppler ABI was 0.71. The average sensitivity and specificity of the oscillometric ABI estimation in PAD diagnosis were 69 and 96% respectively (with Doppler ABI taken as the reference). These authors concluded (with rather comparable figures as obtained by Nelson et al) that an automated ABI measurement obtained by oscillometric blood pressure monitors is a reliable and practical alternative to the conventional Doppler measurement for the detection of PAD. It is a completely different conclusion and point of view. It needs discussion.

Thank you for identifying this just published study. A meta-analysis is a relevant paper for our discussion and perhaps can allay some of the concerns of us not reviewing the specialist literature.

Specific comments
1. The cross-sectional nature of the study is a study limitation. The authors start from the basic assumption that the cut-off for the pragmatic strategy should also be 0.90. Are they confident that there is no need for a more in-depth evaluation to see whether oscillometric determination of ankle and brachial pressure will lead to the same cut-off of 0.90 as for the conventional strategy?

Diagnostic validation studies can be run as randomised controlled trials with clinical outcomes but rarely are. The standard study method by necessity is a cross-sectional study as ideally all participants should receive contemporaneous gold standard and investigative tests. We report such an analysis.

2. Has the OMRON HEM-907 device sufficiently been validated for the measurement of ankle BP?

No this is the purpose of our study.

3. In the conventional strategy a research nurse measured ABI; in the pragmatic strategy a practice nurse measured ABI (no randomization). Did it influence (bias) the results?

Each participant was their own control so this is a valid method. The conduct of the tests differed in 2 important ways. Firstly the method of attainment and secondarily by the operator. This is specified and the limitation of the practice nurse experience/training is alluded to.

4. In the statistical analysis it seemed to have been assumed (as in many other related papers) that conventional ABI is the gold standard for PAD. By definition cut-off of <0.90 obtained from “conventional” methods means PAD. Table 2 has been constructed starting from that point of view. Is the conventional strategy the gold standard or is it a conceivable proxy for the gold standard? Would it be possible to comment on that?

ABI is a valid and reliable clinical measure though as the reviewer points out, an indirect one. The true gold standard would be an intravascular perfusion study but this is invasive, would not be contemporaneous, and potentially harmful. However we have identified one such study and it is now alluded to in the paper1. These were consecutive patients undergoing angiography and therefore oscillometric and Doppler methods could be used to compare against the gold standard. The oscillometric method showed 97% sensitivity, 89% specificity, 98% positive predictive value, and 86% negative predictive value. The Doppler method showed 95% sensitivity, 56% specificity, 91% positive predictive value, and 68% negative predictive value. This study suggests that the oscillometric method had greater diagnostic accuracy but the test is performed by physicians not specifically trained to use the Doppler probe. This has been added to the discussion.

5. Table 1. Statistical comparison between included (n =242) and excluded (n = 8) might be obsolete as even average SBP values of 142 and 154 mmHg will not be significant. The Reviewer suggests removing it from the manuscript. Do the authors have information on 312 excluded subjects from Table 1?

Complied with. We don't have information on the excluded.

6. Of interest, many subjects showed an ABI > 1.2. Did the authors expect it?

No preconceptions on this.

We await the outcome of your reconsideration,

Mark Nelson
On behalf of all authors.

1. Vega J, Romaní S, Garcipérez FJ, Vicente L, Pacheco N, Zamorano J, et al. Peripheral Arterial Disease: Efficacy of the Oscillometric Method. Rev. Esp. Cardiol. 2011;64(07):619-21.

VERSION 2 – REVIEW

REVIEWER	Jesper Mehlsen, MD Director of Research Coordinating Research Centre Frederiksberg Hospital University of Copenhagen Denmark
REVIEW RETURNED	11-Sep-2012

- The reviewer completed the checklist but made no further comments.

REVIEWER	Marc De Buyzere Research Coordinator Dept Cardiology Ghent University Hospital Ghent, Belgium I have no competing interests
REVIEW RETURNED	07-Sep-2012

GENERAL COMMENTS	The authors answered most (not all) questions of the Reviewer. The revised version improved a lot. The Reviewer recommends the revised version of the manuscript for publication in BMJ Open.