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The accuracy and cost-effectiveness of strategies used to identify peripheral artery disease among patients with diabetic foot ulcers

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Background: **Patients with diabetic foot ulcers (DFUs) should be evaluated for peripheral artery disease (PAD). We sought to estimate the overall diagnostic accuracy for various strategies that are used to identify PAD in this population.**

Methods: **A Markov model with probabilistic and deterministic sensitivity analyses was used to simulate the clinical events in a population of 10,000 patients with diabetes. One of 14 different diagnostic strategies was applied to those who developed DFUs. Baseline data on diagnostic accuracy of individual noninvasive tests were based on a meta-analysis of previously reported studies. The overall sensitivity and cost-effectiveness of the 14 strategies were then compared.**

Results: **The overall sensitivity of various combinations of diagnostic testing strategies ranged from 32.6% to 92.6%. Cost-effective strategies included ankle-brachial indices for all patients; skin perfusion pressures (SPPs) or toe-brachial indices (TBIs) for all patients; and SPPs or TBIs to corroborate normal pulse examination findings, a strategy that lowered leg amputation rates by 36%. Strategies that used noninvasive vascular testing to investigate only abnormal pulse examination results had low overall diagnostic sensitivity and were weakly dominated in cost-effectiveness evaluations. Population prevalence of PAD did not alter strategy ordering by diagnostic accuracy or cost-effectiveness.**

Conclusions: **TBIs or SPPs used uniformly or to corroborate a normal pulse examination finding are among the most sensitive and cost-effective strategies to improve the identification of PAD among patients presenting with DFUs. These strategies may significantly reduce leg amputation rates with only modest increases in cost. (J Vasc Surg 2016;64:1682-90.)**

The rising incidence of diabetes mellitus and the increased proportion of elderly populations in the United States,[1] United Kingdom,[2] and other western countries may bring an increased burden of associated complications, including peripheral artery disease (PAD) and diabetic foot ulcers (DFUs). Nearly 50% of patients presenting with DFUs have PAD.[3] Large DFUs accompanied by untreated PAD are associated with leg amputation rates exceeding 30% at 1 year,[4] so the identification and management of PAD have been stressed as important in minimizing limb loss risk.[5] Despite this, PAD diagnosis and treatment are delayed or nonexistent in as many as 30% of patients with DFUs presenting to tertiary care centers.[6,7]

Such delays may be related to challenges inherent to diagnosing PAD among patients with diabetes. The palpation of pedal pulses is known to have mediocre diagnostic accuracy in identifying PAD, even when it is performed by vascular surgeons.[8,9] Noninvasive testing with ankle-brachial indices (ABIs) may produce false-negative rates as high as 35% because of calcification that limits the compressibility of the medial layer of the artery.[10] Diagnostic angiography provides anatomic information but is more costly, does not provide physiologic information, exposes the patient to contrast material and radiation, and may not always be readily available.[7] No particular strategy for navigating these diagnostic challenges has emerged, and relevant multidisciplinary guidelines still generally recommend ABIs despite the known limitations.[11,12]

With these challenges in mind, we designed the current study (1) to evaluate the overall diagnostic accuracy of various strategies (including both single diagnostic tests and combinatorial testing) used to identify PAD among patients with DFUs, with the primary objective of

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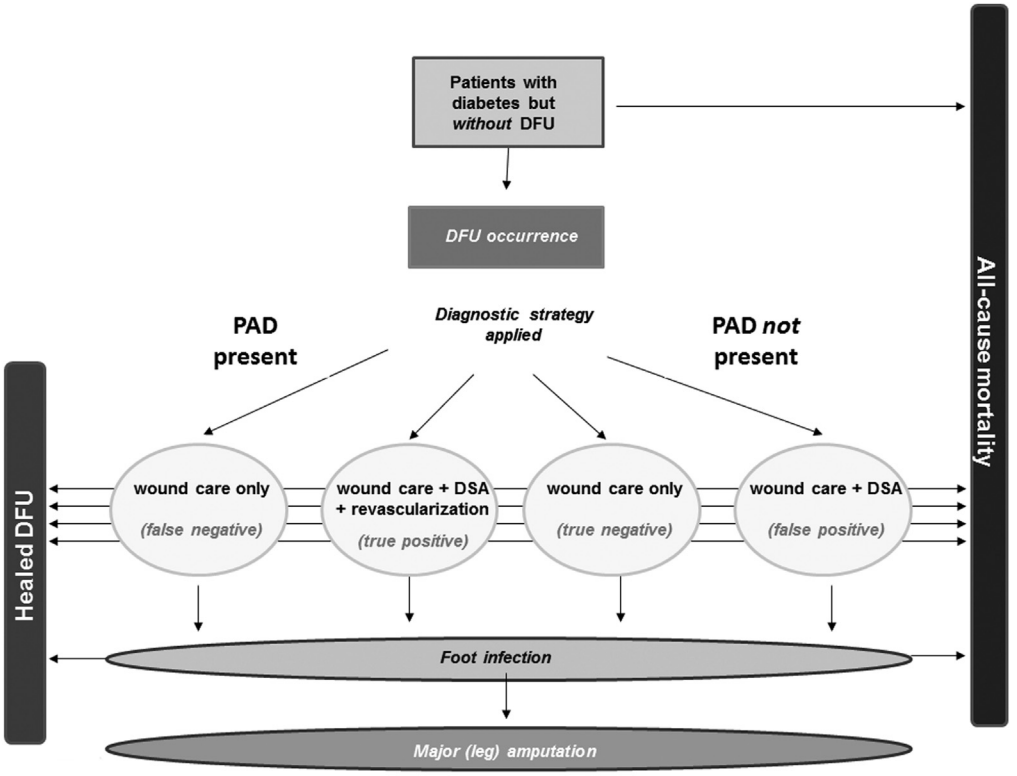

Fig 1. Schematic diagram demonstrating the clinical states featured in the model. *DFU,* Diabetic foot ulcer; *DSA,* digital subtraction angiography; *PAD,* peripheral artery disease.

identifying strategies that would be preferred in various contexts, and (2) to estimate incremental cost-effectiveness ratios of these various options. Here we report the results of these evaluations.

METHODS

Markov model properties. A Markov cohort model with probabilistic and deterministic sensitivity analyses was created to simulate the clinical events occurring in a hypothetical population of 100,000 individuals with diabetes mellitus. At baseline (time = 0), this population had no current DFUs and no prior history of DFU. Each scenario evaluated consisted of 1000 simulations during the course of 5 years. At any given time, patients were in one of six clinical states: (1) intact foot/no DFU; (2) DFU without infection; (3) DFU with infection; (4) limb loss, ie, major (above-ankle) amputation; (5) healed DFU; and (6) death from any cause (Fig 1). Any transitions between clinical states occurred at the beginning of monthly cycles during the 5-year period. Probabilistic sensitivity analyses were achieved through the use of beta and triangular distributions for all state transition probabilities. All modeling and analysis were performed using Microsoft Excel 2010 with additional programming in Visual Basic for Application (Microsoft Corporation, Redmond, Wash). Neither informed consent nor Institutional Review Board approval was obtained as no individual patient information was used for this study.

The probability of moving between clinical states during cycles was modeled on a three-level array of transition probabilities derived from a validation of the International Working Group on the Diabetic Foot risk categorization scheme.[13] Specifically, transition probabilities of the low-risk stratum were based predominantly on the reported clinical outcomes of patients with diabetes but without peripheral neuropathy or PAD. The transition probabilities of the moderate-risk stratum were based on those with peripheral neuropathy but no PAD, whereas those of the high-risk stratum were based on outcomes of patients with PAD. An annual foot ulcer incidence rate of 1.3% (25%-75%; interquartile range, 1.0%-1.6%) was used for low-risk patients, 3.7% (range, 3.0%-4.7%) for moderate-risk patients, and 13.8% (range, 12.7%-15.0%) for high-risk patients (Table I) based on data from a large prospective observational study.[13] In the base case scenario, 72% of the hypothetical population was assumed to be low risk, 17% moderate risk, and 11% high risk.[14] Estimates of the probabilities of clinical events after the development of an initial DFU in patients with and without PAD were obtained from previously published literature reviews.[15,16]

Estimates of the diagnostic accuracy of individual tests. An extensive review identified previously published manuscripts that assessed the diagnostic accuracy of various

Table I. Point estimates for important clinical events (yearly incidence) and cost parameters (in 2013 U.S. dollars) included in the model

Variable	*Normal-low risk*	*Moderate risk*	*High risk*
Clinical events, %			
DFU incidence	0.1	0.3	1.2
Foot infection (with DFU present)	11.4	34.8	63.2
Proportion of DFUs healing			
Without revascularization	93.1	85.8	41.0
With revascularization	N/A	N/A	75.0
Leg amputation with unhealed DFU			
Without revascularization	2.4	5.8	13.5
With revascularization	N/A	N/A	38.0
Leg amputation with healed DFU	0.3	1.5	3.5
DFU recurrence	1.0	2.0	3.1
Mortality	5.8	9.2	13.5
Costs			
DFU care	$1004/mo	$1004/mo	$1421/mo
Noninvasive vascular evaluation (including ABI, TBI, Tc_{PO_2}, or SPP)	$175	$175	$175
Diagnostic angiography	$5000	$5000	$5000
Moderate/severe foot infection	$12,000	$12,000	$12,000
Arterial revascularization	N/A	N/A	$35,572
Major (leg) amputation surgery	$34,201	$34,201	$34,201
Postamputation care	$1290/mo	$1290/mo	$1290/mo

ABI, Ankle-brachial index; *DFU,* diabetic foot ulcer; *N/A,* not applicable; *SPP,* skin perfusion pressure; *TBI,* toe-brachial index; *Tc_{PO_2},* transcutaneous pulse oximetry.

methods used to diagnose lower extremity PAD. This review focused on the following diagnostic tests: (1) pulse examination (ie, feeling for the presence of palpable pulses on physical examination); (2) ABIs or absolute ankle pressures; (3) toe-brachial indices (TBIs) or toe (digit) systolic pressures; (4) transcutaneous oximetry (Tc_{PO_2}); and (5) skin perfusion pressures (SPPs). Primary studies in which any of these diagnostic tests were compared with diagnostic angiography or complete wound healing were preferred, although some studies that used other comparators were included (Supplementary Tables I-V, online only). Studies that failed to report results with detail sufficient for the calculation of diagnostic accuracy were excluded. The frequency of true negatives, true positives, false negatives, and false positives from each study was tallied in a meta-analysis to obtain overall point estimates and beta distributions for sensitivity, specificity, positive predictive value, and negative predictive value of each of the various diagnostic tests. For the purposes of this study, digital subtraction angiography (DSA) was considered the "gold standard" diagnostic test for PAD (ie, 100% sensitivity and specificity).

Evaluation of the overall accuracy of diagnostic testing strategies. The Markov model was used to estimate the overall diagnostic accuracy of various diagnostic strategies that may be used to identify lower extremity PAD among patients with diabetes mellitus and foot ulcers. Specifically, hypothetical patients who developed foot ulcers were subjected to 1 of 14 diagnostic testing strategies (Table II). Strategy 14 modeled the strategy of DSA for all patients who developed DFUs. The remaining 13 strategies used various conditional combinations of tests. Strategy 1 consisted of an initial pulse examination, followed by DSA if the finding on pulse examination was abnormal. Strategies 2 through 5 consisted of an initial physical examination, followed by a noninvasive physiologic test (ABI, TBI, Tc_{PO_2}, or SPP) if the finding was abnormal. Abnormal noninvasive testing results were further interrogated with DSA. Strategies 6 to 9 consisted of an initial pulse examination. Normal pulse examination results were corroborated with noninvasive testing (with subsequent DSA if abnormal), and abnormal pulse examination results were interrogated directly with DSA. Strategies 10 to 13 did not include an initial pulse examination. Instead, all patients underwent an initial noninvasive test; abnormal results were interrogated with DSA (Table II). For purposes of comparison, "strategy 0" consisted of no diagnostic testing to identify lower extremity PAD (and therefore no subsequent treatment for lower extremity PAD).

Hypothetical patients subjected to these various diagnostic testing strategies were then assigned to the appropriate categories of true negative, true positive, false positive, and false negative on the basis of the aforementioned composite estimates of diagnostic accuracy. True negatives (ie, moderate-risk/neuropathic patients without PAD) and true positives (ie, high-risk patients/PAD patients) were assigned treatment outcomes based on those previously described for standard-of-care treatment of populations of these patient (see reviews[15,16]). False positives (moderate-risk patients subjected to DSA) were assigned the additional costs associated with DSA and standard-of-care treatment outcomes. False negatives (high-risk patients with PAD) were assigned the treatment outcomes associated with the natural history of untreated PAD associated with foot ulcers (see review[16]).

Table II. Summary of diagnostic testing strategies compared

Strategy	*Initial evaluation (all DFU patients)*	*Second-order evaluation*		*Third-order evaluation*	
1	Pulse exam	*nl:*	—		—
		abnl:	DSA		—
2	Pulse exam	*nl:*	—		
		abnl:	TBI	*nl:*	—
				abnl:	DSA
3	Pulse exam	*nl:*	—		
		abnl:	ABI	*nl:*	—
				abnl:	DSA
4	Pulse exam	*nl:*	—		
		abnl:	SPP	*nl:*	—
				abnl:	DSA
5	Pulse exam	*nl:*	—		
		abnl:	Tc_{PO_2}	*nl:*	—
				abnl:	DSA
6	Pulse exam	*nl:*	TBI	*nl:*	—
				abnl:	DSA
		abnl:	DSA		
7	Pulse exam	*nl:*	ABI	*nl:*	—
				abnl:	DSA
		abnl:	DSA		
8	Pulse exam	*nl:*	SPP	*nl:*	—
				abnl:	DSA
		abnl:	DSA		
9	Pulse exam	*nl:*	Tc_{PO_2}	*nl:*	—
				abnl:	DSA
		abnl:	DSA		
10	TBI	*nl:*	—		
		abnl:	DSA		
11	ABI	*nl:*	—		
		abnl:	DSA		
12	SPP	*nl:*	—		
		abnl:	DSA		
13	Tc_{PO_2}	*nl:*	—		
		abnl:	DSA		
14	DSA				

ABI, Ankle-brachial index; *abnl*, abnormal; *DFU*, diabetic foot ulcer; *DSA*, digital subtraction angiography; *nl*, normal; *SPP*, skin perfusion pressure; *TBI*, toe-brachial index; *Tc_{PO_2}*, transcutaneous pulse oximetry.

Costs and cost-effectiveness analysis. The costs associated with the management of DFUs in the low- and moderate-risk strata were obtained from previously published estimates. The costs associated with management of the high-risk stratum were obtained from a previous study focusing on this population of patients.[17] Total (direct and indirect) inpatient costs associated with revascularization, wound care, and major and minor amputations were estimated from patients with PAD and foot ulcers undergoing these procedures at a single institution.[17] Outpatient costs, including those associated with outpatient nursing care, wound care, and any needed limb prostheses, were obtained from a thorough literature review.[16] All cost values are reported in 2013 U.S. dollars (USD) and represent a median value unless otherwise noted. The standard discounting rate of 3.5% was applied to all cost values.[18]

Our primary measure for cost-effectiveness was the incremental cost (in 2013 USD) per each additional year of limb preservation (cost per limb-year) gained from a particular diagnostic strategy over its comparator. In addition, incremental costs per patient/member per month (PMPM)[19-21] per additional limb-year gained and per major amputation avoided were calculated. With the 5-year time horizon included in the model, the total costs associated with each diagnostic strategy represented not only diagnostic costs but also "downstream" costs associated with any treatment that would have been initiated on the basis of diagnostic testing. By convention, the lowest cost strategy was used as the comparator.

RESULTS

Cumulative accuracy of diagnostic testing strategies. A total of 31 original studies describing the results of 8086 evaluations using pulse examination or noninvasive vascular testing were identified and included in the meta-analysis. The cumulative results of these studies were then used to obtain point estimates and distributions of overall sensitivity, specificity, positive predictive value, and negative predictive value (Table III) weighted according to study sample size. The overall sensitivity among the eight studies reporting the diagnostic accuracy of pulse examination was 53.3%. ABIs were estimated to have an overall sensitivity of 61.0% among 12 studies. SPP, TBI, and Tc_{PO_2} had overall sensitivity rates ranging from 81.7% to 84.0%. SPP and TBI had comparable overall specificity rates (79.3% and 77.8%, respectively), whereas the overall specificity rate of Tc_{PO_2} was slightly lower (62.8%).

The overall diagnostic accuracy of the various combinatorial diagnostic testing strategies was then evaluated using the probabilistic Markov model (Table IV). Strategies that used noninvasive testing to determine the need for DSA only when the pulse examination findings were abnormal (strategies 2-5) were found to have low-median sensitivity rates (32.6%-44.8%) in the detection of PAD. The use of ABIs for *all* patients with DFUs (strategy 11) had a median sensitivity rate of 60.9%, and the use of ABIs to corroborate *normal* pulse examination findings (strategy 7) had a median sensitivity rate of 81.8%. The three strategies that uniformly used other noninvasive tests for *all* patients with DFUs (strategies 10, 12, and 13) had sensitivity rates ranging from 82.0% to 84.0%. Finally, the three strategies that used these noninvasive tests to confirm *normal* pulse examination findings had the highest median sensitivity rates, ranging from 91.6% for SPP (strategy 8), 92.1% for Tc_{PO_2} (strategy 9), and 92.6% for TBI (strategy 6).

Predicted clinical outcomes. In the base scenario, a median of 1053 DFUs developed during the 5-year period (range, 721-1492). 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. With a PAD prevalence of 9.8% in the general population, the median prevalence was 44.5% (range, 29.7%-61.5%) among those who developed DFUs.

The median number of major amputations occurring during the 5-year time horizon was 220 with strategy 0 (reference strategy of no diagnostic testing; Table V). Among strategies that used noninvasive diagnostic testing,

Table III. Overall sensitivity and specificity of individual tests included among the diagnostic testing strategies

Variable	*Sensitivity*	*Specificity*	*PPV*	*NPV*
Pulse exam	53.3 (52.1-54.6)	82.6 (82.2-83.1)	42.5 (41.4-43.7)	88.0 (87.6-88.4)
ABI	61.0 (59.7-62.1)	89.1 (88.6-89.6)	74.7 (73.7-75.9)	81.2 (80.6-81.8)
SPP	81.7 (79.9-83.6)	79.3 (77.2-81.1)	81.0 (78.9-83.1)	80.1 (78.2-82.4)
Tc_{PO_2}	83.0 (81.8-84.3)	62.8 (61.2-64.4)	66.7 (65.7-68.1)	80.6 (79.1-82.2)
TBI	84.0 (82.8-85.0)	77.8 (76.1-79.5)	86.7 (85.8-87.8)	73.7 (71.9-75.2)

ABI, Ankle-brachial index; *NPV,* negative predictive value; *PPV,* positive predictive value; *SPP,* skin perfusion pressure; *TBI,* toe-brachial index; *Tc_{PO_2},* transcutaneous pulse oximetry.
See Supplementary Tables I-V (online only) for individual studies.

Table IV. Cumulative sensitivity, specificity, positive predictive value, and negative predictive value (*NPV*) of various combinatorial testing strategies, ordered by increasing sensitivity, in the base case scenario (population peripheral artery disease [PAD] prevalence of 9.8%)

Strategy No.	*Brief description*	*Median sensitivity*	*Median specificity*	*Median NPV*
Strategy 3	PE: if abnl, ABI; if abnl, DSA	32.6 (31.6-33.6)	97.4 (97.2-97.6)	69.9 (66.5-73.5)
Strategy 4	PE: if abnl, SPP; if abnl, DSA	43.7 (42.4-45.1)	96.5 (96.0-96.8)	74.0 (70.0-76.6)
Strategy 5	PE; if abnl, Tc_{PO_2}; if abnl, DSA	44.3 (43.0-45.7)	93.5 (93.2-93.9)	73.6 (70.0-76.2)
Strategy 2	PE: if abnl, TBI; if abnl, DSA	44.8 (43.7-46.2)	96.1 (95.8-96.4)	74.3 (70.5-76.9)
Strategy 1	PE: if abnl, DSA	53.3 (52.1-54.6)	82.6 (82.2-83.1)	74.7 (70.8-77.2)
Strategy 11	ABI: if abnl, DSA	60.9 (59.9-62.1)	89.1 (88.6-90.0)	79.1 (75.7-81.2)
Strategy 7	PE: if nl, ABI; if abnl, DSA	81.8 (81.1-82.5)	73.6 (73.0-74.2)	87.0 (84.7-88.6)
Strategy 12	SPP: if abnl, DSA	82.0 (80.0-83.6)	89.1 (88.6-89.6)	89.1 (87.0-90.7)
Strategy 13	$TcPO_2$: if abnl, DSA	83.1 (81.8-84.4)	62.8 (61.3-64.5)	86.1 (83.3-87.6)
Strategy 10	TBI: if abnl, DSA	84.0 (83.0-85.2)	77.8 (76.1-79.4)	88.9 (86.9-90.3)
Strategy 8	PE: if nl, SPP; if abnl, DSA	91.6 (90.7-92.4)	65.7 (63.7-67.2)	92.8 (91.2-93.9)
Strategy 9	PE: if nl, Tc_{PO_2}; if abnl, DSA	92.1 (91.4-92.8)	51.9 (50.6-53.4)	91.7 (89.8-92.6)
Strategy 6	PE: if nl, TBI; if abnl, DSA	92.6 (92.1-93.1)	64.2 (62.8-65.7)	93.4 (92.1-94.3)

ABI, Ankle-brachial index; *abnl,* abnormal; *DSA,* digital subtraction angiography; *nl,* normal; *PE,* pulse examination; *SPP,* skin perfusion pressure; *TBI,* toe-brachial index; *Tc_{PO_2},* transcutaneous pulse oximetry.
Values in parentheses represent the 25%-75% interquartile range of values.

the median number of amputations ranged from 184 with strategy 3 (pulse examination; if abnormal, ABI; if abnormal, DSA) to 116 for strategy 6 (pulse examination; TBI if normal, DSA if abnormal) and strategy 9 (pulse examination; Tc_{PO_2} if normal, DSA if abnormal). Strategy 14 (DSA for all DFU patients) resulted in a median of 107 major amputations. These equated to major amputation annual incidence rates ranging from 536/100,000 population for strategy 0 (no diagnostic testing) to 259 for strategy 14 (DSA for all DFU patients; Table V).

Costs and cost-effectiveness. The median total 5-year cost was 20.5 million USD without any diagnostic testing or treatment for PAD. The total costs for strategies 1 to 13 ranged from 25.1 million USD for strategy 3 (pulse examination; if abnormal, ABI; if abnormal, DSA) to 34.7 million USD for strategy 9 (pulse examination; if normal, Tc_{PO_2}; if abnormal, DSA). When converted to cost per person (member) per month (PMPM), these values were 45.58 USD PMPM for strategy 3, 63.58 USD PMPM for strategy 9, and 67.81 PMPM for strategy 14 (Table V). Strategy 14 (DSA for all DFU patients) resulted in a median 5-year total cost of 37.2 million USD.

Incremental cost-effectiveness ratios were then calculated using the lowest-cost strategy (initial pulse examination; if pulse examination finding is abnormal, ABI; if ABI is abnormal, DSA [strategy 3]) as the comparator. Compared with strategy 3, strategies 6, 8, 10, 11, 12, and 14 (Table V) were all found to be cost-effective. The incremental costs (in USD) per limb-year gained ranged from 58,464 for strategy 11 (ABI for all; if abnormal, DSA) to 75,824 for strategy 14 (DSA for all). When converted to incremental PMPM costs, these values were 1.35 USD PMPM per limb-year gained for strategy 11 and 1.68 USD PMPM per limb-year gained for strategy 14. Seven strategies (strategies 1, 2, 4, 5, 7, 9, and 13) were weakly dominated (ie, lower incremental cost-effectiveness ratios compared with other alternatives; Table V). No strategies were strongly dominated (ie, both more costly and less effective than other alternatives).

Deterministic sensitivity analyses. Two deterministic sensitivity analyses were done. First, the cost of ABIs was reduced to zero to approximate performing this evaluation in the office or at the bedside (rather than in a dedicated noninvasive vascular laboratory with trained personnel). This change reduced the total strategy cost for strategy 11 from 29.2 million USD (53.51 USD PMPM) to 28.9 million USD (53.29 USD PMPM) and the incremental cost-effectiveness ratio from 58,464 USD per limb-year

Table V. 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, $TcPO_2$; 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, $TcPO_2$; 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; *$TcPO_2$,* transcutaneous pulse oximetry; *USD,* 2013 U.S. dollars.

gained (1.35 USD PMPM per limb-year gained) to 55,864 USD per limb-year gained (1.31 USD PMPM per limb-year gained).

Next, the prevalence of PAD in the hypothetical population was varied from the base case prevalence of 9.8% to values ranging from 5% to 40%. The resulting prevalence of PAD among hypothetical patients with DFUs ranged from 28.2% to 80.9% over this range (Supplementary Table VI, online only). Negative predictive values significantly decreased as population PAD prevalence increased from 5% to 40%—an expected result, as higher prevalence rates magnify the number of false-negative results when sensitivity rates are <100%. The ordering of strategies 3, 11, 12, 10, 8, 6, and 14 based on incremental cost-effectiveness ratios remained unchanged, however, as did the weak domination of strategies 4, 2, 5, 1, 13, and 9.

DISCUSSION

The diagnosis of PAD among patients with diabetes mellitus is more than a matter of simply palpating for pedal pulses. Indeed, pedal pulse examination has poor sensitivity and low levels of interobserver agreement.[22] The utility of ABIs in patients with diabetes has been criticized because of the high false-negative rate attributed to tibial artery noncompressibility. Although various guidelines have recommended pulse examination[23] and ABIs,[11,12] clinicians have had few quantitative evaluations to support choosing among various diagnostic strategies for identifying PAD in patients with DFUs.

The focus of this study was on evaluating such diagnostic strategies—not singular diagnostic tests but the combinations of tests available in most clinical practice settings to reliably identify PAD. The primary objective was estimating overall diagnostic accuracy for the various strategies with a particular focus on sensitivity. Additional economic modeling was included to determine if more accurate diagnostic strategies would be within thresholds typically considered cost-effective. To date, only one small (n = 96) single-center trial by de Graaf et al has compared two diagnostic strategies used for the diagnosis of PAD.[24] In comparison to a randomized trial or large observational study, a probabilistic Markov model has several advantages in its ability to incorporate numerous pre-existing estimates of diagnostic accuracy, clinical events, health benefits, and costs in the creation of detailed simulations. Predictions obtained from such simulations would otherwise be available only from rigorously controlled studies or trials enrolling and observing several thousands of patients during a period of several years. Such predictions can at least provide some basis for refining the approach to diagnostic testing for PAD until other studies are performed on this topic.

Results from this analysis suggest that noninvasive tests used to evaluate *absent* pedal pulses (strategies 2-5) have overall sensitivity values ranging from 32.6% to 44.8%, values that are strikingly low for a clinical context in which false negatives (ie, undiagnosed and thereby untreated PAD) can have a significant negative impact on health and function. Indeed, many cases of impaired DFU healing, limb loss, or forms of DFU-related treatment failure occurring in the setting of a "normal" pedal pulse examination or "normal" ABIs have been erroneously attributed to "small-vessel disease" or other misconceptions[25] and are in fact cases in which the diagnosis of macrovascular PAD has been missed.

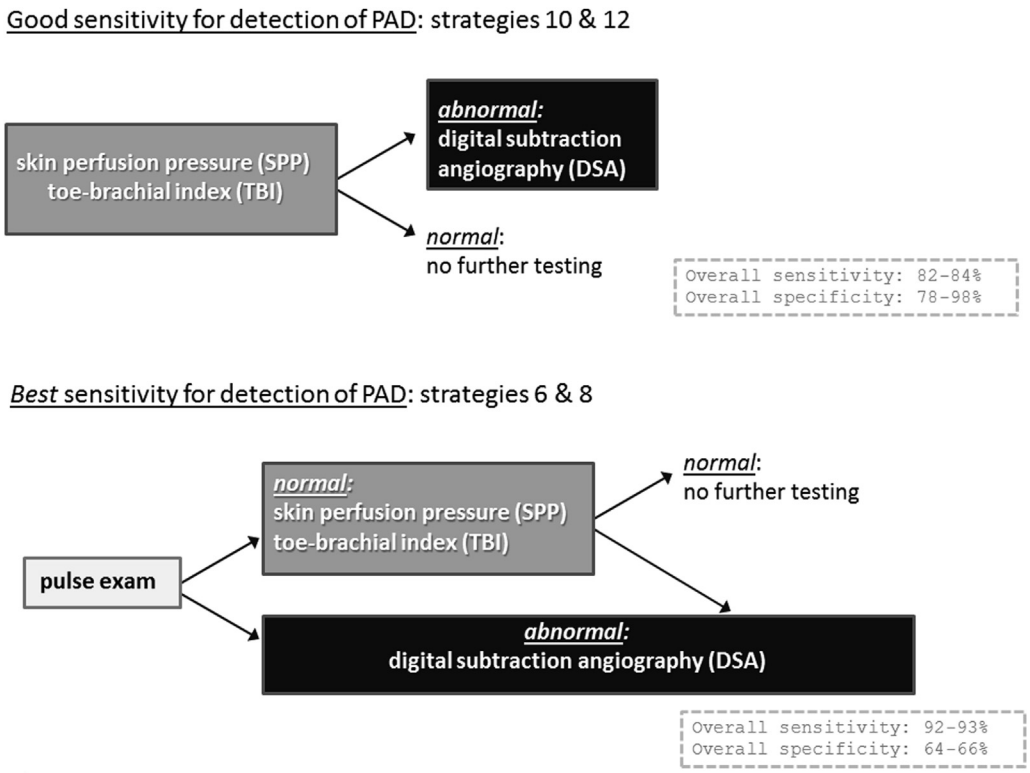

Fig 2. Cost-effective diagnostic strategies with highest sensitivity for the identification of peripheral artery disease (*PAD*) among patients with diabetic foot ulcers (DFUs).

Alternative strategies for using noninvasive testing may improve diagnostic accuracy and decrease limb loss rates at only modest increases in cost. The uniform use of ABIs for all patients who have developed a DFU (strategy 11) would improve overall sensitivity for detecting PAD to 61%. Uniform use of SPPs and TBIs (strategies 12 and 10, respectively) would further increase the overall sensitivity rate to 82.0% to 84.0%. Still higher sensitivity rates (92%-93%) would result from the use of SPPs and TBIs to corroborate a *normal* pulse examination (strategies 8 and 6, respectively; Fig 2). In these latter strategies, patients with an abnormal pulse examination finding (ie, pulses not palpable) appear best served by proceeding directly to angiography without noninvasive testing, as the costs of negative angiography appear to be outweighed by the costs and health effects of a false-negative noninvasive testing result that may occur with noninvasive testing in this situation. Strategies incorporating $TcPO_2$ were weakly dominated (increased benefits but at higher incremental cost-effectiveness ratios compared with other strategies) because of a slightly lower diagnostic accuracy compared with TBIs and SPPs, but use of $TcPO_2$ should still be considered in settings in which these other modalities are not available.

The increased sensitivity in the detection of PAD of these strategies was associated with modest increases in cost. Specifically, the model estimated incremental cost of $58,464 to $65,361 per limb-year gained for the implementation of strategies 6, 8, 10, 11, and 12. Deterministic sensitivity analyses demonstrated that the overwhelming majority of this additional cost is not from the diagnostic testing itself but from treatment indicated subsequent to the identification of PAD. Distributed among the population of patients with diabetes, the additional costs of the strategies 6, 8, 10, 11, and 12 translate to an additional 95 to 210 USD per person per year, 1.35 to 1.49 USD per person per year for every additional limb-year gained, or 2.86 to 3.10 USD per person per year for every leg amputation avoided—cost estimates that should be acceptable to payers in all but the most resource-limited health care settings.

This study does have limitations. First, the analysis is based on published studies that examined the diagnostic accuracy of noninvasive vascular testing. The quality of this literature is mediocre, as most studies included limited numbers of patients, and varying thresholds were used to define PAD. Some but not all studies were specific to patients with diabetes or patients with foot wounds. The use of computed tomography angiography and magnetic resonance angiography was not considered because these tests are more expensive and less is known about their diagnostic accuracy, especially in the popliteal and tibial segments often affected by PAD in the setting of diabetes mellitus. The high cost and (in the case of computed tomography angiography) high doses of iodinated contrast

material and radiation make these modalities less appealing in the setting of DFUs. There are some reports that describe improved sensitivity in identifying PAD with nonstandard variations in diagnostic testing, for example, the addition of pulse oximetry with ABIs[26] and the calculation of a "low ABI."[27] These methods are interesting and may be relevant to cost-effective or resource-limited settings, but there is not yet sufficient literature to make meaningful comparisons to the well-described tests included here. Finally, PAD is often approached as a binary variable in both research endeavors and clinical practice. In reality, various levels of PAD severity may or may not require revascularization to achieve DFU resolution. This observation is reflected in the recent Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) threatened limb classification system[28] but not in most reports of the diagnostic accuracy of individual noninvasive tests.

CONCLUSIONS

Results from this study suggest that several strategies may improve accuracy and cost-effectiveness in the identification of PAD among patients presenting with DFUs. First, standard noninvasive testing should be performed to corroborate normal pulse examination findings, as pulse examination alone should not be considered sufficiently accurate for ruling out PAD in patients with DFUs. Using noninvasive testing to verify normal pulse examination findings (as in strategies 6 and 8) or as an initial test (as in strategies 10 and 12) would successfully identify more patients than using noninvasive testing to determine the need for angiography in patients with absent pedal pulses (ie, strategies 2-5). SPP or TBI should be used in preference to ABI and $Tcpo_2$ when possible. It may be cost-effective to perform DSA on the basis of abnormal pulse examination findings (ie, pedal pulse diminished or absent).

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Conception and design: NB, EF
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Supplementary Table I (online only). Summary of studies examining pedal pulses

Study	*True positive*	*False negative*	*False positive*	*True negative*	*Comparison*
Stoffers[1]	9	36	41	410	Pulse examination vs ABI <0.9 for subset with diabetes mellitus
Boyko[2]	30	16	121	438	"Absent or diminished" pulses vs ABI ≤0.5
Criqui[3]	67	27	46	484	For PT pulse vs ABI ≤0.8
	91	91	119	322	For DP pulse vs ABI ≤0.8
Hiatt[4]	28	102	151	666	Combined findings for either diminished or absent pedal pulses vs various ABI thresholds (including ABI<0.94 at rest); among patients with diabetes
Tan[5]	45	34	25	150	For pulse examination vs ABI ≤0.94
Faglia[6]	79	24	—	—	For the n = 103 who were found to have PAD (stenosis >50% on DSA); not enough information on those without significant stenosis (n = 1)
Williams[7]	39	9	21	20	ABI <0.9 vs color duplex imaging

ABI, Ankle-brachial index; *DP,* dorsalis pedis; *DSA,* digital subtraction angiography; *PAD,* peripheral artery disease; *PT,* posterior tibial.

Supplementary Table II (online only). Summary of studies examining ankle pressures or ankle-brachial indices (*ABIs*)

Study	*True positive*	*False negative*	*False positive*	*True negative*	*Comparison*
Ouriel[8]	43	13	38	234	Ankle pressure <60 mm Hg vs "nonviable" limb
Guo[9]	16	5	28	249	ABI <0.9 vs DSA stenosis >50%
Schroder[10]	77	36	1	102	ABI <0.9 vs color duplex ultrasound ± DSA
Niazi[11]	115	51	7	35	ABI ≤0.9 vs DSA
Parameswaran[12]	22	13	2	77	ABI <0.9 vs monophasic waveform on duplex ultrasound
Williams[7]	29	19	10	31	ABI <0.9 vs color duplex imaging
Okamoto[13]	14	32	0	26	ABI <0.9 vs computed tomography (stenosis >75% above knee or occlusion below knee)
Premalatha[14]	48	20	3	23	ABI <0.9 vs color duplex imaging
Lijmer[15]	63	17	1	13	ABI <0.91 vs DSA (stenosis >50%)
Yamada[16]	38	16	5	14	Ankle pressure <80 mm Hg vs complete wound healing
Wikstöm[17]	19	93	4	417	ABI <0.90 vs magnetic resonance angiography
Carter[20]	25	11	63	84	ABI <0.5 vs complete wound healing

DSA, Digital subtraction angiography.

Supplementary Table III (online only). Summary of studies examining toe-brachial indices (*TBIs*) or toe pressures

Study	*True positive*	*False negative*	*False positive*	*True negative*	*Comparison*
Park[18]	13	0	0	17	TBI <0.6 vs angiograph
Weinberg[19]	92	8	—	—	TBI <0.7 vs angiography
Carter[20]	121	14	—	—	TBI <0.62 vs angiography
Yamada[16]	43	5	6	10	Toe pressure <30 mm Hg vs complete wound healing
Okamoto[13]	21	25	0	26	TBI <0.6 vs computed tomography (stenosis >75% above knee or occlusion below knee)
Williams[7]	47	1	15	26	TBI <0.75 vs angiography
Apelqvist[21]	74	25	43	139	Toe pressure <45 mm Hg vs complete wound healing
Bone[22]	8	2	0	6	Toe pressure <45 mm Hg vs complete wound healing

Supplementary Table IV (online only). Summary of studies examining transcutaneous pulse oximetry (*Tc_{PO_2}*)

Study	*True positive*	*False negative*	*False positive*	*True negative*	*Comparison*
Lo[23]	5	8	30	57	Tc_{PO_2} <30 mm Hg vs complete wound healing
Okamoto[13]	28	18	8	18	Tc_{PO_2} <50 mm Hg vs computed tomography (stenosis >75% above knee or occlusion below knee)
Faglia[6]	95	8	–	–	Tc_{PO_2} <50 mm Hg vs angiography (stenosis >50%)
Yamada[16]	59	9	10	15	Tc_{PO_2} <30 mm Hg vs complete wound healing
Ruangsetakit[24]	26	0	9	15	Tc_{PO_2} <40 mm Hg vs complete wound healing
Andrews[25]	74	17	91	125	Tc_{PO_2} <40 mm Hg vs complete wound healing
Yang[26]	22	3	6	30	$Tp_{O_2}2$ <25 mm Hg vs complete wound healing

Supplementary Table V (online only). Summary of studies examining skin perfusion pressures (*SPPs*)

Study	*True positive*	*False negative*	*False positive*	*True negative*	*Comparison*
Castronuovo[27]	12	2	4	11	SPP <30 mm Hg vs complete wound healing
Lo[23]	5	8	9	78	SPP <30 mm Hg vs complete wound healing
Yamada[16]	61	8	7	18	SPP >40 mm Hg vs complete wound healing
Okamoto[13]	39	7	9	20	SPP <50 mm Hg vs computed tomography (stenosis >75% above knee or occlusion below knee)
Urabe[28]	35	9	7	11	SPP <40 mm Hg vs complete wound healing

Supplementary Table VI (online only). Negative predictive values for diagnostic strategies based on varying levels of incidence of peripheral artery disease (*PAD*)

Variable		*5%*	*10%*	*15%*	*20%*	*30%*	*40%*
Strategy 3	PE: if abnl, ABI; if abnl, DSA	82.8	70.0	59.7	51.5	39.6	30.4
Strategy 5	PE; if abnl, Tc_{PO_2}; if abnl, DSA	84.8	73.0	63.1	55.1	43.0	33.6
Strategy 4	PE: if abnl, SPP; if abnl, DSA	85.0	73.5	63.5	55.4	43.4	34.1
Strategy 2	PE: if abnl, TBI; if abnl, DSA	85.2	73.7	64.0	56.0	43.9	34.3
Strategy 1	PE: if abnl, DSA	85.4	74.1	64.4	56.4	44.3	34.8
Strategy 11	ABI: if abnl, DSA	88.3	78.5	69.9	62.5	50.5	40.8
Strategy 13	Tc_{PO_2}: if abnl, DSA	92.6	85.7	79.2	72.9	62.3	53.2
Strategy 7	PE: if nl, ABI; if abnl, DSA	93.1	86.7	80.5	74.6	64.6	55.1
Strategy 10	TBI: if abnl, DSA	94.1	88.8	83.3	77.8	68.4	59.4
Strategy 12	SPP: if abnl, DSA	94.2	88.8	83.3	77.9	68.6	59.8
Strategy 9	PE: if nl, Tc_{PO_2}; if abnl, DSA	95.6	91.5	87.0	82.8	74.7	66.7
Strategy 8	PE: if nl, SPP; if abnl, DSA	96.2	92.7	88.7	84.7	77.7	70.3
Strategy 6	PE: if nl, TBI; if abnl, DSA	96.6	93.3	89.8	86.2	79.4	72.2
PAD prevalence among DFU patients							
Median		28.2	44.5	55.8	63.7	74.1	80.9
Minimum		17.4	29.7	40.2	50.0	60.9	70.7
Maximum		40.7	61.5	70.6	76.3	85.8	89.0

ABI, Ankle-brachial index; *abnl,* abnormal; *DFU,* diabetic foot ulcer; *DSA,* digital subtraction angiography; *nl,* normal; *PE,* pulse examination; *SPP,* skin perfusion pressure; *TBI,* toe-brachial index; *Tc_{PO_2},* transcutaneous pulse oximetry.

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