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TECHNOLOGY REVIEW (MINI-HTA)

TRANSCUTANEOUS OXYGEN PRESSURE MONITORING (TcPO2)

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
001/2022

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EXECUTIVE SUMMARY

Background

In Malaysia, overall diabetes prevalence in adults ≥18 years in National Health & Morbidity Survey (NHMS) 2015 and 2019 was 13.4% and 18.3% respectively. Prevalence for overall diabetes for adults age 30 years and above was 24.1% in NHMS 2019. The proportion of patients with diabetic foot ulcers remains at 1.23% and 1.24% in 2019 and 2020, respectively. Similarly, the proportion of patients with amputations remains at 0.68% and 0.73% for both years.

Peripheral arterial disease (PAD) is associated with delayed diabetic foot ulcer (DFU) healing and increased risk of lower limb amputation. Its accurate diagnosis is imperative to allow for restoration of blood supply. The detection of PAD in diabetes can be challenging as symptoms are often masked by the presence of neuropathy. Currently, there are several non-invasive modalities used to detect ischaemia and impaired macrocirculation of the lower-limb including ankle-brachial index, toe blood pressure measurement, digital subtraction angiography, and colour Doppler flow imaging. However, these techniques have some limitation when examining the microcirculation of skin adjacent to a diabetic foot ulcer.

Transcutaneous oxygen monitoring, more specifically, transcutaneous partial pressure of oxygen (TcPO2) measurement was first used in neonatology, followed by paediatric intensive care units and then spread to other disciplines including plastic surgery, vascular surgery, anaesthesiology, orthopaedics and hyperbaric medicine. Transcutaneous oxygen measurement is a metabolic test while ankle brachial index, plethysmography and Doppler systolic pressure are haemodynamic index. It provides information about the supply and delivery of oxygen to the underlying microvascular circulation by recording the partial pressure of oxygen at the skin surface. The amount of oxygen detected by the sensor is a balance of oxygen delivery and local physiologic demands and reflects the metabolic status of the skin. The TcPO2 measurement is used in determining amputation level, wound healing evaluation, hyperbaric therapy, and peripheral arterial disease assessment, including the status of spinal cord stimulation and revascularisation procedures.

Hence, this Technology Review (TR) was requested by an Orthopaedic Specialist, Hospital Sultanah Nur Zahirah to assess the feasibility of the technology to be used as one of the modalities in assessing wound healing in Ministry of Health facilities.

Technical features

Transcutaneous oximetry (TcPO2) is a non-invasive test that directly measures the oxygen level of tissue beneath the skin. Because oxygen is carried to tissues by blood flow in the arteries, TcPO2 is an indirect measure of blood flow. TcPO2 electrodes measure the partial pressure of oxygen through the skin. They consist of a platinum cathode and silver reference anode, so-called “Clark electrode,” encased in an electrolyte solution and separated from the skin by an O^2-permeable membrane. Electrodes are heated up to 45ºC and transmit temperature of about 43ºC on the skin to improve oxygen diffusion and to arterialise the capillary blood. Oxygen is reduced at the cathode, generating an electric current proportional to the O^2 concentration in the capillary bed underneath the sensor. The oxygen diffuses according to its pressure gradient from the capillary loops through the vascular epidermis towards the skin surface electrode. The sensors is applied to the skin by a flat, double sided adhesive ring and require 10 to 15 minutes warm-up period after application and have to be calibrated every four to eight hours. A site reading requires an average of 35 minutes.

Objective/ aim

The objective of this technology review was to assess the effectiveness, cost-implication, safety and organisational issues related to the application of transcutaneous oxygen pressure monitoring (TcPO2).

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE(R) ALL <1946 to January 28, 2022>. EBM Reviews - Cochrane Central Register of Controlled Trials January 2022, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 23, 2022, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in INAHTA database, PubMed database and U.S. Food and Drug Administration (USFDA) website. Google and Google Scholar were also used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 28th January 2022.

Appendix 1 showed the detailed search strategies.

Results and conclusions

A total of 559 records were identified through the Ovid interface and PubMed, and seven were identified from other sources (references of retrieved articles). After removal of 77 duplicates, 489 records were screened and 397 were excluded. Of these, 92 relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the 92 full text articles, 12 full text articles were included and 80 full text articles were excluded.

There were 12 full text articles which comprised of three SRs with meta-analysis, one RCT, four prospective cohorts, two retrospective cohorts, one cross sectional analysis and one cost-effectiveness analysis selected for this review. The studies were conducted in Germany, UK, USA, Canada, Sweden, France, Netherlands, India and Thailand.

There was fair to good level of evidence retrieved to suggest that TcPO2 may predict wound healing, amputation and mortality among patients with diabetic foot ulcer, critical limb ischaemia and underlying peripheral arterial disease. However, there was no evidence that TcPO2 is suitable to substitute other modalities. The suggested threshold value for wound healing/tissue perfusion is >25mmHg. No evidence retrieved on the safety.

TABLE OF CONTENTS

ABBREVIATION

ABI	Ankle Brachial Index
ABPI	Ankle–Brachial Pressure Index
APSV	Ankle Peak Systolic Velocity
AUC	Area Under Curve
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
CLI	Critical Limb Ischaemic
CTA	Computed Tomography Angiography
DFU	Diabetic Foot Ulcer
DOR	Diagnostic Odds Ratio
HR	Hazard Ratio
NHMS	National Health & Morbidity Survey
NLR	Negative Likelihood Ratio
NPV	Positive Predictive Value
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PLR	Positive Likelihood Ratio
PPV	Negative Predictive Value
RCT	Randomised Controlled Trial
RR	Risk Ratio
SaO2	Oxygen Saturation
SF-36	The Short Form (36) Health Survey
SMD	Standardised Mean Difference
SPP	Skin Perfusion Pressure
SR	Systematic Review
STP	Systolic Toe Pressure
TBI	Toe Brachial Index
TBP	Toe Systolic Blood Pressure
TcPO2	Transcutaneous oxygen pressure
TP	Toe Pressure
USFDA	US Food & Drug Administration

1.0 BACKGROUND

In Malaysia, overall diabetes prevalence in adults ≥18 years in National Health & Morbidity Survey (NHMS) 2015 and 2019 was 13.4% and 18.3% respectively. Prevalence for overall diabetes for adults age 30 years and above was 24.1% in NHMS 2019.[1] The proportion of patients with diabetic foot ulcers remains at 1.23% and 1.24% in 2019 and 2020, respectively. Similarly, the proportion of patients with amputations remains at 0.68% and 0.73% for both years. [2]

Peripheral arterial disease (PAD) is associated with delayed diabetic foot ulcer (DFU) healing and increased risk of lower limb amputation. Its accurate diagnosis is imperative to allow for restoration of blood supply. The detection of PAD in diabetes can be challenging as symptoms are often masked by the presence of neuropathy.[3] Currently, there are several non-invasive modalities used to detect ischaemia and impaired macrocirculation of the lower-limb including ankle-brachial index, toe blood pressure measurement, digital subtraction angiography, and colour Doppler flow imaging. However, these techniques have some limitation when examining the microcirculation of skin adjacent to a diabetic foot ulcer.[4]

As for ankle-pressure and toe-pressure measurements, they are readily assessable in non-diabetic patients and therefore are regarded as optimal criteria for screening this population group. However, in patients with diabetes mellitus these measurements frequently are inaccessible due to poor or incompressible tibial arteries with the presence of medial arterial calcifications or vessel occlusion. Moreover, surgery, ischaemic wounds, and/or gangrene may interfere with measurement taking. In result, the assessment of ankle-pressure measurements becomes impracticable in a considerable number of patients with diabetes.[5] Audible assessment of arterial waveforms using a handheld Doppler device is the most commonly used test but its interpretation is subjective.[3]

Transcutaneous oxygen monitoring, more specifically, transcutaneous partial pressure of oxygen (TcPO2) measurement was first used in neonatology, followed by paediatric intensive care units and then spread to other disciplines including plastic surgery, vascular surgery, anaesthesiology, orthopaedics and hyperbaric medicine. [6] Transcutaneous oxygen measurements is a metabolic test while ankle brachial index, plethysmography and Doppler systolic pressure are haemodynamic index. [7] It provides information about the supply and delivery of oxygen to the underlying microvascular circulation by recording the partial pressure of oxygen at the skin surface. The amount of oxygen detected by the sensor is a balance of oxygen delivery and local physiologic demands and reflects the metabolic status of the skin. The TcPO2 measurement is used in determining amputation level, wound healing evaluation, hyperbaric therapy, and peripheral arterial disease assessment, including the status of spinal cord stimulation and revascularisation procedures. [8]

Hence, this Technology Review (TR) was requested by an Orthopaedic Specialist, Hospital Sultanah Nur Zahirah to assess the feasibility of technology to be used as one of the modalities in assessing wound healing in Ministry of Health facilities.

2.0 OBJECTIVE / AIM

The objective of this technology review was to assess the effectiveness, cost-implication, safety and organisational issues related to the application of transcutaneous oxygen pressure monitoring (TcPO2).

3.0 TECHNICAL FEATURES

Transcutaneous oximetry (TcPO2) is a non-invasive test that directly measures the oxygen level of tissue beneath the skin. Because oxygen is carried to tissues by blood flow in the arteries, TcPO2 is an indirect measure of blood flow. TcPO2 electrodes measure the partial pressure of oxygen through the skin. They consist of a platinum cathode and silver reference anode, so-called “Clark electrode,” encased in an electrolyte solution and separated from the skin by an O^2-permeable membrane. Electrodes are heated up to 45ºC and transmit temperature of about 43ºC on the skin to improve oxygen diffusion and to arterialize the capillary blood. Oxygen is reduced at the cathode, generating an electric current proportional to the O^2 concentration in the capillary bed underneath the sensor. The oxygen diffuses according to its pressure gradient from the capillary loops through the vascular epidermis towards the skin surface electrode. The sensors is applied to the skin by a flat, double sided adhesive ring and require 10 to 15 minutes warm-up period after application and have to be calibrated every four to eight hours. A site reading requires an average of 35 minutes. [7,9]

The TcPO2 reading is affected by both methodological and physiological factors. These procedural issues include the temperature in the tissues, shift of haemoglobin dissociation curve, degree of oxygen metabolism in tissues and response time of the electrodes in the equipment, while the physiological considerations include circulatory status, peripheral blood perfusion, and local skin and anatomical conditions.[10]

Figure 1: Images of TcPO2 device [11]

4.0 METHODS

4.1 SEARCHING

Electronic databases were searched through the Ovid interface: Ovid MEDLINE(R) ALL <1946 to January 28, 2022>. EBM Reviews - Cochrane Central Register of Controlled Trials January 2022, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 23, 2022, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in INAHTA database, PubMed database and U.S. Food and Drug Administration (USFDA) website. Google and Google Scholar were also used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 28th January 2022.

Appendix 1 showed the detailed search strategies.

4.2 SELECTION

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then appraised the full text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patient with diabetes foot ulcer, peripheral arterial disease, critical limb ischaemia, chronic wound healing
Interventions	Transcutaneous oxygen pressure monitoring (TcPO2)
Comparators	Other non-invasive measurement such as computed tomography angiography (CTA), ABI, TBI, clinical assessment, continuous wave Doppler, toe pressure
Outcomes	• Effectiveness [predicting healing, predicting complication, predicting amputation, limb survival] • Economic implication • Safety • Organisational issues
Study design	Systematic Review (SR), Randomised Controlled Trial (RCT) or non-randomised controlled trial (Non-RCT), Health Technology Assessment (HTA), economic evaluation study, cohort study, pre- and post-intervention study, diagnostic accuracy study, cross sectional study
	English full text articles

Exclusion criteria

Study design	In-vitro lab studies, case series, case report, studies conducted in animals, narrative reviews, studies on TcPO2 used together with hyperbaric oxygen therapy
	Non-English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and graded according to the US/Canadian preventive services task force (Appendix 2). Data were extracted and summarised in evidence table as in Appendix 3.

5.0 RESULTS

A total of 559 records were identified through the Ovid interface and PubMed, and seven were identified from other sources (references of retrieved articles). After removal of 77 duplicates, 489 records were screened and 397 were excluded. Of these, 92 relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the 92 full text articles, 12 full text articles were included and 80 full text articles were excluded. The articles were excluded as they were already included in the SR (n=18), irrelevant study design (n=43), and irrelevant outcome (n=19). The flow chart of study selection is shown in figure 2.

There were 12 full text articles which comprised of three SRs with meta-analysis, one RCT, four prospective cohorts, two retrospective cohorts, one cross sectional analysis and one cost-effectiveness analysis selected for this review. The studies were conducted in Germany, UK, USA, Canada, Sweden, France, Netherlands, India and Thailand.

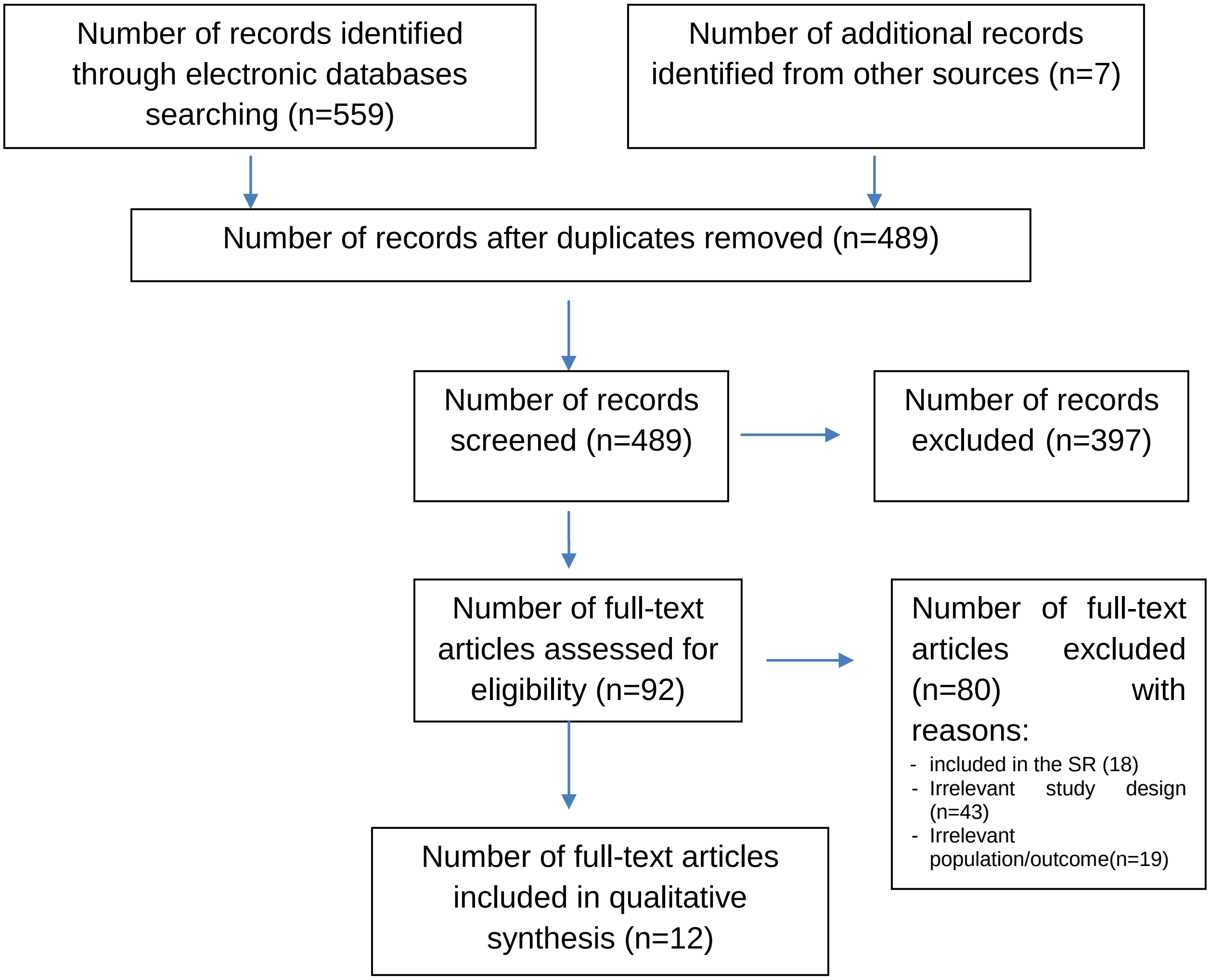


Figure 2: Flow chart of study selection

5.1 RISK OF BIAS

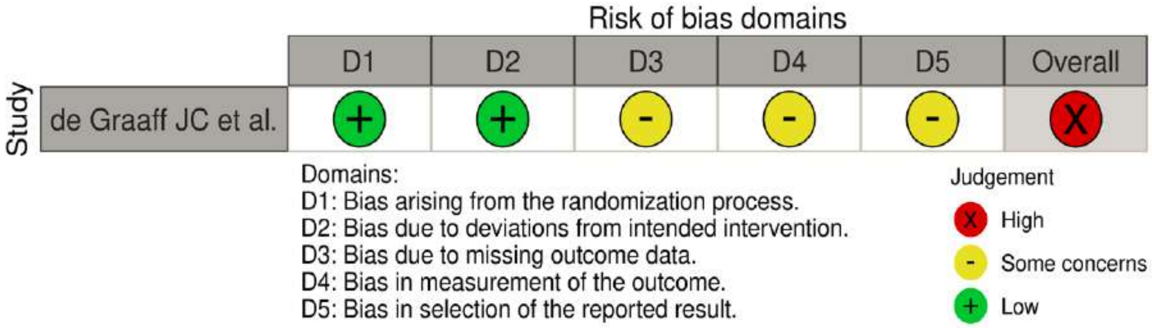
The risk of bias of included studies was assessed using domain-based evaluation. For RCT, the ROB 2.0 Tool for assessing the risk of bias comprising of five domains was used whereas for other studies, the risk of bias assessment are adapted from the CASP checklist. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement to the risk of bias either.

+	Indicates low risk of bias
?	Indicates unclear risk of bias
-	Indicates high risk of bias

Overall, the risk of bias was low for SRs although all of the SR was combined with high heterogeneity. One of the RCT has high risk of bias due to lack of information and some concerns on the outcome data and reporting of the results. For the cohort studies, the bias was due to the lack of information on outcome measurement and control of the confounding. The results of the risk of bias included studies are summarised in Figure 3, Figure 4, Figure 5 and Figure 6.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Wang Z et al. (2016)	+	+	+	?
Arsenault KA et al. (2011)	+	+	+	?
Arsenault KA et al. (2012)	+	+	+	?

Figure 3: Assessment of risk of bias of systematic review (CASP)



Risk of bias domains

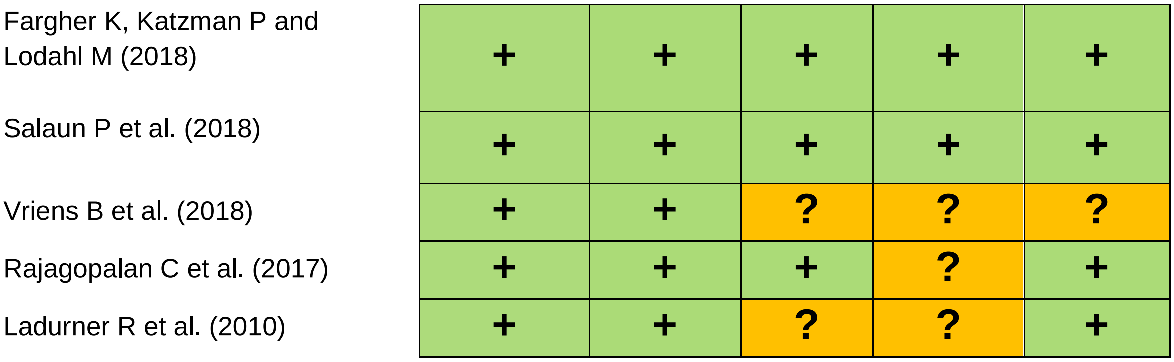
Study	D1	D2	D3	D4	D5	Overall
de Graaff JC et al.	+	+	-	-	-	X

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

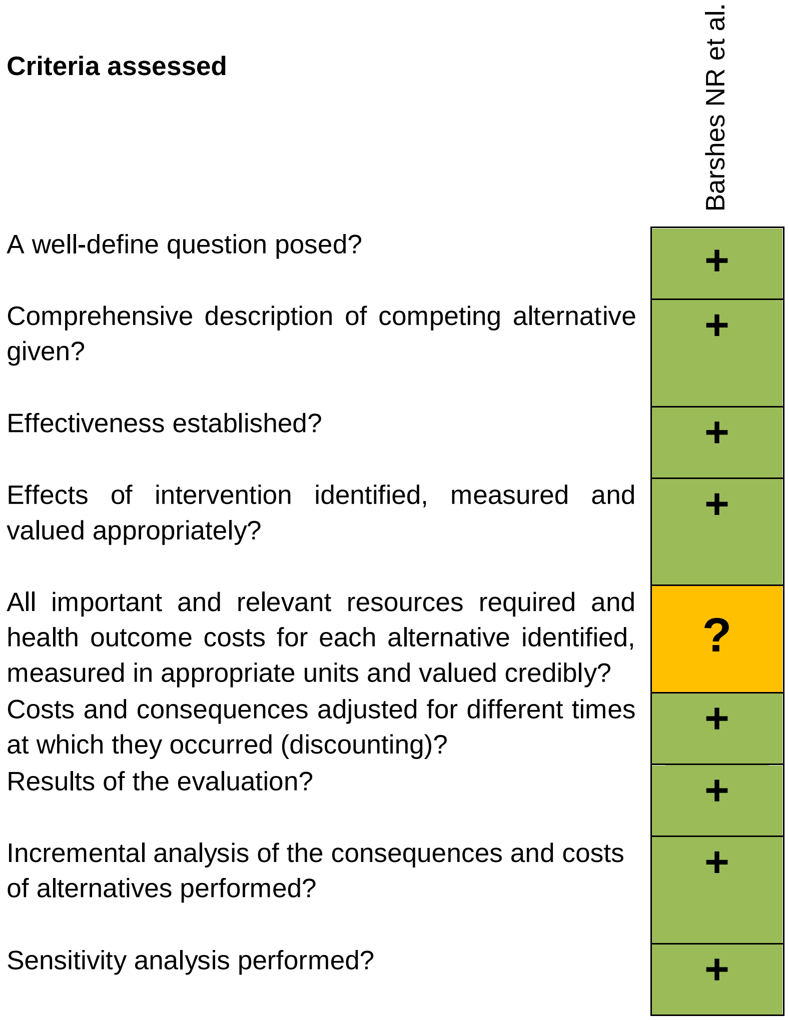
Figure 4: Assessment of risk of bias of RCT
(Cochrane ROB 2.0 reference: Traffic Light Plot

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Fargher K and Lodahl M (2021)	+	+	+	+	+



Fargher K, Katzman P and Lodahl M (2018)	+	+	+	+	+
Salaun P et al. (2018)	+	+	+	+	+
Vriens B et al. (2018)	+	+	?	?	?
Rajagopalan C et al. (2017)	+	+	+	?	+
Ladurner R et al. (2010)	+	+	?	?	+

Figure 5: Assessment of risk of bias of cohort (CASP)



Criteria assessed	Barshes NR et al.
A well-define question posed?	+
Comprehensive description of competing alternative given?	+
Effectiveness established?	+
Effects of intervention identified, measured and valued appropriately?	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	?
Costs and consequences adjusted for different times at which they occurred (discounting)?	+
Results of the evaluation?	+
Incremental analysis of the consequences and costs of alternatives performed?	+
Sensitivity analysis performed?	+

Figure 6: Assessment of risk of bias of economic evaluation (CASP)

5.2 EFFICACY/ EFFECTIVENESS

5.2.1 PREDICTING WOUND HEALING/COMPLICATION

a)Diagnostic Utility

Wang Z et al. conducted a systematic review to summarise the evidence of available tests and to compare the performance of eight non-invasive tests in predicting wound healing of diabetic foot ulcers (DFUs). They systematically searched a few databases for clinical trials or observational studies that used one of those eight non-invasive tests [ankle brachial Index (ABI), ankle peak systolic velocity (APSV), TcPO2, toe brachial index (TBI), toe systolic blood pressure (TBP), microvascular oxygen saturation (SaO2), skin perfusion pressure (SPP), and hyperspectral imaging (HIS)] which reported the incidence of subsequent healing of DFUs or the need for subsequent amputation. They pooled the sensitivity, specificity, and diagnostic odds ratio (DOR) and compared test performance. A total of 37 studies were included in the review. However, only ABI and TcPO2 provided sufficient data for the pooled analysis. They reported that, the pooled ABI values were slightly significant higher in the healed ulcer group than in the non-healed group [standardised mean difference (SMD) 0.42 (95% confidence interval (CI) 0.05 to 0.79); I^2 =15.7%; p=0.32]. Combined difference between the amputated limb group and the non-amputated group was also slightly significant [SMD 0.99 (95% CI 1.44 to 0.54); I^2=44.5%; p =0.13]. There was a significant difference of TcPO2 values between the healed group and the non-healed group [SMD 1.80 (95% CI 1.06 to 2.54); I^2 =92.3%; p=<0.001]. There was also a significant different when the amputated limb group was compared with the non-amputated group [SMD 2.26 (95% CI 4.13 to 0.40); I^2=96.8%; p=<0.001]. In this context, CI referring to the statistical significant of the result, meanwhile p value was for the heterogeneity. [12, level I]

For the TcPO2 test, the pooled DOR was 15.81 (95% CI 3.36 to 74.45) for wound healing and 4.14 (95% CI 2.98 to 5.76) for the risk of amputation. Ankle Brachial Index was also predictive but to a lesser degree of the risk of amputations [DOR 2.89 (95% CI 1.65 to 5.05)] but not of wound healing [DOR 1.02 (95% CI 0.40 to 2.64)]. [12, level I]

Rajagopalan C et al. conducted a six month period cohort study to find out the comparative utility of ABI and TcPO2 in predicting wound outcomes in DFU and to define cut-off values for both measurements in Indian diabetic patients presenting with foot ulcers of Wagner Grade II and III. A total of 564 patients were included in the study and were followed up to complete wound healing or up to three months. Complete epithelisation of the ulcer or healed amputation stump was considered as primary wound outcome. They reported that, the DOR for wound healing for ABI was 23 and TcPO2 was 4.23 with positive predictive value of 75% and 35% respectively. However, the value could not be determined.[13, level II-2]

From the receiver operating characteristic (ROC) curve, ABI value of 0.6 was found to have 99% sensitivity and 68% specificity and TcPO2 value of 22.5mmHg was found to have 100% sensitivity and 75% specificity in predicting wound healing. As for the amputation state, 0.6 ABI was found to have 68% sensitivity and 99% specificity. Meanwhile, the TcPO2 value of 22.5mmHg was found to have 75% sensitivity and 100% specificity. Multivariate logistic regression analysis showed an OR 3.5 (95% CI 2.2 to 5.7) for the effect of wound healing with ABI and an OR 3.0 (95% CI 2.1 to 4.3) for the effect of abnormal TcPO2 in amputation. They concluded that, both ABI and TcPO2 were complementary, but TcPO2 was a better predictor for amputation while ABI was a better predictor for ulcer healing. [13, level II-2]

Vriens B et al. conducted a prospective cohort study to investigate the utility of clinical examination and non-invasive bedside tests in screening for peripheral arterial disease in diabetes foot ulceration. Accuracy of pulses, ankle pressure (AP), toe pressure (TP), toe–brachial index, ankle–brachial pressure index (ABPI), pole test at ankle, TcPO2 and distal tibial waveform on ultrasound were examined. The gold standard diagnostic test used was > 50% stenosis in any artery or monophasic flow distal to calcification in any ipsilateral vessel on duplex ultrasound. A total of 60 people presenting with new-onset ulceration participated in the study. They reported that, the negative and positive likelihood ratios of pedal pulse assessment (0.75, 1.38) and the other clinical assessment tools were poor. The negative and positive likelihood ratios of ABPI (0.53, 1.69), TcPO2 (1.10, 0.81) and ankle pressure (0.67, 2.25) were unsatisfactory. The lowest negative likelihood ratios were for tibial waveform assessment (0.15) and TBI (0.24). The highest positive likelihood ratios were for toe pressure (17.55) and pole test at the ankle (10.29) but the negative likelihood ratios were poor at 0.56 and 0.74. They concluded that pulse assessment and ABPI have limited utility in the detection of peripheral artery disease in people with diabetes foot ulceration (Table 1).[14, level II-2]

Table 1: Diagnostic utility of physical examination of and screening tests to identify peripheral artery disease compared to Duplex ultrasound scan

	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Ankle pressure	0.47 (0.25–0.70)	0.79 (0.66–0.92)	0.53 (0.29–0.77)	0.75 (0.62–0.88)	2.25 (1.03–4.90)	0.67 (0.42–1.05)
Toe pressure	0.45 (0.23–0.67)	0.97 (0.92–1.00)	0.90 (0.71–1.00)	0.78 (0.66–0.89)	17.55 (2.39–128.96)	0.56 (0.38–0.84)
Toe brachial pressure index	0.89 (0.76–1.00)	0.45 (0.29–0.61)	0.45 (0.29–061)	0.89 (0.76–1.00)	1.62 (1.17–2.2)	0.24 (0.06–0.91)
Ankle brachial pressure index	0.68 (0.48–0.89)	0.59 (0.44–0.75)	0.46 (0.28–0.65)	0.79 (0.63–0.94)	1.69 (1.03–2.77)	0.53 (0.26–1.08)
Pole test and ankle	0.28 (0.07–0.48)	0.97 (0.92–1.00)	0.83 (0.54–1.00)	0.73 (0.61–0.86)	10.29 (1.29–81.60)	0.74 (0.55–0.99)
TcPo2	0.28 (0.07–0.48)	0.66 (0.51–0.81)	0.28 (0.07–0.48)	0.66 (0.51–0.81)	0.81 (0.34–1.93)	1.10 (0.76–1.58)
Waveform analysis	0.85 (0.69–1.00)	1‡	1‡	0.93 (0.85–1.00)	Diagnoses PAD‡	0.15 (0.05–0.43)

Values in parentheses are 95% CI.

*Not discriminatory because dependent rubor was not elicited in any patient.

† Not discriminatory because impairment of venous filling was not elicited in any patient.

‡ The gold standard definition of peripheral arterial disease (PAD) used included monophasic (damped) waveforms in any vessel, therefore the specificity and positive predictive value ratios are 1 and, positive likelihood is effectively infinite and diagnoses PAD.

de Graaff JC et al. conducted an RCT to evaluate the diagnostic value of TcPO2 and toe pressure in management of clinically suspected critical leg ischaemia. Patients who were referred to the vascular laboratory for diagnostic work-up by a vascular surgeon because of clinically suspected critical limb ischaemia (CLI) were included in the study. Clinical CLI was defined as pain at rest in the lower leg for more than two weeks, ulcers that persisted for more than two weeks, or diffuse gangrene of the forefoot. Patients were randomised into two diagnostic management strategies: a) conventional strategy; clinical judgment and ankle pressure determined the diagnostic and therapeutic approach, and b) a new strategy in which TcPO2 and toe pressure determined the diagnostic and therapeutic approach. Main outcome measures were clinical outcome, defined as pain relief, wound healing, and limb survival. A total of 96 patients (128 legs) were included in the study (conventional=46, new =50). At 18-month follow-up, 26 of 62 (41.9%) legs treated with the conventional approach and 28 of 66 (42.4%) legs treated with the new approach were treated conservatively.[15, level II-1]

They reported that, the number of diagnostic procedures and vascular interventions was not significantly different between the two management strategies. As for the clinical outcome, pain per involved leg did not differ between the two groups (p=0.9). The prevalence of wounds was significantly lower in conventional treatment (p=0.04), whereas severity of wounds was not significantly differed (p=0.55). Quality of life assessed with the SF-36 physical and mental summary score was not significantly different between groups (p=0.10 and p=0.28, respectively). Kaplan-Meier estimate of patient survival was not significantly different between the two groups (log-rank statistic, 0.12; P=0.7). In both groups, 12 patients (25%) died during the study period. The number of major and minor amputations and interventions did not differ significantly between the two groups (p=0.59 and p=0.68, respectively). They concluded that diagnostic tests, toe pressure and TcPO2, did not improve clinical outcome when incorporated into routine management of suspected critical limb ischaemia. [15, level II-1]

b) Cut-Off Value

Arsenault KA et al. conducted a systematic review to determine the value of TcPO2 as a predictor of healing complication of lower limb amputation. They searched for studies evaluating healing of lower limb amputations for vascular complications in adult patients. The studies reported at least one pre-operative TcPO2 measurement, reported post healing status of surgical wound and provided data to assess TcPO2 measurement as a predictor of amputation healing. Unadjusted relative risks (RR) were calculated for each study at each cut-off level and were pooled using random effect model. A total of 31 studies (N=1824 patients with 1960 amputations) were included in the review with indications of peripheral vascular disease, occlusive arterial disease, non-healing ischaemic ulcers, infection, gangrene and rest pain and diabetes mellitus. Only one study reported undertaking a multivariable analysis, which demonstrated that a TcPO2 level below 20 mmHg was an independent predictor of re-amputation occurrence [adjusted odds ratio (OR) 3.08, 95% CI 1.19 to 7.98]. Fourteen prospective cohort studies (n=626 patients with 658 amputations) reported data that allowed for the calculation of an unadjusted relative risk of lower limb amputation healing complications. They found that TcPO2 value less than 10 mmHg displayed the strongest association with healing complication [Risk ratio (RR) 1.80, (95% CI 1.19 to 2.72); I^2=47% based on 11 studies. The 20 mmHg subgroup included all 14 of the studies and resulted in a pooled RR 1.75 (95% CI 1.27 to 2.40); I^2=68%. Cut-offs of 30 mmHg and 40 mmHg displayed pooled RRs 1.41 (95% CI 1.22 to 1.62); I^2=44% and 1.24 (95% CI 1.13 to1.39); I^2=22%, respectively. A sensitivity analysis assessing plausible explanatory variables with TcPO2 cut-off value, year of publication and length of follow up found no statistical significant (p>0.05). The authors concluded, the evidence was insufficient to judge whether TcPO2 adds relevant information beyond clinical data and to suggest an optimal TcPO2 threshold value.[16, level I]

Previously, Arsenault KA et al. conducted another systematic review to determine the value of transcutaneous oximetry as an independent predictor of chronic wound healing complications and the reported threshold values. They systematically searched for studies evaluated chronic wound healing in adult who had at least one TcPO2 measurement , reported healing status and had assessment of TcPO2 as an independent predictor of chronic wound complications through multivariable analysis, propensity analysis or matched cases and controls. The main outcome data collected was adjusted odds ratio. Summary estimates that were reported as adjusted relative risk were converted to OR. The ORs were pooled using DerSimonian and Laird random effects model. Heterogeneity was assessed and >25% was defined as heterogeneous. A total of four studies with 901 patients were included in the meta-analysis evaluated 910 chronic wound of lower extremity from various types of wounds. They reported that a peri-wound TcPO2 level below a cut-off of 20 mmHg or 30 mmHg was an independent predictor of chronic wound healing complications with OR 3.21 (95% CI 1.07 to 9.69); I^2=77%. A threshold value of 20mmHg was used most frequently in the included studies and showed the strongest association. However, it was limited by the small number of studies and possible reporting bias and heterogeneity.[17, level I]

Ruangstekit C et al. conducted a cross sectional study to investigate the threshold of TcPO2 values in predicting ulcer healing inpatients with critical limb ischaemia. A total of 50 critical limb ischaemia patients with chronic ischaemic ulcers or gangrenous toes were enrolled. Their demographic data and ankle brachial pressure index (ABPI) were collected and baseline ulcers were measured with a wound measurement system (Visitrak, Smith & Nephew). The TcPO2 was measured at rest in the supine position and with 30° leg elevation. The patients with infective and ischaemic ulcers underwent debridement and gangrenous toes were amputated. The patients were divided into three groups according to their resting, supine values [Group 1: patients with a TcPO2 value <20mmHg, Group 2: patients with a TcPO2 of 20‒40mmHg and Group 3: patients with a TcPO2 value >40mmHg]. Ulcer outcome was classified as either: (a) healing ulcer (good epithelialisation or granulation at both base and edges, or a decrease in ulcer area during the study); or (b) non-healing ulcer (poor granulation tissue formation or a pale base and necrotic edges, or deterioration in an ischaemic ulcer). They descriptively reported that, 13 patients (26%) had a TcPO2 of less than 20mmHg, of which none showed any improvement in ulcer healing (p<0.001). A total of 15 patients (30%) had a TcPO2 of more than 40mmHg, of which all progressed to complete ulcer healing (p<0.001). In the borderline group (20–40mmHg), more patients who had a TcPO2 drop of ≤10mmHg with 30° leg elevation achieved complete ulcer healing (<0.001). However, more patients showed no ulcer healing if the value drop >10mmHg with 30° leg elevation (p<0.001) as explained in Table 2. [18]

Table 2: Outcome of TcPO2 measurement.

Outcome data	Healed	Non-healed	Total	p-value
Group 1 (<20mmHg)	0	13	13	p<0.001
Group 2 (20-40mmHg	9	13	22	
TcPO2 decrease (30º leg elevation) • Subgroup 1 ≤10mmHg • Subgroup 2>10mmHg	8 1	2 11	10 12	p<0.001 p<0.001
Group 3 (>40mmHg)	15	0	15	p<0.001

Ladurner R et al. conducted a prospective cohort study to evaluate the usage of daily TcPO2 measurement to predict the risk of non-healing and amputation in diabetic foot ulcer patients with non-palpable pedal pulses. Patients with clinical signs of soft tissue infection at the initial presentation were excluded. A total of 141 patients were enrolled and followed up in an outpatient setting according to a comprehensive wound-care protocol. The TcPO2 measurements were performed at the dorsum of the forefoot in a standardised setting. Patients were divided into three subgroups according to their initial TcPO2-readings (TcPO2 <20 mmHg, TcPO2 20–40 mmHg, TcPO2 >40 mmHg). They reported that, wounds associated with a TcPO2 reading <20 mmHg demonstrated a significantly decreased probability of healing compared with those associated with a TcPO2 >40 mmHg (p=0.008) after one year treatment. The overall amputation rate increased with decreasing TcPO2 (p=0.014) although there was no significant difference for major amputations (p=0.448).[19, level II-2]

5.2.2 PREDICTING LOWER LIMB AMPUTATION/REAMPUTATION

Salaun P et al. conducted a cohort study to compare the prediction of major amputation by three haemodynamic methods [ankle pressure (AP), systolic toe pressure (STP), and transcutaneous oxygen pressure (TcPO2)] after one year. The patients were selected from the Cohorte des Patients ARTe´riopathes, a cohort of patients hospitalised for peripheral arterial disease. Patients with CLI were enrolled according to the TransAtlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II definition and followed up for at least one year. A total of 556 patients were included and divided into surgical (264) and medical (292) groups.

The surgical group comprised those who underwent endovascular or open surgery, and the medical one included patients with no-option CLI, that is, surgery impossible for anatomic reasons, patient too frail to undergo anaesthesia, or failure of revascularisation. The AP failed to identify 42% of patients with CLI. After one year, 27% of medical and 17% of surgical patients had undergone major amputation. They reported that the STP <30 mm Hg predicted major amputation in the whole sample and in the medical group [OR 3.5 (95% CI 1.7 to 7.1) and OR 5 (95% CI 2 to 12.4), respectively], but AP did not. The TcPO2 <10 mm Hg also predicted major amputation [OR 2.3 (95% CI 1.5 to 3.5) and OR 3.8 (95% CI 2.1 to 6.8), respectively]. However, the value was not statistically differed at among surgical group.[20, level II-2]

According to ROC curve, the best method in predicting amputation in the whole sample was STP: area under curve (AUC) 0.678 versus 0.638 for TcPO2 and 0.548 for AP. In the medical group, the best method was also STP: AUC 0.738 versus 0.691 for TcPO2 and 0.6 for AP. All the methods were poorly predictive of the risk of amputation in the surgical group: AUC 0.573 for STP, 0.589 for TcPO2, and 0.495 for AP. They concluded that, the best predictive thresholds to predict major amputation were STP <30 mm Hg and TcPO2 <10 mm Hg. However, none of those methods performed before surgery was able to predict outcome in the revascularised patients.[17, level II-2]

5.2.3 PREDICTING MORTALITY/SURVIVAL

Fargher K et al. (2018) conducted a retrospective cohort study to evaluate the predictive value of TcPO2 in comparison with ABI and toe blood pressure on one year mortality in type II diabetes patients with DFU. A total of 236 type II diabetes patients aged ≤ 90 years, with one DFU who attended the multidisciplinary DFU-unit during year 2013 to 2015 were screened with TcPO2, ABI and TBP were retrospectively evaluated. Baseline characteristics were assessed from patient’s medical records. Ulcer healing was defined as complete epithelialisation within 12 weeks and above-ankle amputation during follow-up were assessed from patients chart. One-year mortality was assessed from the national death register in Sweden. Patients were stratified according to TcPO2 < 25mmHg and ≥ 25 mmHg. Survival analyses were performed with Kaplan–Meier estimates, and significances calculated with log-rank tests. They reported that within one year, 14.8% of the patients died. TcPO2 < 25 mmHg was associated with a higher one year mortality compared with TcPO2 ≥ 25 mmHg (27.7 vs. 11.6%, p = 0.003). Toe blood pressure and ABI did not significantly influence one year mortality (Figure 7).[21, level II-2]

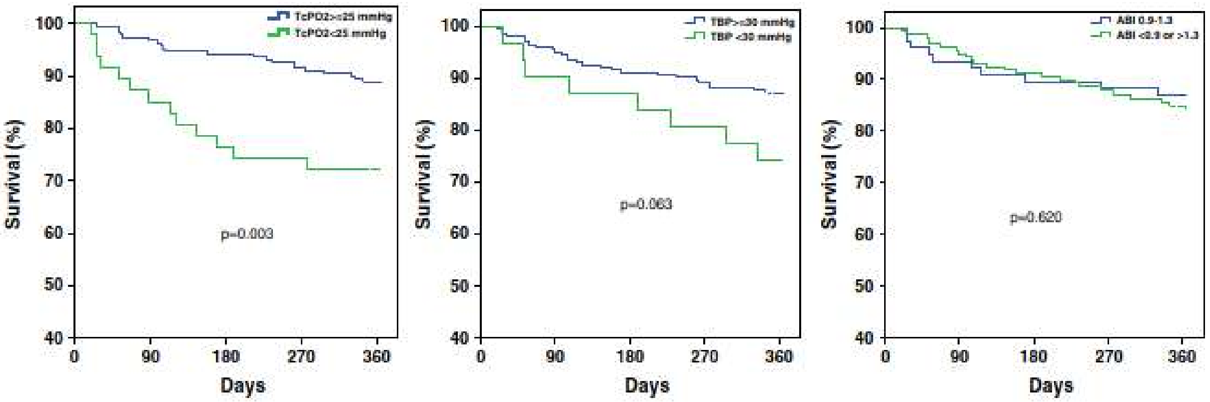


Fig. 7: Kaplan - Meier survival curve with log-rank test in DFU patients grouped according to a) TcPO2 < 25 mmHg and ⩾ 25 mmHg, p = 0.003, b)TBP < 30 mmHg and ⩾ 30 mmHg, p = 0.063 and c) ABI 0.9 - 1.3 and < 0.9 or > 1.3, p = 0.620

Meanwhile, in a Cox regression analysis adjusted for confounders, TcPO2 was independently predicting one year mortality with a hazard ratio for TcPO2 < 25 mmHg of 2.8 (95% CI 1.34 to 5.91, p = 0.006).

Fargher K et al. conducted another study of the same cohort to evaluate the combined impact of a low TcPO2 (<30 mmHg) and a pathological ABI (<0.9 or ≥1.4) on three-year mortality in patients with DFU. Type II diabetes patients aged <90 years, with at least one DFU who underwent vascular assessment with ABI and TcPO2 were screened for participation. The primary endpoint was mortality after three years, assessed from the National Death Registry in Sweden. Patients were stratified into three groups; group 1: both pathological ABI and low TcPO2, group 2: pathological ABI or low TcPO2 and group 3: normal ABI and normal TcPO2. They reported that at three years of follow-up, 43% of the participants died. [22, level II-2]

They reported that there was no difference in mortality rate between the groups of individuals with a low ABI <0.9 compared to those with abnormally high ABI ≥1.4 (p = 0.569). Both high and low ABI were significantly associated with increased three-year mortality compared to normal ABI (p = 0.002). However, the highest mortality rate was seen in the group of the individuals with a combination of either a high or low ABI together with a low TcPO2. It was also the strongest independent predictor of mortality, with a hazard ratio of 2.19 (95% CI 1.11 to 4.33). [22, level II-2]

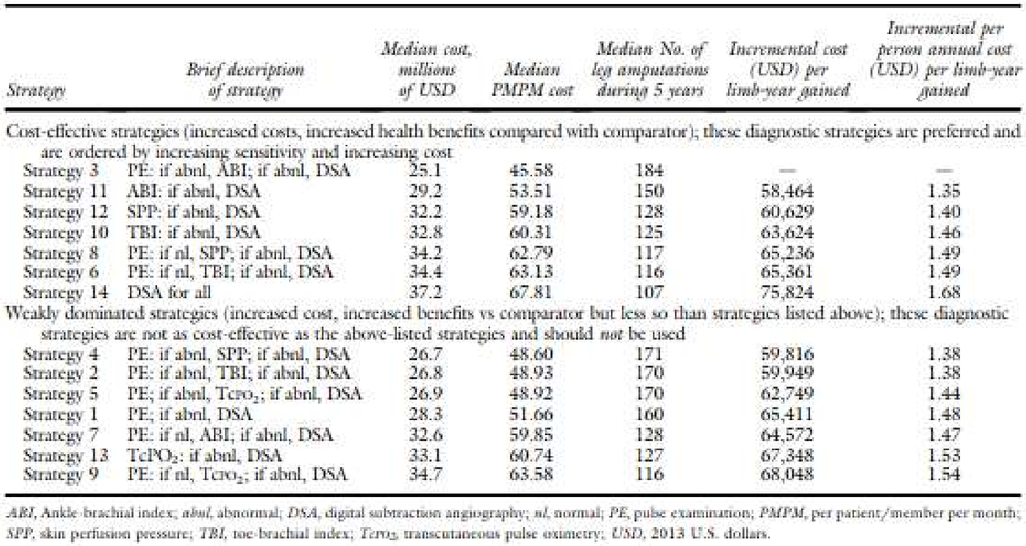
5.3 SAFETY

There was no evidence retrieved on the adverse events related to usage of TcPO2. Several brands of TcPO2 device in the market had received approval from USFDA and classified as class II medical device. [23]

5.4 COST/ COST-EFFECTIVENESS

Barshes NR et al. conducted a cost-effectiveness analysis to estimate the overall diagnostic accuracy for various strategies that are used to identify PAD in patients with diabetic foot ulcer. They used a Markov model with probabilistic and deterministic sensitivity analysis to simulate the clinical events in a population of 10,000 patients with diabetes. One of the 14 different diagnostic strategies was applied to those who developed DFUs. Strategy 14 modelled the strategy of digital subtraction angiography (DSA) for all patients who developed DFUs. The remaining 13 strategies used various conditional combinations of tests such as ankle brachial index (ABI), skin perfusion pressure (SPP), toe brachial index (TBI), pulse examination and TcPO2 as illustrated in Table 3. For purposes of comparison, “strategy 0”consisted of no diagnostic testing to identify lower extremity PAD. Baseline data on diagnostic accuracy of individual non-invasive test were based on a meta-analysis of previously reported study. The overall sensitivity and cost-effectiveness of the 14 strategies were then compared. Incremental cost-effectiveness ratios were then calculated using the lowest strategy (physical examination; if abnormal, ABI; if abnormal DSA) namely strategy 3 as comparator. They reported that the overall sensitivity of various combinations of diagnostic testing strategies ranged from 32.6% to 92.6%. When compared with strategy 3, six strategies (strategy 6, 8,10,11,12 and 14) were found to be cost effective with incremental cost per limb-year gained ranged from USD 58,464 to USD 75,824. Meanwhile, seven strategies (strategy 1, 2, 4, 5, 7, 9 and 13) were weakly dominated. As for the TcPO2, there were three strategies included (strategy 5, 9 and 13) and all of them were weakly dominated with incremental cost per limb-year gained of USD62,749, USD67,348 and USD68,048 respectively. However, the values of the different strategies did not differ much (Table 3).[24]

Table 3: A comparison of incremental costs and health benefits associated with various strategies to identify and to treat peripheral artery disease (PAD) among a hypothetical cohort of patients with diabetic foot ulcers (DFUs)



Strategy	*Brief description of strategy*	*Median cost, millions of USD*	*Median PMPM cost*	*Median No. of leg amputations during 5 years*	*Incremental cost (USD) per limb-year gained*	*Incremental per person annual cost (USD) per limb-year gained*
Cost-effective strategies (increased costs, increased health benefits compared with comparator); these diagnostic strategies are preferred and are ordered by increasing sensitivity and increasing cost						
Strategy 3	PE: if abnl, ABI; if abnl, DSA	25.1	45.58	184	—	—
Strategy 11	ABI: if abnl, DSA	29.2	53.51	150	58,464	1.35
Strategy 12	SPP: if abnl, DSA	32.2	59.18	128	60,629	1.40
Strategy 10	TBI: if abnl, DSA	32.8	60.31	125	63,624	1.46
Strategy 8	PE: if nl, SPP; if abnl, DSA	34.2	62.79	117	65,236	1.49
Strategy 6	PE: if nl, TBI; if abnl, DSA	34.4	63.13	116	65,361	1.49
Strategy 14	DSA for all	37.2	67.81	107	75,824	1.68
Weakly dominated strategies (increased cost, increased benefits vs comparator but less so than strategies listed above); these diagnostic strategies are not as cost-effective as the above-listed strategies and should *not* be used						
Strategy 4	PE: if abnl, SPP; if abnl, DSA	26.7	48.60	171	59,816	1.38
Strategy 2	PE: if abnl, TBI; if abnl, DSA	26.8	48.93	170	59,949	1.38
Strategy 5	PE; if abnl, T_{CPO_2}; if abnl, DSA	26.9	48.92	170	62,749	1.44
Strategy 1	PE; if abnl, DSA	28.3	51.66	160	65,411	1.48
Strategy 7	PE: if nl, ABI; if abnl, DSA	32.6	59.85	128	64,572	1.47
Strategy 13	$TcPO_2$: if abnl, DSA	33.1	60.74	127	67,348	1.53
Strategy 9	PE: if nl, T_{CPO_2}; if abnl, DSA	34.7	63.58	116	68,048	1.54

ABI, Ankle-brachial index; *abnl*, abnormal; *DSA*, digital subtraction angiography; *nl*, normal; *PE*, pulse examination; *PMPM*, per patient/member per month; *SPP*, skin perfusion pressure; *TBI*, toe-brachial index; T_{CPO_2}, transcutaneous pulse oximetry; *USD*, 2013 U.S. dollars.

Source: Barshes NR, Flores E, Belkin M et al.

5.5 COST ANALYSIS

A cost analysis was conducted comprises of an analysis of the costs and resources associated with the use of TcPO2 using the Microsoft Excel 2013.The direct medical costs included were cost of device, consumables and maintenance or calibration. The cost of device and consumables were based on written communication with a clinical expert. For reusable equipment, a 5% discount rate was applied to determine the annuity factor with an estimated life span of 5 years. Maintenance cost were calculated with an estimation of 10% yearly increment. A scenario analysis was conducted to explore the uncertainties on the use of TcPO2 device.

Based on the analysis, the total cost of using TcPO2 to test for tissue perfusion was estimated as MYR 168,884.00 for 5 years. To account for uncertainties in the consumption of consumables and life span years of equipment, a scenario analysis was conducted and summarized as Figure 1. The total cost of using TcPO2 for 10 years with various cost of consumables ranged between MYR 337,000 to MYR 418,000 and MYR 279,000 to MYR 360,000 for life span of 5 years and 10 years respectively. Due to the limitation in availability of local data, no further analysis could be conducted beyond this.

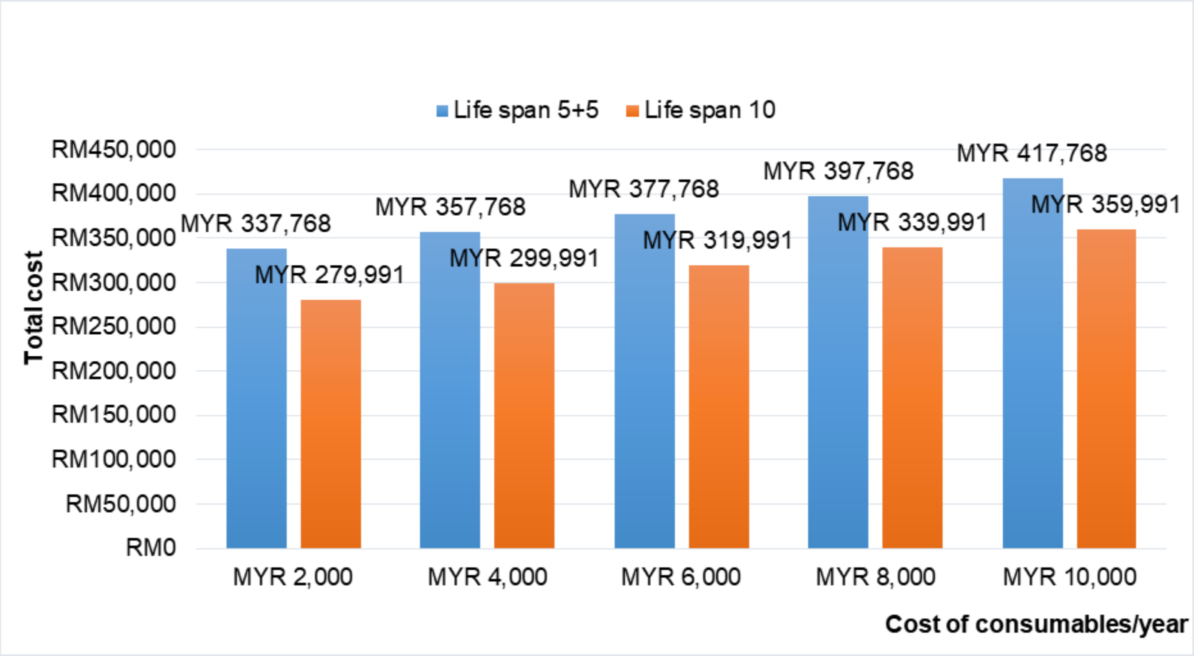


Figure 8: Total cost of TcPO2

5.6 ORGANISATIONAL ISSUES

There was no evidence retrieved on the organisational issues on the TcPO2.

The International Working Group on the Diabetic Foot (IWGDF) through their evidence based guideline recommended to perform at least one of the bedside tests in patient with diabetic foot ulcer and PAD such as a skin transfusion pressure of ≥ 40 mmHg, a toe pressure of ≥ 30 mmHg or a TcPO2 of ≥25mmHg [any of which increases the test probability of healing by 25% (strong: moderate)]. They also recommend to always considering an urgent vascular imaging and revascularisation in the patient with diabetic foot ulcer and an ankle pressure of <50mmHg, ABI of <0.5, a toe pressure of <30 mmHg or TcPO2 of <25mmHg (strong: low).[25]

In patients with Type II diabetes mellitus and a foot ulcer, clinical examination alone may not exclude PAD hence combined modality testing of continuous wave Doppler of ankle arteries (CWD) and ABI or TBI is recommended. [1]

5.7 LIMITATION

This technology review has several limitations. The studies retrieved were heterogeneous in terms of the study design, lack of head to head comparison and with limited number of participants. Primary studies included in SRs were with potential risk of bias. Although there was no restriction in the language during the search only English full-text articles were included in this review.

6.0 CONCLUSION

There was fair to good level of evidence retrieved to suggest that TcPO2 may predict wound healing, amputation and mortality among patients with diabetic foot ulcer, critical limb ischaemia and underlying peripheral arterial disease. However, there was no evidence that TcPO2 is suitable to substitute other modalities. The suggested threshold value for wound healing/tissue perfusion is >25mmHg. No evidence retrieved on the safety.

7.0 REFERENCES

1. Ministry of Health Malaysia. Clinical Practice Guidelines for the Management of Type 2 Diabetes Mellitus 6th edition. 2020.Available at https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/CPG_T2DM_6th_Edition_2020_13042021.pdf. Accessed on 15 February 2022

2. Ministry of Health Malaysia. National Diabetes Registry Report 2020. Available at https://www.moh.gov.my/moh/resources/Penerbitan/Rujukan/NCD/Diabetes/National_Diabetes_Registry_Report_2020.pdf. Accessed on 15 February 2022

3. Normahani P, Poushpas S, Alaa M et al. Study protocol for a comparative diagnostic accuracy study of bedside tests used to detect arterial disease in diabetes: TEsting for Arterial disease in Diabetes (TrEAD) study. BMJ Open. 2020;10(2):e033753

4. Yang C, Weng H, Chen L et al. Transcutaneous oxygen pressure measurement in diabetic foot ulcers: mean values and cut-point for wound healing. J Wound Ostomy Continence Nurs. 2013;40(6):585-589

5. Redlich U, Xiong YY, Pech M et al. Superiority of transcutaneous oxygen tension measurements in predicting limb salvage after below-the-knee angioplasty: a prospective trial in diabetic patients with critical limb ischemia. Cardiovasc Intervent Radiol. 2011;34(2):271-279

6. Ercengiz A and Mutluoglu M. Hyperbaric Transcutaneous Oximetry.In: StatPearls [Internet]; 2021

7. Catella J, Long A, Mazzolai L. What Is Currently the Role of TcPO2 in the Choice of the Amputation Level of Lower Limbs? A Comprehensive Review. J Clin Med. 2021;10(7):1413

8. de Meijer VE, Van't Sant HP, Spronk S et al. Reference value of transcutaneous oxygen measurement in diabetic patients compared with nondiabetic patients. J Vasc Surg. 2008;48(2):382-388

9. Pulse oximetry vs. transcutaneous monitoring in neonates: practical aspects. Available at https://acutecaretesting.org/en/articles/pulse-oximetry-vs-transcutaneous-monitoring-in-neonates-practical-aspects. Accessed on 19 January 2022

10. Yip WL. Evaluation of the clinimetrics of transcutaneous oxygen measurement and its application in wound care. Int Wound J. 2015;12(6):625-629

11. PeriFlux 6000 TcpO2 System. Available at https://www.perimed-instruments.com/content/periflux-6000-TcPO2-system/. Accessed on 20 February 2022

12. Wang Z, Hasan R, Firwana B et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg. 2016;63(2 Suppl):29S-36S.e1-2.

13. Rajagopalan C, Viswanathan V, Rajsekar S et al. Diabetic foot ulcers -comparison of performanceof ankle-brachial index and transcutaneous partial oxygen pressure in predicting outcome. Int J Diabetes Dev Ctries. 2017;38(2):1-6

14. Vriens B, D'Abate F, Ozdemir BA, et al. Clinical examination and non-invasive screening tests in the diagnosis of peripheral artery disease in people with diabetes-related foot ulceration. Diabet Med. 2018;35(7):895-902

15. de Graaff JC, Ubbink DT, Legemate DA et al. Evaluation of toe pressure and transcutaneous oxygen measurements in management of chronic critical leg ischemia: a diagnostic randomized clinical trial. J Vasc Surg. 2003;38(3):528-534

16. Arsenault KA, Al-Otaibi A, Devereaux PJ et al. The use of transcutaneous oximetry to predict healing complications of lower limb amputations: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2012;43(3):329-336

17. Arsenault KA, McDonald J, Devereaux PJ et al. The use of transcutaneous oximetry to predict complications of chronic wound healing: a systematic review and meta-analysis. Wound Repair Regen. 2011 ;19(6):657-663

18. Ruangsetakit C, Chinsakchai K, Mahawongkajit P et al. Transcutaneous oxygen tension: a useful predictor of ulcer healing in critical limb ischaemia. J Wound Care. 2010;19(5):202-206

19. Ladurner R, Küper M, Königsrainer I, et al. Predictive value of routine transcutaneous tissue oxygen tension (TcPO2) measurement for the risk of non-healing and amputation in diabetic foot ulcer patients with non-palpable pedal pulses. Med Sci Monit. 2010;16(6):CR273-277

20. Salaun P, Desormais I, Lapébie FX et al. Comparison of Ankle Pressure, Systolic Toe Pressure, and Transcutaneous Oxygen Pressure to Predict Major Amputation After 1 Year in the COPART Cohort. Angiology. 2019;70(3):229-236

21. Fagher K, Katzman P, Löndahl M. Transcutaneous oxygen pressure as a predictor for short-term survival in patients with type 2 diabetes and foot ulcers: a comparison with ankle-brachial index and toe blood pressure. Acta Diabetol. 2018 ;55(8):781-788

22. Fagher K, Löndahl M. The combined impact of ankle-brachial index and transcutaneous oxygen pressure on mortality in patients with type 2 diabetes and foot ulcers. Acta Diabetol. 2021;58(10):1359-1365

23. Perimed AB available at https://www.accessdata.fda.gov/cdrh_docs/pdf15/K152930.pdf. Accessed on 23 February 2022

24. Barshes NR, Flores E, Belkin M et al. The accuracy and cost-effectiveness of strategies used to identify peripheral artery disease among patients with diabetic foot ulcers. J Vasc Surg. 2016;64(6):1682-1690

25. Hinchliffe RJ, Forsythe RO, Apelqvist J et al. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3276.

APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS / DIAGNOSTIC STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: ***US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2015)***

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE(R) ALL <1946 to January 28, 2022>

1 Diabetic foot/ (10163)
2 diabetic foot.tw. (9519)
3 foot ulcer, diabetic.tw. (11)
4 diabetic feet.tw. (215)
5 WOUND HEALING/ (100855)
6 healing*, wound.tw. (753)
7 wound healing*.tw. (74491)
8 PERIPHERAL ARTERIAL DISEASE/ (9711)
9 peripheral arterial disease*.tw. (9976)
10 peripheral artery disease*.tw. (6242)
11 tissue perfusion.tw. (5161)
12 isch?emia*.tw. (189591)
13 peripheral vascular disease.tw. (9186)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (368172)
15 BLOOD GAS MONITORING, TRANSCUTANEOUS/ (2445)
16 transcutaneous blood gas monitoring.tw. (34)
17 cutaneous oximetr*.tw. (10)
18 transcutaneous oximetr*.tw. (208)
19 oxygen partial pressure determination, transcutaneous.tw. (0)
20 TcPO2.tw. (1069)
21 Transcutaneous oxygen pressure monitoring.tw. (3)
22 TCOM.tw. (36)
23 Transcutaneous oximetry.tw. (207)
24 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (3168)
25 14 and 24 (432)

PubMeD

Search: ((((((((((((Diabetic foot[Title/Abstract]) OR (diabetic foot[Title/Abstract])) OR (foot ulcer, diabetic[Title/Abstract])) OR (diabetic feet[Title/Abstract])) OR (WOUND HEALING[Title/Abstract])) OR (healing*, wound[Title/Abstract])) OR (wound healing*[Title/Abstract])) OR (PERIPHERAL ARTERIAL DISEASE[Title/Abstract])) OR (peripheral arterial disease*[Title/Abstract])) OR (peripheral artery disease*[Title/Abstract])) OR (tissue perfusion[Title/Abstract])) OR (ischemia*[Title/Abstract])) OR (peripheral vascular disease[Title/Abstract])) AND (((((((((BLOOD GAS MONITORING, TRANSCUTANEOUS[Title/Abstract]) OR (transcutaneous blood gas monitoring[Title/Abstract])) OR (cutaneous oximetr*[Title/Abstract])) OR (15 transcutaneous oximetr*[Title/Abstract])) OR (oxygen partial pressure determination, transcutaneous[Title/Abstract])) OR (TcPO2[Title/Abstract])) OR (Transcutaneous oxygen pressure monitoring[Title/Abstract])) OR (TCOM[Title/Abstract])) OR (Transcutaneous oximetry[Title/Abstract]))

APPENDIX 3: EVIDENCE TABLE

Evidence Table **:Eficacy/Effectiveness/safety/cost-effective**
Question **:Is TcPO2 effective, safe and cost-effective?**

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1.Wang Z, Hasan R, Firwana B et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg. 2016;63(2 Suppl):29S-36S.e1-2. doi: 10.1016/j.jvs.2015.10.004.	**Study design** SR with meta-analysis **Objective** To summarise the evidence of available tests and to compare the performance of eight non-invasive tests in predicting wound healing of DFUs **Methods** Six databases were systematically searched until October 2011 The methodology and reporting SR used PRISMA Study selection, data abstraction was done by two reviewers Risk of bias were carried out using Newcastle and Ottawa scale and quality was evaluated using GRADE Outcome: Number of healed foot ulcers and number of amputated limbs	I	37 articles included (32 observational, 5 RCTs) (ABI:20, TcPO2:25, SPP:2, TBP:2, TBI: 2, microvascular SaO2:1,APSV:1, hyperspectral imaging:1)	ABI, APSV, TcPO2,TBI, TBP, microvascular SaO2, SPP, and hyperspectral imaging			Meta-analysis was possible on studies of ABI and TcPO2. **ABI (20 studies, 2376 patients)** • The pooled ABI values were significantly higher in the healed ulcer group than in the non-healed group (SMD 0.42; 95% CI: 0.05, 0.79; I^2=15.7%; P=0.32) • Combined difference between the amputated limb group and the non-amputated group was also significant (SMD 0.99; 95% CI: 1.44, 0.54; I^2=44.5%; P =0.13) **TcPO2 (25 studies, 3789 patients)** • There was a significant difference of TcPO2 values between the healed group and the non-healed group (SMD 1.80; 95% CI: 1.06, 2.54; I^2 =92.3%; P=0 <.001). • SMD was 2.26 (95% CI: 4.13, 0.40; I^2=96.8%; P 0<.001) when the amputated limb group was compared with the non-amputated group Based on calculated pooled DOR, ABI had poor performance in predicting the healing of foot ulcers and modest performance in predicting limb amputations. TcPO2 was a better test for predicting both outcomes. (Table 1)	

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	Outcomes were extracted at longest duration of complete follow-up Predefined threshold (ABI: 0.8, TcPO2: 30mmHg) Data synthesis: sensitivity and specificity were calculated for each test using bivariate binomial mixed models. Diagnostic odd ratio (DOR) were calculated based on pooled sen and spec. Standardised mean difference (SMD) was calculated for effect size Heterogeneity was assessed using I^2 and Cochran Q test Multivariate nested random-effects meta-regression models was constructed for sensitivity analysis						Table 1: pooled sensitivity, specificity and diagnostic odd ratio of ABI and TcPO2 test	

	ABI		$TcPO_2$	
Outcome	estimate	95%CI	estimate	95%CI
Complete ulcer healing				
Sensitivity	0.48	0.36, 0.61	0.72	0.61, 0.81
Specificity	0.52	0.2,0.63	0.86	0.68, 0.95
DOR	1.02	0.40, 2.65	15.81	3.36, 74.45
Limb amputation				
Sensitivity	0.52	0.49, 0.54	0.75	0.73, 0.77
Specificity	0.73	0.63, 0.81	0.58	0.52, 0.64
DOR	2.89	1.65, 5.05	4.14	2.98, 5.76

Evidence Table :**Eficacy/Effectiveness/safety/cost-effective**
Question :**Is TcPO2 effective, safe and cost-effective?**

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2.Rajagopalan C, Viswanathan V, Rajsekar S et al. Diabetic foot ulcers - comparison of performance of ankle-brachial index and transcutaneous partial oxygen pressure in predicting outcome. Int J Diabetes Dev Ctries. 2017;38(2):1-6. DOI:10.1007/s13410-017-0580-3	**Study design** Prospective cohort study **Objective** To compare the performances of ankle-brachial index (ABI) and transcutaneous partial pressure of oxygen (TcPO2) measurement in predicting wound healing in diabetic ulcers and to define the optimal cut-off value for Indian patients. **Methods** Conducted for a period of 6 months from September 2015 to February 2016, at MV Diabetic Research Center, Chennai. All diabetic patients who attended the out-patient department with Wagner Grade II and III foot ulcers were included in this study. On evaluation, biochemistry investigation reports, microbiology lab results, ABI, and TcPO2 were recorded for all patients. All patients were followed up to complete wound	II-2	564 patients mean age 58 years	TcPO2	Nil	3 months	➢ Out of 470 healed ulcers, 65% (304 patients) healed within 41 to 45 days. ➢ Only 81/470 patients (17%) had delayed healing of > 45 days. ➢ The average healing days were 42.6 ± 2.7 days. ➢ A total of 94 patients underwent amputation, 32 patients with minor and 62 patients with major amputation. The diagnostic ODDS ratio for wound healing for ABI was 23 and for TcPO2 was 4.23, with a positive predictive value of 75 and 35%, respectively By plotting the ROC curve, for the state of healed, a TcPO2 value of 22.5 must have 100% sensitivity and 75% specificity. The corresponding value for ABI was 0.6, with sensitivity of 99% and specificity of 68%. By decreasing the value of ABI to 0.4, it had the sensitivity of 100% and specificity of 80% By plotting the ROC curve, for the positive state of amputation, an ABI value of < 0.6 was found to have 68% sensitivity and 99% specificity. The corresponding value for TcPO2 was 22.5, with sensitivity of 75% and specificity of 100% Multivariate logistic regression analysis showed an ODD ratio of 3.5 (95% CI 2.2 to 5.7) for the effect of wound healing with ABI	

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	healing or up to 3 months. Complete epithelialization of the ulcer or healed amputation stump was considered as primary wound outcome. Amputations were defined as minor which includes mid-foot and distal amputations, while major amputation was defined as amputations above the ankle. Continuous demographic factors and outcome variables were summarized using a mean with 95% standard deviation and compared between outcome groups by using t test. The performances and optimal cut-off values for the studies factors were calculated and presented using an ROC curve.						and an odds ratio of 3.0 (95% CI 2.1 to 4.3) for the effect of abnormal TcPO2 in Amputation **Authors' conclusion:** Both ABI and TcPO2 are complementary, but TcPO2 is a better predictor for amputation while ABI is a better predictor for ulcer healing.	

Evidence Table :**Eficacy/Effectiveness/safety/cost-effective**
Question :**Is TcPO2 effective, safe and cost-effective?**

Bibliographic citation	**Study Type/ Methods**	**LE**	**Number of Patients & Patient Characteristic**	**Intervention**	**Comparison**	**Length of Follow Up (If Applicable)**	**Outcome Measures/Effect Size**	**General Comments**
3.Vriens B, D'Abate F, Ozdemir BA, et al. Clinical examination and non-invasive screening tests in the diagnosis of peripheral artery disease in people with diabetes-related foot ulceration. Diabet Med. 2018;35(7):895-902. doi: 10.1111/dme.13634.	**Study design** Prospective observational study (cohort study) **Objective** To investigate the utility of clinical examination and non-invasive bedside tests in screening for peripheral artery disease in diabetes-related foot ulceration. **Methods** People with diabetes presenting to either a multidisciplinary diabetes foot clinic or emergency department with foot ulceration of < 2 months duration were recruited into this prospective, single-centre observational study All individuals with diabetes, regardless of type, presenting with primary lower limb ulceration were potentially eligible. Accuracy of pulses, ankle pressure, toe pressure, toe–brachial index (TBI), ankle–brachial pressure index (ABPI), pole test at ankle, transcutaneous oxygen pressure and distal tibial waveform on ultrasound were examined.	II-2	60 patients 20 (33%) participants had peripheral artery disease on diagnostic ultrasound.	Pedal pulse, ankle pressure, toe pressure, toe–brachial index (TBI), ankle–brachial pressure index (ABPI), pole test at ankle, transcutaneous oxygen pressure and distal tibial waveform	Duplex ultrasound.		➢ The NLR and PLR of pedal pulse assessment (0.75, 1.38) and the other physical examination findings were poor (Table 1). ➢ Similarly, the NLR and PLR of ABPI (0.53, 1.69), TcPO2 (1.1, 0.81) and ankle pressure (0.67, 2.25) as screening tools to identify peripheral artery disease were unsatisfactory. ➢ The lowest NLR was for tibial waveform assessment (0.15) and TBI (0.24). ➢ The highest PLR were for toe pressure (17.55) and pole test at the ankle (10.29), but the NLR values were again poor at 0.56 and 0.74, respectively (Table 1).	

Table 1: Diagnostic utility of physical examination of and screening tests to identify peripheral artery disease compared to Duplex ultrasound scan

	Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio	Negative likelihood ratio
Ankle pressure	0.47 (0.25–0.70)	0.79 (0.66–0.92)	0.53 (0.29–0.77)	0.75 (0.62–0.88)	2.25 (1.03–4.90)	0.67 (0.42–1.05)
Toe pressure	0.45 (0.23–0.67)	0.97 (0.92–1.00)	0.90 (0.71–1.00)	0.78 (0.66–0.89)	17.55 (2.39–128.96)	0.56 (0.38–0.84)
Toe brachial pressure index	0.89 (0.76–1.00)	0.45 (0.29–0.61)	0.45 (0.29–061)	0.89 (0.76–1.00)	1.62 (1.17–2.2)	0.24 (0.06–0.91)
Ankle brachial pressure index	0.68 (0.48–0.89)	0.59 (0.44–0.75)	0.46 (0.28–0.65)	0.79 (0.63–0.94)	1.69 (1.03–2.77)	0.53 (0.26–1.08)
Pole test and ankle	0.28 (0.07–0.48)	0.97 (0.92–1.00)	0.83 (0.54–1.00)	0.73 (0.61–0.86)	10.29 (1.29–81.60)	0.74 (0.55–0.99)
TcPo2	0.28 (0.07–0.48)	0.66 (0.51–0.81)	0.28 (0.07–0.48)	0.66 (0.51–0.81)	0.81 (0.34–1.93)	1.10 (0.76–1.58)
Waveform analysis	0.85 (0.69–1.00)	1‡	1‡	0.93 (0.85–1.00)	Diagnoses PAD‡	0.15 (0.05–0.43)

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	The gold standard diagnostic test used was > 50% stenosis in any artery or monophasic flow distal to calcification in any ipsilateral vessel on duplex ultrasound. Descriptive analysis of the negative likelihood ratio (NLR) was the primary outcome of interest. The positive likelihood ratio (PLR), sensitivity, specificity, positive and negative predictive values are also reported.							

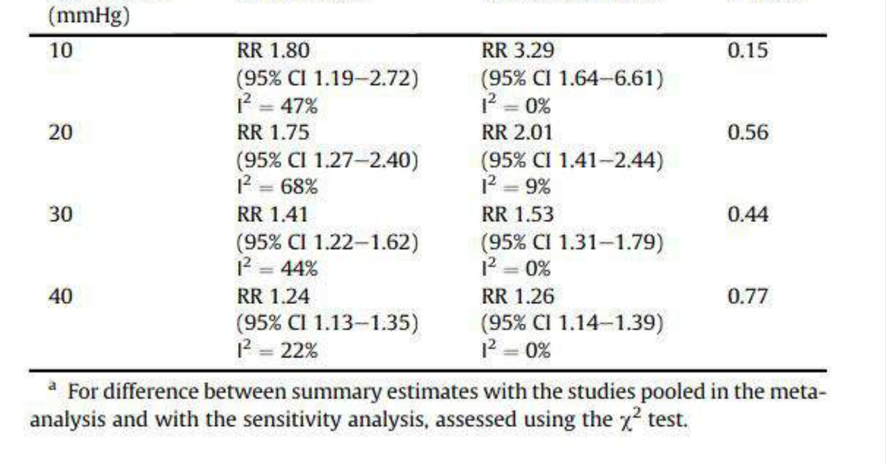
Evidence Table :**Eficacy/Effectiveness/safety/cost-effective**
Question :**Is TcPO2 effective, safe and cost-effective?**

Bibliographic citation	**Study Type/ Methods**	**LE**	**Number of Patients & Patient Characteristic**	**Intervention**	**Comparison**	**Length of Follow Up (If Applicable)**	**Outcome Measures/Effect Size**	**General Comments**
4.de Graaff JC, Ubbink DT, Legemate DA et al. Evaluation of toe pressure and transcutaneous oxygen measurements in management of chronic critical leg ischaemia: a diagnostic randomized clinical trial. J Vasc Surg. 2003;38(3):528-34. doi: 10.1016/s0741-5214(03)00414-2.	**Study design** Randomised controlled trial **Objective** To evaluate the diagnostic value of TcPO2 and TP in management of clinically suspected critical leg ischaemia. **Methods** Patients who clinically suspected CLI were randomized to receive either conventional treatment or the new management technique randomization was performed by computer Patients with suspected acute arterial occlusion and had clear-cut cases were excluded Clinical CLI was defined as pain at rest in the lower leg for more than 2 weeks, ulcers that persisted for more than 2 weeks, or diffuse gangrene of the forefoot AP was measured in all patients.	II-1	96 patients (128 legs)	TP +TcPO2	Ankle Pressure		Pain per involved leg did not differ between two groups Prevalence of wounds was significantly lower in the conventional treatment Group (P =0 .04), however, severity of wounds was not differ (P=0.55) Quality of life assessed with the SF-36 physical and mental summary score was not significantly different between groups (P =0 .10 and P=0 .28, respectively) Survival was not significantly different between the two groups (log-rank statistic, 0.12; P=0 .7)	

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	TP and TcPO2 were measured only in patients assigned to the new strategy group. Main outcome measures included clinical outcome, defined as pain relief, wound healing, and limb survival.							

Evidence Table :Eficacy/Effectiveness/safety/cost-effective
Question :Is Digital Assisted Oral & Cranio-maxillofacial Surgery effective, safe and cost-effective?

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
5.Arsenault KA, Al-Otaibi A, Devereaux PJ et al. The use of transcutaneous oximetry to predict healing complications of lower limb amputations: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2012;43(3):329-336. doi: 10.1016/j.ejvs.2011.12.004. Epub 2012 Jan 10.	**Study design** SR with meta-analysis **Objective** To determine the validity of transcutaneous oximetry (TcPO2) as a predictor of lower limb amputation healing complications **Methods** Databases were systematically searched for amputation and transcutaneous oximetry. Hand searched was also carried out Inclusion: conducted at least one preoperative TcPO2 measurement at the site of the planned amputation; reported the postoperative healing status of the surgical wound or rate of amputation revision to a more proximal level; and provided data to assess TcPO2 measurements as a predictor of amputation healing Selection, data extraction, assessment quality of study was carried out by two reviewers. Unadjusted relative risks	I	31 studies (1824 patients with 1960 amputations) Indications for lower limb amputation: -peripheral vascular disease -Occlusive arterial disease -Non-healing ischaemic ulcers -Infection -Gangrene -Rest pain -Diabetes mellitus	TcPO2	nil		**Qualitative outcome** • 1 study reported an adjusted odds ratio for the association between a preoperative TcPO2 level below 20 mmHg and occurrence of re-amputation was calculated to be 3.08 (95% (CI: 1.19, 7.98; p = 0.021) • 2 studies suggested that there was a correlation between low TcPO2 values and amputation stump healing complication. • 2 studies performed lower limb amputations at the level where TcPO2 was 24 or 30 mmHg, respectively. • 19 studies reported the results of a univariable association through Student's t-test or the Manne Whitney U test • 7 studies did not report a univariable association between TcPO2 levels and lower limb amputation healing complications, but presented data that allowed for the calculation of an unadjusted RR of lower limb amputation healing complication associated with a TcPO2 level below a cut-off of 10, 20, 30 or 40 mmHg. **Meta-analysis (14 studies)** **Unadjusted RR of lower limb amputation healing complication** • TcPO2 <10mmHg (11 studies) displayed the strongest association with healing complication [RR 1.80 (95% CI: 1.19, 2.72) • TcPO2 <20-mmHg (14 studies) resulted in a pooled RR of 1.75	

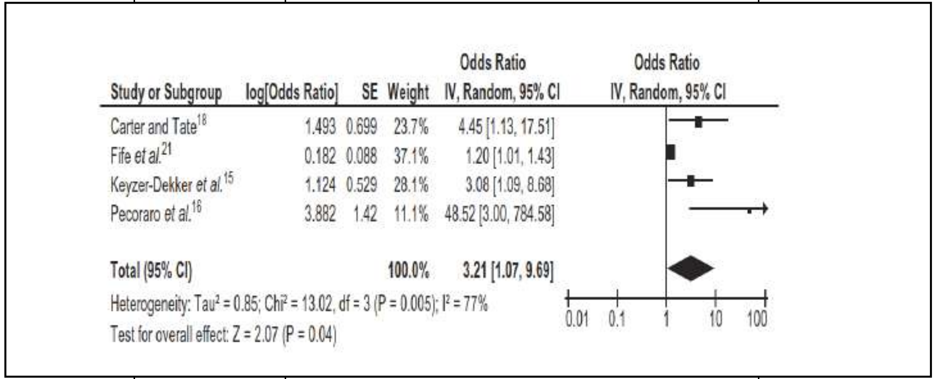
Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	(RRs) were calculated for each study at each cut-off level. The unadjusted RRs were pooled using the DerSimonian and Laird random-effects model24 based on the Mantele Haenszel estimate. Substantial heterogeneity was defined as an I^2 of ≥ 50%. A random-effects meta-regression of the log RR was used to assess the plausible explanatory variables of TcPO2 cut-off value, year of publication and length of patient follow-up						(95% CI: 1.27, 2.40) • Cut-offs of 30 mmHg and 40 mmHg displayed pooled RRs of 1.41 (95% CI: 1.22, 1.62) and 1.24 (95% CI: 1.13, 1.39), respectively • Sensitivity analysis found no significant different  **Authors' conclusion** This review suggests that there is a positive and statistically significant association between TcPO2 values below a cut-off level and healing complications of lower limb amputations. There is, however, insufficient evidence to judge whether this tool adds important information to clinical examination.	

Cut-off value (mmHg)	Meta-analysis	Sensitivity analysis	p-value[a]
10	RR 1.80 (95% CI 1.19–2.72) $I^2 = 47\%$	RR 3.29 (95% CI 1.64–6.61) $I^2 = 0\%$	0.15
20	RR 1.75 (95% CI 1.27–2.40) $I^2 = 68\%$	RR 2.01 (95% CI 1.41–2.44) $I^2 = 9\%$	0.56
30	RR 1.41 (95% CI 1.22–1.62) $I^2 = 44\%$	RR 1.53 (95% CI 1.31–1.79) $I^2 = 0\%$	0.44
40	RR 1.24 (95% CI 1.13–1.35) $I^2 = 22\%$	RR 1.26 (95% CI 1.14–1.39) $I^2 = 0\%$	0.77

[a] For difference between summary estimates with the studies pooled in the meta-analysis and with the sensitivity analysis, assessed using the χ^2 test.

Evidence Table :**Eficacy/Effectiveness/safety/cost-effective**
Question :**Is TcPO2 effective, safe and cost-effective?**

Bibliographic citation	**Study Type/ Methods**	**LE**	**Number of Patients & Patient Characteristic**	**Intervention**	**Comparison**	**Length of Follow Up (If Applicable)**	**Outcome Measures/Effect Size**	**General Comments**
6.Arsenault KA, McDonald J, Devereaux PJ et al. The use of transcutaneous oximetry to predict complications of chronic wound healing: a systematic review and meta-analysis. Wound Repair Regen. 2011 ;19(6):657-663. doi: 10.1111/j.1524-475X.2011.00731.x. Epub 2011 Oct 10.	**Study design** SR with meta-analysis **Objective** To determine the value of PtcO2 as an independent predictor of chronic wound healing complications and the reported threshold values **Methods** Databases were systematically searched for chronic wound healing, transcutaneous oximetry and diabetic foot. Hand searched was also carried out Inclusion: at least one PtcO2 measurement at the site of the wound; reporting of the healing status of the wound or amputation occurrence; and assessment of PtcO2 as an independent predictor of chronic wound healing complications through multivariable analysis, propensity analysis, or matched cases and controls. Selection, data extraction, assessment quality of study were carried out by two reviewers.	I	4 studies included (1 clinical trial, 2 prospective cohort, 1retrospective cohort) 901 patients with 910 wounds All studies evaluated chronic wound of lower extremity: -only diabetic patients(2 studies) -ischaemic wound (1 study) - ischaemic wound plus amputation wound (1study)	TcPO2	nil	Range: 28 days to 4 years	The definition of an event varied between studies: • 2 studies utilized the occurrence of amputation or re-amputation as an end point that represented failed healing. • 1 study designed a categorical scale that defined healing as complete epithelialization of the wound as determined by a third-party assessor via a photograph. Death during the study period or amputation of the limb resulted in a score in the most critical or second-most critical category, respectively • 1 study used a combination of wound contour tracing, re-epithelialization, and occurrence of amputation or death • The event rates varied from 17.4% to 36.0%. Meta-analysis showed an independent association between PtcO2 levels below a cut-off point and chronic wound healing complications. Figure 1	

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	Outcome: adjusted odds ratios (OR) and measures of variance for chronic wound healing complications associated with a PtcO2 level below a cut-off point Summary estimates that were reported as adjusted relative risks were converted to OR using the proportion of patients with PtcO2 levels above the study cut-off whose chronic wounds failed to heal (P_0) Adjusted OR were pooled using the DerSimonian and Laird random effects model A sensitivity analysis to determine the effect of estimates of the P_0 values on the pooled results Heterogeneity was assessed (cut off :25%)						 Figure 1: Pooled adjusted odds ratio of chronic wound healing complications in patients with PtcO2 levels below a cut-off of 20 mmHg or 30 mmHg.	

Evidence Table :**Eficacy/Effectiveness/safety/cost-effective**
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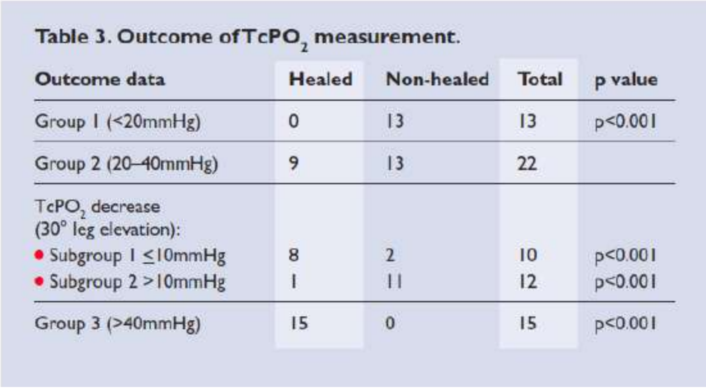
Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
7.Ruangsetakit C, Chinsakchai K, Mahawongkajit P et al. Transcutaneous oxygen tension: a useful predictor of ulcer healing in critical limb ischaemia. J Wound Care. 2010;19(5):202-206. doi: 10.12968/jowc.2010.19.5.48048.	**Study design** Cross sectional study **Objective** To investigate the threshold of TcPO2 values in predicting ulcer healing in patients with critical limb ischaemia **Methods** Patients were enrolled between January 2008 to December 2008 Demographic data and ankle brachial pressure index were collected Baseline ulcer were measured at rest in the supine and with 30^{0}C leg elevation Ulcer outcome were classified as healing or non- healing Descriptive data analyses are given as mean ± standard deviation for continuous data or as percentages for discrete variables. The Chi-square test was used to compare TcPO2 data between the two ulcer		50 patients Male (28) /female(22) Age 67.6 ± 10.8 Presenting symptom: Ischaemic ulcer: 26 ● Toes 14 (53.9%) ● Heel 3 (11.5%) ● Lateral or medial aspects 7 (26.9%) ● Other 2 (7.7%)	TcPO2	Nil		➢ None of patients with a TcPO2 of <20mmHg (group 1) showed signs of ulcer healing ➢ All patients with a TcPO2 of >40mmHg (group 3) showed a progression towards healing (p<0.001). ➢ In the borderline group (20–40mmHg, group 2), 10 patients had a decrease in TcPO2 of <10mmHg with leg elevation (subgroup 1), of whom eight (80%) healed (p<0.001). ➢ In contrast, 12 patients had a decrease in TcPO2 of >10mmHg with leg elevation (subgroup 2), and 11 of these (92%) failed to heal (p<0.001).  **Authors conclusion** TcPO2 measurement is an accurate, non-invasive, and good predictor of ischaemic ulcer healing, for cut-off TcPO2 values of less than 20mmHg and more than 40mmHg.	

Table 3. Outcome of $TcPO_2$ measurement.

Outcome data	Healed	Non-healed	Total	p value
Group 1 (<20mmHg)	0	13	13	p<0.001
Group 2 (20–40mmHg)	9	13	22	
$TcPO_2$ decrease (30° leg elevation):				
● Subgroup 1 ≤10mmHg	8	2	10	p<0.001
● Subgroup 2 >10mmHg	1	11	12	p<0.001
Group 3 (>40mmHg)	15	0	15	p<0.001

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	outcomes. A value of $p<0.05$ was considered to be statistically significant.							

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8.Ladurner R, Küper M, Königsrainer I, et al. Predictive value of routine transcutaneous tissue oxygen tension (TcpO2) measurement for the risk of non-healing and amputation in diabetic foot ulcer patients with non-palpable pedal pulses. Med Sci Monit. 2010;16(6):CR 273-277.	**Study design** Prospective cohort study **Objective** To investigate whether TcPO2 measurement is a suitable daily routine screening tool for estimating the risk of non-healing and amputation in diabetic foot ulcer patients with non-palpable pedal pulses. **Methods** February 2001 and December 2006 All ulcers were located below the ankle. At every visit, wound size (by planimetry), wound depth, and the clinical presence of soft tissue infection were assessed. Prospective documentation was followed-up for 365 days or until healing or amputation, if earlier, through scheduled regular visits. Healing was defined as complete epithelialization Amputation was classified	II-2	141 patients with non-palpable pedal pulses median initial wound area was 1.33 (0.10–99) cm2 and TcPO2 29 (0–89) mmHg	TcPO2	Nil	Median duration of follow-up was 119 (7–365) days	The patients were divided into three subgroups according to their initial TcPO2 readings (group 1: TcPO2 <20 mmHg, group 2: TcPO2 20–40 mmHg, group 3: TcPO2 >40 mmHg) ➢ significant difference in the probability of healing between groups 1 and 3 after one year of treatment (48% vs. 73%, p=0.008). ➢ no significant differences comparing group 2 with group 1 (p=0.131) or group 3 (p=0.195) ➢ soft tissue infection during follow-up (group 1: 49%, group 2: 61%, group 3: 37%, p=0.057) ➢ The need for hospitalisation (group 1: 77%, group 2: 59%, group 3: 46%, p=0.019) were less frequent with rising TcPO2 value The overall amputation rate increased with decreasing TcPO2 readings (group 1: 26%, group 2: 10%, group 3: 5%, p=0.014), although there was no significant difference for major amputations (group 1: 8%, group 2: 3%, group 3: 2%, p=0.448)	

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	as minor (toe or forefoot amputation) or major (above knee or below knee amputation). The amputation rate was defined as the percentage of patients undergoing minor or major amputation within the observation period.							

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Question :**Is TcPO2 effective, safe and cost-effective?**

Bibliographic citation	**Study Type/ Methods**	**LE**	**Number of Patients & Patient Characteristic**	**Intervention**	**Comparison**	**Length of Follow Up (If Applicable)**	**Outcome Measures/Effect Size**	**General Comments**
9.Salaun P, Desormais I, Lapébie FX et al. Comparison of Ankle Pressure, Systolic Toe Pressure, and Transcutaneous Oxygen Pressure to Predict Major Amputation After 1 Year in the COPART Cohort. Angiology. 2019;70(3):229-236. doi: 10.1177/0003319718793566. Epub 2018 Aug 16.	**Study design** Prospective Cohort **Objective** To compare AP, STP, and transcutaneous oxygen pressure (TcPO2) in order to predict the rate of major amputation after 1 year. **Methods** Patients who fulfilled the TASC II criteria for CLI were selected from Cohorte des Patients ARTe´riopathes (COPART) cohort Thay were divided into surgical and medical groups All the patients were followed up for at least 1 year, and the principal end point was defined as major amputation above the ankle. Death, coronary events, and stroke were also reported They analyzed the prediction of amputation rate and secondary end	II-2	556 surgical group, 264 medical group, 292	Ankle Pressure (AP) Systolic toe pressure (STP) Transcutaneous oxygen pressure (TcPO2)			After 1 year, 23%patients underwent major amputation (27%in the medical group vs 17% in the surgical one, P < .01). **Ankle pressure.** None of the values used for AP to define CLI in the different definitions (50 or 70 mm Hg) was predictive of major amputation **Systolic toe pressure**. The STP <30 mm Hg predicted a 3-fold increase in the risk of major amputation (P < .01) in the whole sample and in the medical group **Transcutaneous oxygen pressure.** Amputation rate was twice as high for TcPO2 <10 mm Hg as for 30 mm Hg in the whole sample and in the medical group The most predictive values in the **whole sample** were 10 mmHg OR 2.3 (95% CI 1.5 to 3.5), 20 mm Hg OR 2.4 (95% CI 1.5 to 4.1), and 30 mmHg OR 3 (95% CI 1.3 to 6.9). The most predictive values in **the medical group** were 10 mm Hg OR 3.8 (95% CI 2.1 to 6.8), 20 mm Hg OR 3.2 (95% CI 1.7 to 6.1]), and 30 mm Hg OR 3 (95% CI 1.3 to 6.9). The amputation rate estimated by logistic regression was twice as high for TcPO2 <10 mmHg as for TcPO2 <30 mmHg in the whole sample and in the medical group. **Comparison of AP, STP, and TcPO2 for the prediction of amputation.** In the whole sample, the best method was	

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	points by haemodynamics: AP, STP, and TcPO2. The frequency of events was estimated by the Kaplan-Meier method, and the differences were measured by the log-rank test. Receiver–operating characteristic curves (ROC curves) were used to define the best sensitivity (Se) and specificity (Sp) for each method. Univariate logistic regression was used to measure the association between the levels and the risk of amputation.						STP: area under curve (AUC) 0.678 versus 0.638 for TcPO2 and 0.548 for AP. In the medical group, the best method was also STP: AUC 0.738 versus 0.691 for TcPO2 and 0.6 for SAP. All the methods were poorly predictive of the risk of amputation in the surgical group: AUC 0.573 for STP, 0.589 for TcPO2, and 0.495 for AP.	

Evidence Table :Eficacy/Effectiveness/safety/cost-effective
Question :Is TcPO2 effective, safe and cost-effective?

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
10.Fagher K, Katzman P, Löndahl M. Transcutaneous oxygen pressure as a predictor for short-term survival in patients with type 2 diabetes and foot ulcers: a comparison with ankle-brachial index and toe blood pressure. Acta Diabetol. 2018 ;55(8):781-788. doi: 10.1007/s00592-018-1145-8. Epub 2018 Apr 30.	**Study design** Retrospective cohort study **Objective** To evaluate the predictive value of TcPO2 in comparison with ABI and toe blood pressure (TBP) on 1-year mortality in type 2 diabetes patients with DFU. **Methods** They retrospectively enrolled patients with type 2 diabetes aged <90 years with at least one DFU between year 2013 to 2015 All patients were examined with TcPO2, ABI and TBP at resting and supine position Patients were stratified according to TcPO2 less or >25mmHg measured at dorsum Patient were grouped into TcPO2 quartiles to evaluate mortality at different level ABI was calculated by dividing the systolic ankle pressure with systolic arm	II-2	236 patients with type 2 diabetes Median age 76 (69-82)	TcPO2 ABI TBP	Nil	12 months	(Table X, below) **ABI < 0.9 or > 1.3** was significantly associated with worse ulcer outcome (12-week healing rate of 15.7 vs. 32.7%, in patients with normal ABI, p = 0.004), but no significant association between ulcer healing and **TBP** was found (both < 30 mmHg and < 50 mmHg analysed).However, data not shown. After 1year follow-up, 35(14.8%) patients deceased • TcPO2 < 25 mmHg was significantly associated with a higher 1-year mortality rate compared to >25mmHg (27.7 vs. 11.6%, p = 0.003) • No significant trend (p = 0.061) in the Kaplan–Meier analysis of worse survival rates in patients with TBP < 30 mmHg	

Table X: TcPO2 outcome stratified by <25mmHG and >25mmHg

Baseline characteristic	**TcPO2 <25mmHg n=47**	**TcPO2 >25mmHg n=189**	**P value**
Ulcer healed within 3 months (%)	**8.8**	**25.5**	**0.045**
Revascularisation during follow-up (%)	**25.5**	**13**	**0.073**
Vascular intervention not possible (%)	**21.3**	**6.3**	**<0.001**
Above-ankle amputation during follow-up (%)	**23.4**	**4.2**	**<0.001**

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	pressure and value of 0.9 to 1.3 was considered as normal TBP was measured at great toe (TBP< 30 and TBP < 50 was used in analyses Baseline characteristic was obtained from patients medical record. Lowest value of ABI,TBP and TcPO2 of the two legs was used in the mortality analysis, while the value of affected foot was use when analysing ulcer healing (defined as complete epithelialisation within 12 weeks and above –ankle amputation during follow up assessed from patients chart) Mortality data were obtained from National Death Registry of Sweden. Continous data expressed as median andIQR range 25-75, assessed using Mann-Whitney Fisher exact used to compare difference Survival analysis used Kaplan Meier estimates Cox analysis used to adjust for confounding (expressed as Hazard ratio (HR) with 95% CI						• Either ABI < 0.9 or > 1.3 was not linked to a higher mortality rate Multivariate analysis shows TcPO2 < 25 mmHg was an independent predictor for 1-year mortality with a HR of 2.8 (95% CI 1.34–5.91, p = 0.006). Also, when analysing TcPO2 as a continuous variable, a significant association between increased survival with each mmHg increasing TcPO2 level was found. TBP was not an independent predictor for mortality.	

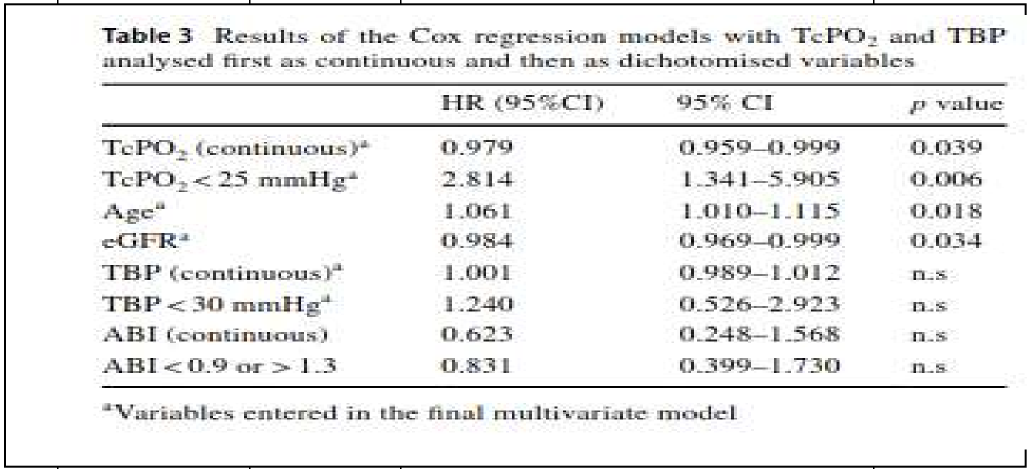

Table 3 Results of the Cox regression models with $TcPO_2$ and TBP analysed first as continuous and then as dichotomised variables

	HR (95%CI)	95% CI	*p* value
$TcPO_2$ (continuous)[a]	0.979	0.959–0.999	0.039
$TcPO_2 < 25$ mmHg[a]	2.814	1.341–5.905	0.006
Age[a]	1.061	1.010–1.115	0.018
eGFR[a]	0.984	0.969–0.999	0.034
TBP (continuous)[a]	1.001	0.989–1.012	n.s
TBP < 30 mmHg[a]	1.240	0.526–2.923	n.s
ABI (continuous)	0.623	0.248–1.568	n.s
ABI < 0.9 or > 1.3	0.831	0.399–1.730	n.s

[a] Variables entered in the final multivariate model

Evidence Table :**Eficacy/Effectiveness/safety/cost-effective**
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<table>
<tr><th>Bibliographic citation</th><th>Study Type/ Methods</th><th>LE</th><th>Number of Patients & Patient Characteristic</th><th>Intervention</th><th>Comparison</th><th>Length of Follow Up (If Applicable)</th><th>Outcome Measures/Effect Size</th><th>General Comments</th></tr>
<tr>
<td>11.Fagher K, Löndahl M. The combined impact of ankle-brachial index and transcutaneous oxygen pressure on mortality in patients with type 2 diabetes and foot ulcers. Acta Diabetol. 2021;58(10):1359-1365. doi: 10.1007/s00592-021-01731-9. Epub 2021 May 8</td>
<td>Study design

Retrospective cohort

Objective

To evaluate the combined impact of a low TcPO2 (<30 mmHg) and a pathological ABI (<0.9 or ≥1.4) on three-year mortality in patients with DFU.

Methods

Type 2 diabetes patients aged <90 years, with at least one DFU who underwent vascular assessment with ABI and TcPO2 from 2013 to 2015 were screened for participation.

Patients were followed at regular basis until ulcer healing or until major amputation.

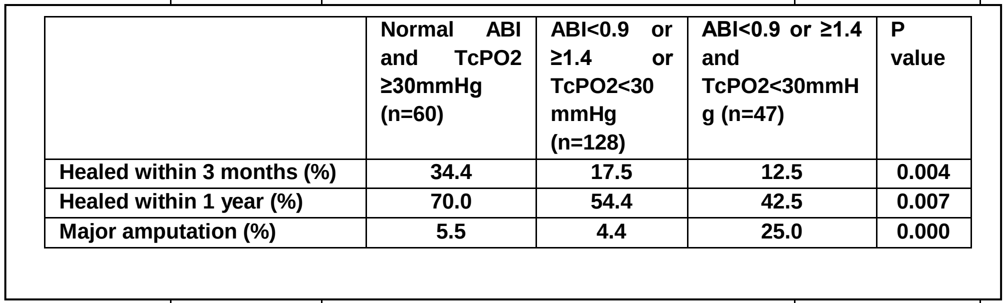
Ulcer healing was defined as complete epithelialization without a major amputation, and this parameter was retrospectively evaluated from patients' medical records after 3 and 12 months. Major amputation was defined as amputation</td>
<td>II-2</td>
<td>235 patients
Median age 76</td>
<td>Normal ABI and TcPO2 ≥30mmHg

ABI<0.9 or ≥1.4 or TcPO2<30mmHg

ABI<0.9 or ≥1.4 and TcPO2<30mmHg</td>
<td></td>
<td></td>
<td>There were no statistical differences regarding age, diabetes duration, HbA1c or hyperlipidaemia between the groups.

The combination of a low TcPO2 level and a pathological ABI was significantly associated with worse ulcer healing rates and higher rates of major amputation during the follow-up period, as demonstrated in Table 1

Table 1: Differences in ulcer healing, and major amputation during follow-up in patients stratified by baseline ABI and TcPO2


<table>
<tr><th></th><th>Normal ABI and TcPO2 ≥30mmHg (n=60)</th><th>ABI<0.9 or ≥1.4 or TcPO2<30 mmHg (n=128)</th><th>ABI<0.9 or ≥1.4 and TcPO2<30mmHg (n=47)</th><th>P value</th></tr>
<tr><td>Healed within 3 months (%)</td><td>34.4</td><td>17.5</td><td>12.5</td><td>0.004</td></tr>
<tr><td>Healed within 1 year (%)</td><td>70.0</td><td>54.4</td><td>42.5</td><td>0.007</td></tr>
<tr><td>Major amputation (%)</td><td>5.5</td><td>4.4</td><td>25.0</td><td>0.000</td></tr>
</table>

Relative risk of having an unhealed ulcer after one year was 1.9 (95% CI 1.3–2.9) and the risk of having a major amputation was 4.6 (95% CI 1.8–13.2) among individuals with both pathological ABI and a low TcPO2 compared to those with normal values.

During the three years of follow-up, 43% participants died.

There was no difference in mortality rate between the groups of individuals with a low</td>
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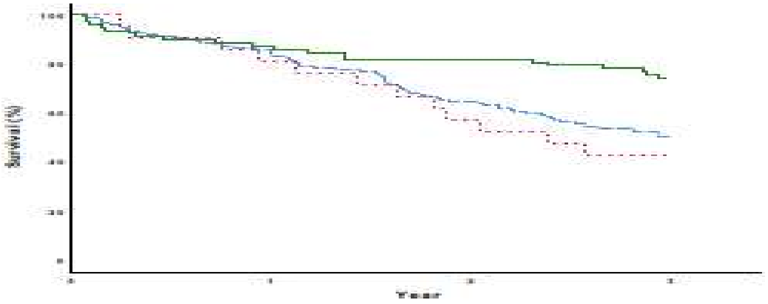
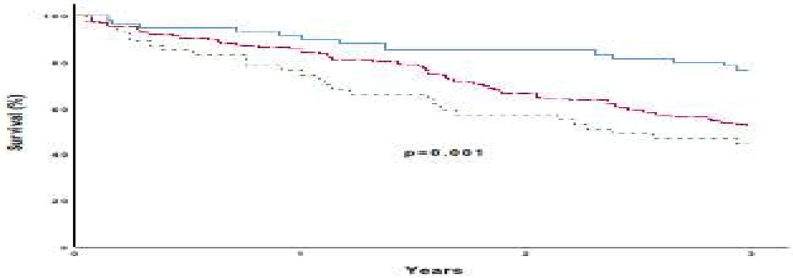
	level above the ankle and data were collected from surgical records. Survival status after three years was assessed from the national death registry in Sweden. A threshold of <0.9 or ≥1.4 was used to define pathologically low or high ABI A cut-point of TcPO2 <30 mmHg was used in the analyses Patients were stratified into three groups; group 1: both pathological ABI/low TcPO2, group 2: pathological ABI or low TcPO2 and group 3: normal ABI /TcPO2. Comparisons between groups were performed with Kruskal–Wallis one-way ANOVA test or with Chi 2 tests. Kaplan–Meier methodology with Log-rank test was used to evaluate mortality between groups. Cox proportional hazard models were used to adjust for plausible confounders to assess hazard ratios (HR) with 95% confidence intervals (CIs).						ABI <0.9 compared to those with abnormally high ABI ⩾1.4 (p = 0.569). Both high and low ABI were significantly associated with increased three-year mortality compared to normal ABI (p = 0.002). Figure 1  **Fig. 1** Kaplan–Meier survival curves analyzed with Log-rank test, for the primary endpoint of mortality during the three year of follow-up, within the different groups of ABI. Green solid line: Individuals with normal ABI. Blue dashed line: Individuals with ABI<0.9. Red dotted line: Individuals with ABI ≥ 1.4. $p = 0.002$ comparing normal ABI with either ABI<0.9 or ABI≥1.4. $p = 0.569$ comparing ABI<0.9 with ABI ≥ 1.4. The highest mortality rate was seen in the group of the individuals with a combination of either a high or low ABI together with a low TcPO2, as demonstrated in Fig. 2.  **Fig. 2** Kaplan–Meier survival curves with Log-rank test, for the primary endpoint of mortality during the three year of follow-up when combining ABI and $TcPO_2$. Blue solid line: Individuals with normal ABI and $TcPO_2 \geq 30$ mmHg. Red dashed line: Individuals with either pathological ABI (<0.9 or≥1.4) or low $TcPO_2 < 30$ mmHg. Green dotted line: Individuals with both pathologically ABI and low $TcPO_2$	

							The result of the final multivariate Cox model is given in Table 3. In this analysis, the combination of a pathological ABI and a low TcPO2 was the strongest independent predictor of mortality, with a HR of 2.19 (1.11–4.33). If only one parameter was pathological (ABI TcPO2) no significant association was found after adjustment [HR was 1.78(0.97–3.26)]. Ulcer healing after three months, the presence of CVD, diabetes duration and age were also independently associated with mortality.	

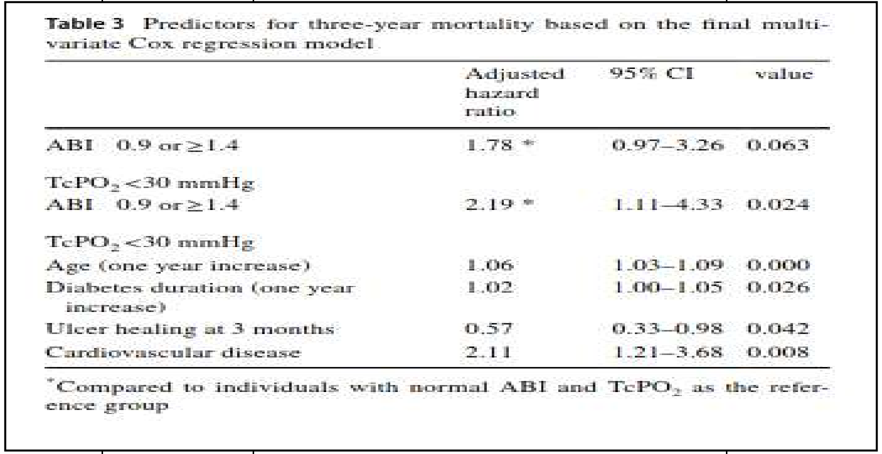


Table 3 Predictors for three-year mortality based on the final multivariate Cox regression model

	Adjusted hazard ratio	95% CI	value
ABI 0.9 or ≥1.4	1.78 *	0.97–3.26	0.063
$TcPO_2 < 30$ mmHg			
ABI 0.9 or ≥1.4	2.19 *	1.11–4.33	0.024
$TcPO_2 < 30$ mmHg			
Age (one year increase)	1.06	1.03–1.09	0.000
Diabetes duration (one year increase)	1.02	1.00–1.05	0.026
Ulcer healing at 3 months	0.57	0.33–0.98	0.042
Cardiovascular disease	2.11	1.21–3.68	0.008

*Compared to individuals with normal ABI and $TcPO_2$ as the reference group

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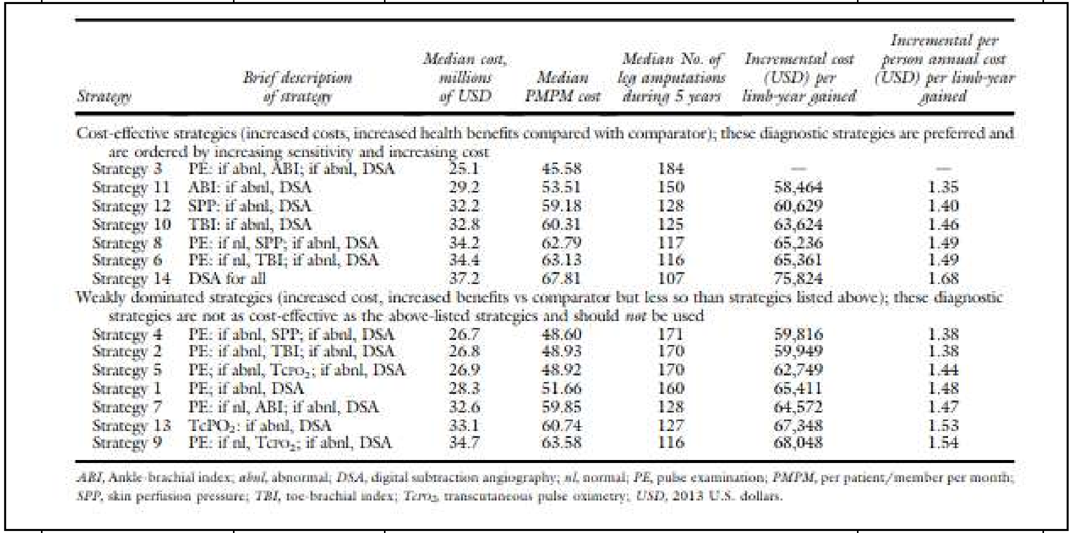
Barshes NR, Flores E, Belkin M. The accuracy and cost-effectiveness of strategies used to identify peripheral artery disease among patients with diabetic foot ulcers. J Vasc Surg. 2016 ;64(6):1682-1690.e3. doi: 10.1016/j.jvs.2016.04.056.	**Study design** Cost effectiveness analysis **Objective** To estimate the overall diagnostic accuracy for various strategies that are used to identify PAD in patients with diabetic foot ulcers (DFUs) **Methods** A Markov cohort model with probabilistic and deterministic sensitivity analyses with 5-year time horizon baseline (time=0), patients no current DFUs and no prior history of DFU Diagnostic accuracy of various methods used to diagnose lower extremity PAD obtained from identified reviews. Digital subtraction angiography (DSA) was considered as gold standard. Strategy 14 modelled the strategy of DSA for all patients who developed DFUs. For purposes of		1053 DFUs were developed during 5 years period	13 strategies used various conditional combinations of tests (Pulse exam, ABI, SPP,TcPO2, TBI)	Strategy 0 (no diagnostic testing)		1053 DFUs were developed during 5 years period Overall 5-year survival was 68.7%, with stratified 5-year survival rates of 72.5%, 61.8%, and 54.3% for the low-, medium-, and high-risk groups. Table 1:A comparison of incremental costs and health benefits associated with various strategies to identify and to treat peripheral artery disease (PAD) among a hypothetical cohort of patients with diabetic foot ulcers (DFUs)	



Strategy	*Brief description of strategy*	*Median cost, millions of USD*	*Median PMPM cost*	*Median No. of leg amputations during 5 years*	*Incremental cost (USD) per limb-year gained*	*Incremental per person annual cost (USD) per limb-year gained*
Cost-effective strategies (increased costs, increased health benefits compared with comparator); these diagnostic strategies are preferred and are ordered by increasing sensitivity and increasing cost						
Strategy 3	PE: if abnl, ABI; if abnl, DSA	25.1	45.58	184	—	—
Strategy 11	ABI: if abnl, DSA	29.2	53.51	150	58,464	1.35
Strategy 12	SPP: if abnl, DSA	32.2	59.18	128	60,629	1.40
Strategy 10	TBI: if abnl, DSA	32.8	60.31	125	63,624	1.46
Strategy 8	PE: if nl, SPP; if abnl, DSA	34.2	62.79	117	65,236	1.49
Strategy 6	PE: if nl, TBI; if abnl, DSA	34.4	63.13	116	65,361	1.49
Strategy 14	DSA for all	37.2	67.81	107	75,824	1.68
Weakly dominated strategies (increased cost, increased benefits vs comparator but less so than strategies listed above); these diagnostic strategies are not as cost-effective as the above-listed strategies and should *not* be used						
Strategy 4	PE: if abnl, SPP; if abnl, DSA	26.7	48.60	171	59,816	1.38
Strategy 2	PE: if abnl, TBI; if abnl, DSA	26.8	48.93	170	59,949	1.38
Strategy 5	PE; if abnl, Tcro$_2$; if abnl, DSA	26.9	48.92	170	62,749	1.44
Strategy 1	PE; if abnl, DSA	28.3	51.66	160	65,411	1.48
Strategy 7	PE: if nl, ABI; if abnl, DSA	32.6	59.85	128	64,572	1.47
Strategy 13	TcPO$_2$: if abnl, DSA	33.1	60.74	127	67,348	1.53
Strategy 9	PE: if nl, Tcro$_2$; if abnl, DSA	34.7	63.58	116	68,048	1.54

ABI, Ankle-brachial index; *abnl*, abnormal; *DSA*, digital subtraction angiography; *nl*, normal; *PE*, pulse examination; *PMPM*, per patient/member per month; *SPP*, skin perfusion pressure; *TBI*, toe-brachial index; *Tcro$_2$*, transcutaneous pulse oximetry; *USD*, 2013 U.S. dollars.

Bibliographic citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	comparison, “strategy 0” consisted of no diagnostic testing to identify lower extremity PAD (and therefore no subsequent treatment for lower extremity PAD). The costs associated with the management of DFUs in the low- and moderate-risk strata were obtained from previously published estimates. The standard discounting rate of 3.5% was applied to all cost values, presented in USD							

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