# A Prognostic Risk Index for Long-term Mortality in Patients With Peripheral Arterial Disease

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**Background:** Prognostic information in peripheral arterial disease (PAD) may provide the basis for optimal management strategies at an early stage. This study aimed to develop a prognostic risk index for long-term mortality in patients with PAD.

**Methods:** In a single-center observational cohort study, 2642 patients with an ankle-brachial index of 0.90 or lower were randomly divided into derivation (n=1332) and validation (n=1310) cohorts. Cox regression analysis with stepwise backward elimination identified predictors of 1-year, 5-year, and 10-year mortality in the derivation cohort. Weighted points were assigned to each predictor. Index discrimination was determined in both the derivation and validation cohorts.

**Results:** During 10 years of follow-up, 42.2% and 40.4% of patients died in the derivation and validation cohorts, respectively. The risk index for 10-year mortality (+ points) included renal dysfunction (+12), heart failure (+7), ST-segment changes (+5), age greater than 65 years (+5), hypercholesterolemia (+5), ankle-brachial index lower than 0.60 (+4), Q-waves (+4), diabetes (+3), cerebrovascular disease (+3), and pulmonary disease (+3). Statins (–6), aspirin (–4), and β-blockers (–4) were associated with reduced 10-year mortality. Patients were stratified into low (<0 points), low-intermediate (0-5 points), high-intermediate (6-9 points), and high (>9 points) risk categories, according to risk score. Ten-year mortality rates were 22.1%, 32.2%, 45.8%, and 70.4%, respectively ($P<.001$) and comparable to mortality in the validation cohort. C statistics demonstrated good discrimination in both the derivation (0.72) and validation cohorts (0.73).

**Conclusions:** A prognostic risk index for long-term mortality stratified patients with PAD into different risk categories. This may be useful for risk stratification, patient counseling, and medical decision making.

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LOWER EXTREMITY PERIPHERAL arterial disease (PAD) is a manifestation of systemic atherosclerosis and is associated with increased cardiovascular morbidity and mortality.[1-3] Patients with PAD have a 3-fold increased risk to die from all causes and a 6-fold increased risk to die from cardiovascular disease within a period of 10 years compared with patients without PAD.[1] The prevalence of PAD has been reported to range from 4% in patients 40 years and older to over 20% in patients 70 years and older.[4-9] It has been estimated that approximately 8 to 12 million people in the United States have this disease.[4] However, prevalence values may be even higher since a substantial proportion of the population has undetected PAD.[3,4,7]

An increased awareness of PAD may help to improve identification of patients with underlying PAD. Patients who present with PAD may benefit from antiplatelet therapy, walking exercise, risk factor reduction, and lifestyle modifications.[10,11] Many clinical risk factors have been identified as predictors of adverse events; however, to our knowledge, a prognostic risk index including clinical risk factors, electrocardiographic data, ankle-brachial index (ABI) values, and long-term use of cardiovascular medication has not yet been developed in patients with PAD.

A comprehensive prognostic risk index may provide an overall framework for physicians to identify risk factors and to help make predictions based on these risk factors at an early stage of the disease. After risk factors in the individual patient have been identified, a risk score can be calculated, and the patient can be classified into a particular risk category. Prognostic information may help the clinician in the decision for targeted treatment interventions. The objective of this study was to develop and provide an accurate and easy-to-use prognostic risk index for long-term mortality that could stratify pa-

tients with PAD into different risk groups. This risk index was validated in 2 independent patient samples.

## METHODS

The Erasmus Medical Center in Rotterdam, the Netherlands, serves a population of approximately 3 million people and acts as a tertiary referral center for approximately 30 affiliated hospitals. A total of 2642 consecutive patients with PAD were referred to our Department of Vascular Medicine between January 1983 and August 2005 for the evaluation and management of their disease. Patients with or without diabetes mellitus with ABI values higher than 0.90 were not included in the study. All patients gave informed consent, and the hospital's ethics committee approved the protocol.

### ANKLE-BRACHIAL INDEX

The ABI at rest was measured in each patient by trained technicians, using a Doppler ultrasonic instrument with an 8-MHz vascular probe (Imexdop CT+ Vascular Doppler; Nicolet Vascular, Madison, Wisconsin). The ABI in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the 2 brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used if a discrepancy in systolic blood pressure between the 2 arteries was measured.[11] Of the ABI values obtained in each leg, the lower was used, and PAD was defined as a resting ABI of 0.90 or lower. An ABI lower than 0.60 was considered severe PAD.

### CLINICAL VARIABLES

A detailed cardiovascular history was obtained, including a history of stable angina pectoris, myocardial infarction, coronary revascularization (coronary bypass grafting or percutaneous coronary angioplasty), congestive heart failure, and cerebrovascular event. Patients were also screened for the following clinical risk factors: diabetes mellitus, hypertension, hypercholesterolemia, renal dysfunction, current smoking, and chronic obstructive pulmonary disease. Diabetes mellitus was recorded for patients presenting with a fasting glucose level of 126.1 mg/dL or higher and for those undergoing medical treatment for diabetes mellitus. Hypertension was recorded if patients presented with a blood pressure of 140/90 mm Hg or higher or if patients received medical treatment for hypertension. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level of 212.4 mg/dL or higher or if the diagnosis was established by the referring physician. Renal dysfunction of any cause was recorded if patients presented with a serum creatinine level of 2.0 mg/dL or higher or in those who required dialysis.

To convert fasting glucose to millimoles per liter, multiply by 0.0555; plasma cholesterol to millimoles per liter, multiply by 0.0259; and creatinine to micromoles per liter, multiply by 76.25.

Patients with a body mass index (calculated as weight in kilograms divided by height in meters squared) higher than 30 were considered obese. Baseline 12-lead electrocardiography was evaluated for Q-waves, ST-segment depression or elevation, left ventricular hypertrophy, right bundle branch block, left bundle branch block, and atrial fibrillation. All patients were assessed for cardiac medication use, including aspirin, angiotensin-converting enzyme inhibitors, β-blockers, and statins. To ascertain the long-term use of cardiovascular medication, medication had to be documented at least 2 months after the first visit.

### DEFINITION OF OUTCOME

The median follow-up period was 8 years (interquartile range, 4-11 years). The end points were all-cause mortality at 1, 5, and 10 years. Mortality data were collected from the medical records, the Office of Civil Registry, and through follow-up interviews with patients, family members, and referring physicians.

### DEVELOPMENT OF THE PROGNOSTIC RISK INDEX

A random sample of 1332 patients of the total cohort (50%) were assigned to the derivation cohort (50%), which was used for developing the prognostic index (Rotterdam derivation cohort).[12,13] A total of 1310 patients were assigned to the validation cohort (Rotterdam validation cohort) (50%). A descriptive comparison between the derivation and validation cohorts was performed using the $\chi^2$ test for categorical variables and the *t* test for continuous variables. Cox proportional hazards regression analysis was used to analyze the association between clinical variables and mortality. A prognostic risk index was developed for 1-, 5-, and 10-year mortality. To select a final set of significant risk factors in the derivation cohort ($P<.05$), all baseline clinical variables were entered into a multivariate Cox proportional hazards regression model with stepwise backward elimination of the least significant variable. The nonmodifiable variables age and sex were always entered into the multivariate regression model, despite the level of significance, and were eliminated at the final model if nonsignificant. Separate risk scoring systems for 1-, 5-, and 10-year mortality were then constructed by assigning weighted points to each independent and significant predictor in the derivation cohort. Weighted points were calculated by multiplying the coefficient of the predictor by 10 and by rounding it off to the nearest integer. In each patient, a risk score for 1-, 5-, and 10-year mortality was calculated by adding up the points for each risk factor present. Based on their risk score, patients were categorized into 4 different risk groups (low, low-intermediate, high-intermediate, and high), using the quartiles as cutoff values.

### VALIDATION OF PROGNOSTIC RISK INDEX

The 1-, 5-, and 10-year prognostic risk index was applied to the Rotterdam validation cohort, and the predicted 1-, 5-, and 10-year mortality rates were compared. The prognostic risk index was also validated in an independent cohort outside the Erasmus Medical Center (Netherlands Heart Survey[14] cohort). This cohort constituted 688 patients with PAD who came from 11 hospitals in the Netherlands. Five hospitals were located in the central part of the country, 3 in the northern region, and 3 in the southern region. The participating sites included 2 small centers (<400 beds), 5 intermediate size centers (400-800 beds), and 4 large centers (>800 beds). Two centers were university hospitals. Data collection in this cohort was part of a survey of clinical practice supported by the Netherlands Heart Foundation in the context of the Euro Heart Survey Programme.[14] Since follow-up in this cohort was 1 year, only the 1-year prognostic risk index was validated in this Netherlands Heart Survey cohort.[14]

To examine the discrimination of our prognostic risk indexes, we determined the area under the receiver operating characteristic (ROC) curve, which is comparable to the C statistic.[15]

**Table 1. Baseline Characteristics of the Derivation and Validation Cohorts**

| Characteristic | Patients, No. (%) | | *P* Value |
|---|---|---|---|
| | Rotterdam Derivation Cohort (n=1332) | Rotterdam Validation Cohort (n=1310) | |
| Age > 65 y | 686 (51.5) | 636 (48.5) | .13 |
| Men | 964 (72.4) | 934 (71.3) | .56 |
| Angina pectoris | 317 (23.8) | 316 (24.1) | .85 |
| Previous MI | 506 (38.0) | 481 (36.7) | .50 |
| Previous CABG | 266 (20.0) | 223 (17.0) | .051 |
| CAD (summary variable) | 601 (45.1) | 584 (44.6) | .78 |
| History of CHF | 105 (7.9) | 119 (9.1) | .27 |
| History of CVA/TIA | 101 (7.6) | 99 (7.6) | .98 |
| Diabetes mellitus | 229 (17.2) | 234 (17.9) | .65 |
| Hypercholesterolemia | 291 (21.8) | 274 (20.9) | .56 |
| Hypertension | 609 (45.7) | 627 (47.9) | .27 |
| Current smoking | 461 (34.6) | 464 (35.4) | .66 |
| Renal dysfunction | 67 (5.0) | 66 (5.0) | .99 |
| COPD | 149 (11.2) | 171 (13.1) | .14 |
| Obesity | 160 (12.0) | 148 (11.3) | .57 |
| ABI < 0.60 | 590 (44.3) | 589 (45.0) | .73 |
| Electrocardiography | | | |
| Q-waves | 373 (28.0) | 341 (26.0) | .25 |
| ST-segment changes | 204 (15.3) | 195 (14.9) | .76 |
| Left ventricular hypertrophy | 74 (5.6) | 72 (5.5) | .95 |
| Right bundle branch block | 20 (1.5) | 27 (2.1) | .28 |
| Left bundle branch block | 50 (3.8) | 47 (3.6) | .82 |
| Atrial fibrillation | 21 (1.6) | 38 (2.9) | .02 |
| Medication | | | |
| Aspirin | 291 (21.8) | 284 (21.7) | .92 |
| ACE inhibitors | 340 (25.5) | 347 (26.5) | .57 |
| β-Blocker | 335 (25.2) | 319 (24.4) | .63 |
| Statins | 257 (19.3) | 258 (19.7) | .80 |
| Enrollment after 1995 | 553 (41.5) | 585 (44.7) | .10 |

Abbreviations: ABI, ankle-brachial index; ACE, angiotensin converting enzyme; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; MI, myocardial infarction.

**Table 2. Univariate Analysis of Clinical Characteristics and Mortality in the Derivation Cohort[a]**

| Characteristic | Mortality (n=1332) | | | | | |
|---|---|---|---|---|---|---|
| | 1 Year | *P* Value | 5 Year | *P* Value | 10 Year | *P* Value |
| Age > 65 y | 4.59 (2.63-8.02) | <.001 | 2.10 (1.66-2.65) | <.001 | 1.65 (1.39-1.95) | <.001 |
| Men | 1.02 (0.63-1.66) | .93 | 0.81 (0.64-1.03) | .08 | 1.01 (0.83-1.22) | .93 |
| Angina pectoris | 1.71 (1.09-2.68) | .02 | 1.26 (0.99-1.60) | .06 | 1.16 (0.96-1.41) | .12 |
| Previous MI | 2.20 (1.43-3.38) | <.001 | 1.61 (1.29-2.00) | <.001 | 1.53 (1.30-1.81) | <.001 |
| Previous CABG | 2.01 (1.28-3.16) | .002 | 0.87 (0.66-1.15) | .32 | 1.08 (0.88-1.32) | .47 |
| History of CHF | 2.71 (1.55-4.74) | <.001 | 3.07 (2.30-4.09) | <.001 | 3.01 (2.35-3.85) | <.001 |
| History of CVA/TIA | 2.41 (1.37-4.25) | .002 | 2.34 (1.71-3.19) | <.001 | 1.70 (1.28-2.25) | <.001 |
| Diabetes mellitus | 1.41 (0.84-2.37) | .20 | 1.61 (1.23-2.10) | <.001 | 1.45 (1.17-1.80) | .001 |
| Hypercholesterolemia | 1.29 (0.76-2.19) | .35 | 1.25 (0.93-1.66) | .14 | 1.21 (0.97-1.51) | .10 |
| Hypertension | 1.41 (0.92-2.15) | .12 | 1.14 (0.91-1.42) | .25 | 1.23 (1.04-1.46) | .02 |
| Current smoking | 1.05 (0.68-1.63) | .83 | 1.01 (0.81-1.27) | .91 | 1.02 (0.86-1.22) | .79 |
| Renal dysfunction | 5.49 (3.22-9.35) | <.001 | 4.99 (3.60-6.93) | <.001 | 4.11 (3.07-5.51) | <.001 |
| COPD | 1.16 (0.62-2.15) | .64 | 1.38 (1.01-1.88) | .045 | 1.41 (1.11-1.79) | .005 |
| Obesity | 1.38 (0.40-4.69) | .61 | 0.80 (0.39-1.65) | .55 | 0.72 (0.40-1.27) | .26 |
| ABI < 0.60 | 3.02 (1.91-4.79) | <.001 | 2.19 (1.75-2.73) | <.001 | 1.62 (1.38-1.92) | <.001 |
| Electrocardiography | | | | | | |
| Q-waves | 2.88 (1.88-4.41) | <.001 | 1.75 (1.40-2.19) | <.001 | 1.71 (1.44-2.04) | .001 |
| ST-segment changes | 2.18 (1.33-3.57) | .002 | 1.73 (1.33-2.26) | <.001 | 1.71 (1.36-2.13) | <.001 |
| LVH | 0.62 (0.20-1.96) | .41 | 1.12 (0.71-1.79) | .62 | 1.38 (0.99-1.91) | .06 |
| RBBB | 1.70 (0.42-6.91) | .46 | 1.90 (0.90-4.02) | .09 | 2.48 (1.43-4.31) | .001 |
| LBBB | 0.62 (0.15-2.52) | .50 | 1.19 (0.71-2.00) | .51 | 1.20 (0.81-1.76) | .37 |
| Atrial fibrillation | 2.48 (0.78-7.84) | .12 | 1.21 (0.54-2.72) | .64 | 1.39 (0.72-2.69) | .33 |
| Medication | | | | | | |
| Aspirin | 0.58 (0.32-1.07) | .08 | 0.72 (0.54-0.95) | .02 | 0.86 (0.70-1.06) | .16 |
| ACE inhibitor | 1.69 (1.09-2.61) | .02 | 0.94 (0.73-1.20) | .60 | 1.14 (0.94-1.37) | .19 |
| β-Blocker | 0.26 (0.12-0.57) | .001 | 0.77 (0.58-1.01) | .06 | 0.68 (0.54-0.84) | <.001 |
| Statins | 0.43 (0.21-0.89) | .02 | 0.65 (0.48-0.89) | .008 | 0.63 (0.49-0.80) | <.001 |
| Enrollment after 1995 | 1.04 (0.68-1.60) | .85 | 0.93 (0.74-1.17) | .53 | 0.56 (0.46-0.69) | <.001 |

Abbreviations: ABI, ankle-brachial index; ACE, angiotensin converting enzyme; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; MI, myocardial infarction; RBBB, right bundle branch block.

[a] Data are reported as hazard ratio (95% confidence interval) or as *P* value.

**Table 3. The Prognostic Risk Index for 1-, 5-, and 10-Year Mortality**

| Risk Index | Mortality[a] | *P* Value | Coefficient | Points |
|---|---|---|---|---|
| **1 Year (Area Under ROC Curve, 0.80)** | | | | |
| Age >65 y | 4.47 (2.54-7.88) | <.001 | 1.50 | +15 |
| Renal dysfunction | 4.37 (2.38-8.02) | <.001 | 1.48 | +15 |
| Hypercholesterolemia | 3.60 (1.91-6.78) | <.001 | 1.28 | +13 |
| History of congestive heart failure | 2.58 (1.42-4.69) | .002 | 0.94 | +9 |
| Ankle-brachial index <0.60 | 2.26 (1.41-3.60) | .001 | 0.81 | +8 |
| Q-waves | 1.98 (1.24-3.15) | .004 | 0.68 | +7 |
| Diabetes mellitus | 1.77 (1.02-3.04) | .04 | 0.57 | +6 |
| β-Blockers | 0.53 (0.29-0.95) | .03 | −0.64 | −6 |
| Aspirin | 0.46 (0.24-0.87) | .02 | −0.77 | −8 |
| Statins | 0.17 (0.07-0.44) | <.001 | −1.78 | −18 |
| **5 Year (Area Under ROC Curve, 0.74)** | | | | |
| Renal dysfunction | 4.30 (3.05-6.08) | <.001 | 1.46 | +15 |
| History of congestive heart failure | 2.19 (1.58-3.02) | <.001 | 0.78 | +8 |
| Ankle-brachial index <0.60 | 2.08 (1.64-2.62) | <.001 | 0.73 | +7 |
| Age >65 y | 1.93 (1.51-2.45) | <.001 | 0.66 | +7 |
| History of cerebrovascular events | 1.92 (1.37-2.69) | <.001 | 0.65 | +7 |
| Hypercholesterolemia | 1.67 (1.14-2.45) | .01 | 0.51 | +5 |
| ST-segment changes | 1.62 (1.23-2.14) | .001 | 0.48 | +5 |
| Diabetes mellitus | 1.51 (1.14-1.99) | .004 | 0.41 | +4 |
| Q-waves | 1.34 (1.05-1.71) | .02 | 0.29 | +3 |
| β-Blockers | 0.70 (0.52-0.93) | .01 | −0.36 | −4 |
| Statins | 0.53 (0.35-0.80) | .003 | −0.64 | −6 |
| Aspirin | 0.49 (0.36-0.67) | <.001 | −0.71 | −7 |
| **10 Year (Area Under ROC Curve, 0.72)** | | | | |
| Renal dysfunction | 3.27 (2.40-4.46) | <.001 | 1.19 | +12 |
| History of congestive heart failure | 2.10 (1.60-2.75) | <.001 | 0.74 | +7 |
| ST-segment changes | 1.60 (1.26-2.02) | <.001 | 0.47 | +5 |
| Age >65 y | 1.59 (1.33-1.89) | <.001 | 0.46 | +5 |
| Hypercholesterolemia | 1.56 (1.17-2.08) | .002 | 0.45 | +5 |
| Ankle-brachial index <0.60 | 1.51 (1.28-1.80) | <.001 | 0.41 | +4 |
| Q-waves | 1.48 (1.23-1.78) | <.001 | 0.39 | +4 |
| Diabetes mellitus | 1.39 (1.11-1.74) | .004 | 0.33 | +3 |
| History of cerebrovascular events | 1.40 (1.04-1.88) | .03 | 0.33 | +3 |
| Chronic obstructive pulmonary disease | 1.34 (1.05-1.72) | .02 | 0.29 | +3 |
| Aspirin | 0.69 (0.55-0.87) | .001 | −0.37 | −4 |
| β-Blockers | 0.62 (0.50-0.78) | <.001 | −0.47 | −4 |
| Statins | 0.54 (0.39-0.75) | <.001 | −0.62 | −6 |

Abbreviation: ROC, receiver operating characteristic.
[a]Hazard ratio (95% confidence interval) in multivariate regression analysis with stepwise deletion.

C statistics in the validation cohorts were calculated based on the mortality risk score system created from the derivation cohort. Hazard ratios are reported with corresponding 95% confidence intervals. For all tests, a 2-sided *P* value less than .05 was considered significant. All analysis was performed using SPSS statistical software, version 11.0 (SPSS Inc, Chicago, Illinois).

## RESULTS

In the Rotterdam derivation cohort, the median age was 65.2 years (interquartile range, 57.3-72.1 years); 72.4% were men; and the median ABI was 0.60 (interquartile range, 0.50-0.75). In the Rotterdam validation cohort, the median age was 64.7 years (interquartile range, 56.5-72.1 years); 71.3% were men; and the median ABI was 0.60 (interquartile range, 0.45-0.75). No significant differences in baseline characteristics between the 2 cohorts were observed except for atrial fibrillation, which was less frequent in the derivation cohort (**Table 1**). At 1-, 5-, and 10-year follow-up, 81 (6.1%), 298 (22.4%), and 562 (42.2%) patients, respectively, died in the derivation cohort, and 88 (6.7%), 306 (23.4%), and 529 (40.4%) patients, respectively, died in the Rotterdam validation cohort. In the group of patients who survived at 1-, 5-, and 10-year follow-up, 100% were followed for at least 1 year, 92% for at least 5 years, and 72% for at least 10 years. At 1-year follow-up, 74 patients died in the Netherlands Heart Survey[14] validation cohort (10.8%).

In univariate analysis, risk factors associated with increased 1-, 5-, and 10-year mortality included age greater than 65 years, previous myocardial infarction, history of congestive heart failure, history of cerebrovascular events, renal dysfunction, ABI lower than 0.60, and electrocardiographic Q-waves and ST-segment deviations (**Table 2**). Angina pectoris and a history of coronary artery bypass grafting were associated with an increased risk of 1-year mortality. Diabetes mellitus and chronic

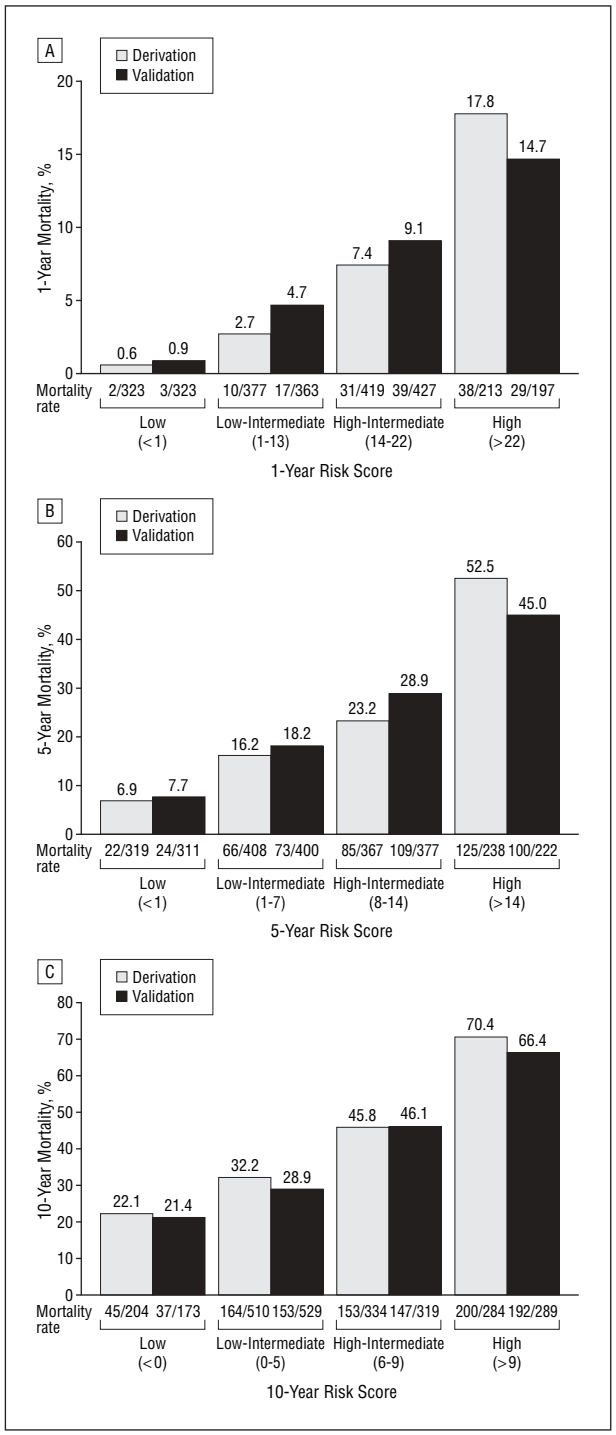


**Figure 1.** Mortality rates at 1-year (A), 5-year (B), and 10-year (C) follow-up in the derivation and validation cohorts, stratified according to 4 different risk classification groups (low, low-intermediate, high-intermediate, and high risk group).

pulmonary disease were associated with an increased risk of 5- and 10-year mortality. Hypertension and right bundle branch block were associated with an increased risk of 10-year mortality. Univariate analysis also demonstrated that statin therapy was associated with a reduced risk of 1-, 5-, and 10-year mortality, aspirin with a reduced risk of 5-year mortality, and β-blocker therapy with a reduced risk of 1- and 10-year mortality.

Multivariate proportional hazards regression analysis using stepwise backward deletion of the least significant variables identified 10, 12, and 13 clinical variables as independent and significant predictors of 1-, 5-, and 10-year mortality, respectively (**Table 3**). Year of enrollment was not a significant predictor of mortality in multivariate analysis. A risk score for 1-, 5-, and 10-year mortality from each multivariate model was calculated for each individual patient, and scores ranged from –25 to 59 for 1-year mortality (median, 13; interquartile range, 0-22), from –11 to 32 for 5-year mortality (median, 7; interquartile range, 0-14), and from –13 to 38 for 10-year mortality (median, 5; interquartile range, –1 to 9). **Figure 1** summarizes the proportion of patients who died within 1, 5, and 10 years in the derivation cohort stratified according to the 4 different risk classification groups. One-, 5-, and 10-year mortality rates increased significantly from the low-risk group to the high-risk group ($P < .001$ for all).

The mortality rate in each category in the derivation cohort was comparable to those in the Rotterdam validation cohort (Figure 1). Kaplan-Meier curves stratified according to the 4 risk groups showed that the Kaplan-Meier survival curves in the derivation cohort were comparable to the survival curves in the Rotterdam validation cohort (**Figure 2**). The C statistic discrimination of the final multivariate model for 1-year mortality was better in the derivation cohort (0.80) than in the Rotterdam validation cohort (0.74) and the Netherlands Heart Survey[14] cohort (0.73) (**Figure 3**). In addition, for 5-year mortality, a better discrimination of the final model was observed in the derivation cohort than in the validation cohort (areas under the ROC curve, 0.74 and 0.73, respectively). Interestingly, the discrimination of the final model for 10-year mortality was lower in the derivation cohort (0.72) than in the Rotterdam validation cohort (0.73).

## COMMENT

In this study, we developed a prognostic risk index for 1-, 5-, and10-year mortality that can be used as a point scoring system to stratify patients with PAD into low, low-intermediate, high-intermediate, and high risk groups. The risk scoring system included nonmodifiable variables such as age and sex and modifiable clinical variables obtained from medical history, physical examination, laboratory testing, electrocardiography, and ABI measurements. Long-term cardiac medication use was also included in the risk scoring system.

### RISK FACTORS IN PAD

Results from the Framingham Heart Study[16] identified age, male sex, serum cholesterol level, hypertension, smoking, diabetes mellitus, and coronary artery disease as risk factors for the occurrence of intermittent claudication. The National Health and Nutrition Examination Survey[8] revealed diabetes mellitus, hypercholesterolemia, low kidney function, coronary artery disease, smoking, and black race as risk factors for prevalent PAD in adults 40 years or older.[8] The Rotterdam Study[9] showed

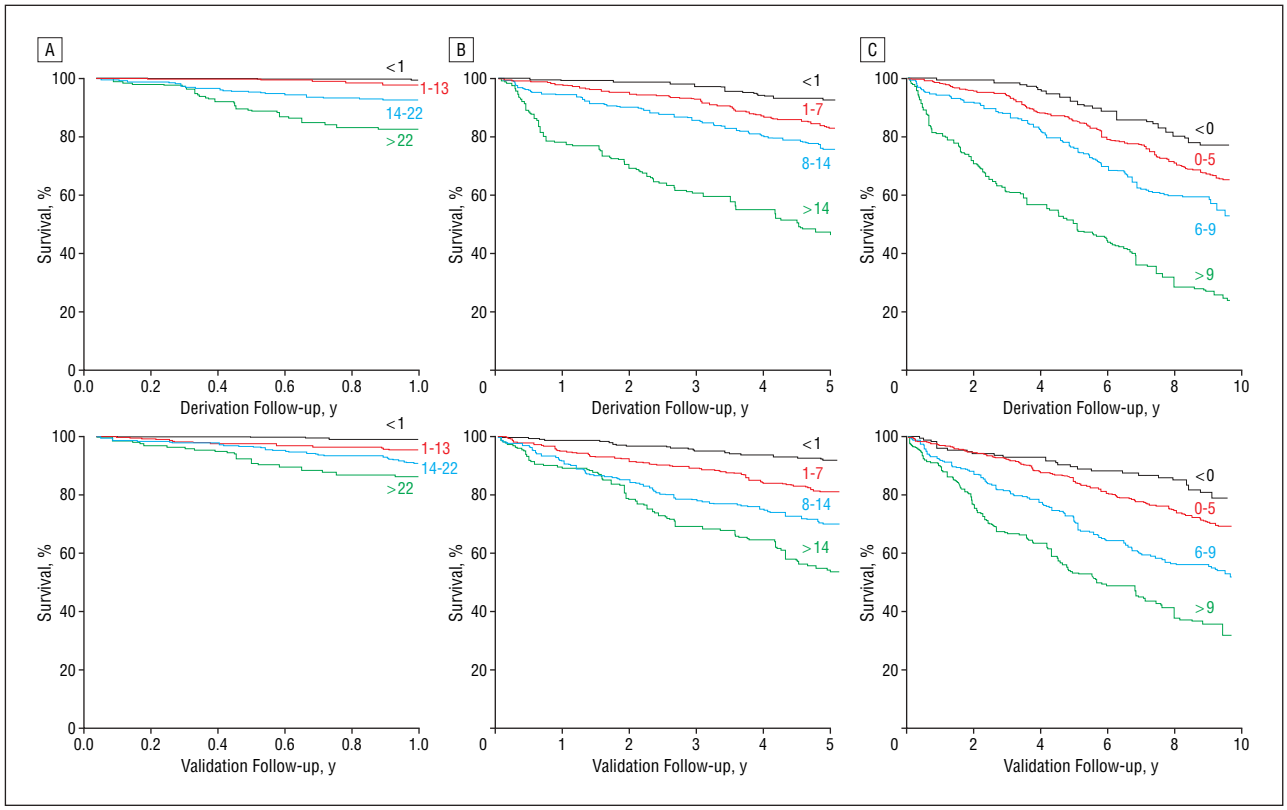


**Figure 2.** Kaplan-Meier curves for 1-year (A), 5-year (B), and 10-year (C) survival in the derivation and validation cohorts stratified according to 4 different risk classification groups by risk score (low, low-intermediate, high-intermediate, and high risk). $P<.001$ for all categories.

that age over 75 years, smoking, diabetes mellitus, hypertension, low high-density lipoprotein cholesterol levels, and increased fibrinogen levels were significant determinants for PAD. Independent risk factors for PAD in the Cardiovascular Health Study[17] included age, diabetes mellitus, smoking, hypertension, hypercholesterolemia, increased creatinine levels, low body mass index, and nonwhite ethnicity. These risk factors are common to the development of atherosclerosis, and most were included in our risk index. In our study, coronary artery disease was present in almost half of the study population (49.2% in the derivation cohort and 48.0% in the validation cohort). ST-segment changes and Q-waves were strong predictors of long-term outcome. This finding supports the use of routine electrocardiography screening for prognostic risk assessment in patients with PAD.

## RENAL DYSFUNCTION

Incidental atherosclerotic renal artery stenosis is a frequent finding in patients with PAD, with prevalence values of 33% in patients with chronic ischemic PAD, as detected by angiography.[18] Atherosclerotic renal artery stenosis may lead to ischemic nephropathy and impaired renal function. Renal dysfunction is a strong predictor for cardiovascular disease and mortality. Moreover, it was one of the strongest predictors in our study cohort, associated with a 4.4-, 4.3-, and 3.3-fold increased risk of 1-, 5-, and 10-year mortality, respectively.

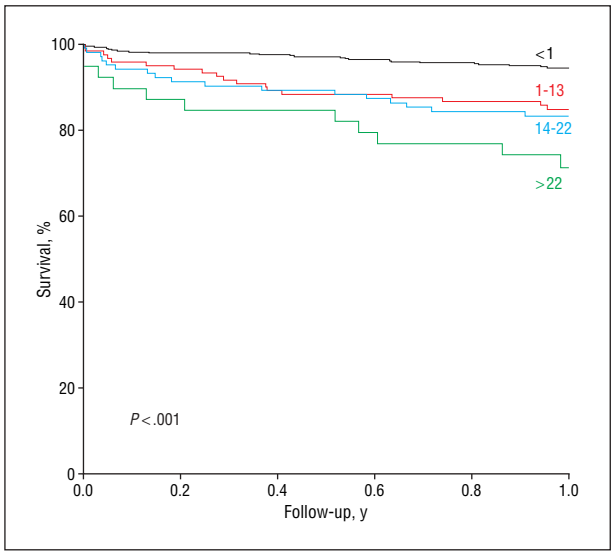


**Figure 3.** One-year survival in the Netherlands Heart Survey[14] cohort according to 4 different risk classification groups (low, low-intermediate, high-intermediate, and high risk).

## ABI AND LONG-TERM MORTALITY

A decrease in ABI is commonly used for the diagnosis of PAD.[19] Ankle-brachial index values of 0.90 or lower and 0.85 or lower have been associated with an increased risk of overall and cardiovascular mortality, respectively, compared with ABI values above 0.90 and 0.85.[1,17,20-24] In our

derivation cohort, we observed 1-, 5-, and 10-year mortality rates of 6%, 22%, and 42%, respectively. These values are in accordance with previously published studies reporting long-term mortality rates in patients with PAD. In a study by Newman et al,[20] mortality during a mean follow-up of 16 months occurred in 27 of 392 patients with PAD (6.9%). McKenna et al[21] showed estimated 5- and 10-year mortality rates of 37% and 54%, respectively, in patients with ABI values of 0.85 or lower. Leng et al[22] demonstrated an all-cause 5-year mortality rate of 22% (63 of 288) in patients with an ABI of 0.90 or lower. Criqui et al[1] found a 10-year mortality rate of 49% (32 of 67) in patients with PAD. The Edinburgh Artery Study[23] found a 12-year mortality incidence of 49% in patients with ABI of 0.90 or lower (119 of 245). In addition, significantly higher mortality rates have been reported in patients with ABI values lower than 0.40[21] and lower than 0.70[22] compared with patients within higher ABI categories. The present study demonstrates that measurement of ABI, even in patients who already present with ABI values of 0.90 or lower, is a consistent, independent stepwise increased risk factor for mortality and therefore highly important in risk stratification.

## MEDICATION THERAPY

We included the use of cardiac drugs that have been demonstrated to improve prognosis in PAD. As demonstrated in our prognostic risk index, patients undergoing treatment with statin, aspirin, and β-blocker therapy were at significantly lower risk for 1-, 5-, and 10-year mortality. Antiplatelet drugs form the cornerstone of pharmacologic intervention in PAD. The Antithrombotic Trialists' Collaboration[25] showed in a meta-analysis a proportional reduction of 23% in serious vascular events among 9214 patients with PAD using antiplatelet therapy (primary aspirin) compared with those using no antiplatelet therapy (5.8% vs 7.1%; $P<.004$). Hydroxymethyl glutaryl coenzyme A reductase inhibitor drugs (statins) have been demonstrated to improve leg functioning, walking performance, ABI values, and symptoms of claudication.[26-28] The Heart Protection Study[29] demonstrated that simvastatin significantly lowered the risk of vascular events in patients with PAD with or without clinically evident coronary heart disease. β-Blockers have also been associated with a significant reduction in new coronary events, independent of other confounding variables.[30,31] According to previous studies, angiotensin-converting enzyme inhibitors should also be considered in patients with PAD for mortality reduction.[32]

## RISK CLASSIFICATION MODEL IN PAD

A PAD risk classification system may help identify patients at increased risk for long-term mortality and subsequently may improve management and treatment strategies.[12] A multivariate Cox hazard model showed in male patients with intermittent claudication that advanced age, stroke, lower ABI, and diabetes were associated with long-term mortality.[33] To our knowledge, no other risk indices have been developed in PAD. We aimed to develop a simple risk scoring system in which points are assigned to prognostic clinical variables obtained through medical history, laboratory testing, electrocardiography, and ABI measurement. The risk of 1-, 5-, and 10-year mortality can then be estimated. Our risk index for 1-, 5-, and 10-year mortality had good discrimination and was successfully validated in 2 independent patient samples, suggesting its generalizability to other PAD patient groups.

## LIMITATIONS

Several limitations in our study should be addressed. Unfortunately, our study did not include recently emerging risk factors such as fibrinogen, homocysteine, C-reactive protein, and lipoprotein-a, which may have prognostic value in PAD patients.[34] Second, we used mortality from all causes as an end point. A better discriminatory capacity might have been achieved if mortality from cardiovascular causes was used as the end point, especially because PAD is closely associated with the risk of myocardial infarction and death from vascular causes. Third, interpretation of this index in nonwhite patients should be done with caution.

In conclusion, a prognostic risk index for long-term mortality based on cardiovascular risk factors, ABI measurements, electrocardiographic abnormalities, and cardioprotective medication stratifies patients into different risk categories. This index may offer practical help to physicians in risk stratification, patient counseling, and medical decision making at an early stage of the disease.

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