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Risk Chart for Future Mortality and Ischaemic Events Following Peripheral Bypass Surgery

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WHAT THIS PAPER ADDS
The BOA Risk Chart 2 predicts mortality and ischemic events after peripheral bypass surgery.

Objectives: A prediction model to identify determinants and quantify the risk of future ischaemic events in patients with peripheral arterial disease (PAD) provides a personal risk profile to offer individualized patient care. A risk chart was derived and validated in patients who received infrainguinal bypass surgery.
Methods: The Bypass Oral anticoagulants or Aspirin Risk Chart (BOA-RC2) was based on a pre-defined subgroup of the Dutch BOA trial ($N = 482$), the derivation cohort. The primary outcome event for BOA-RC2 was the composite of all cause death, non-fatal myocardial infarction, or non-fatal ischaemic stroke during a 10 year follow up. Determinants and long-term risk were identified with multivariate Cox regression analyses. Validation of the BOA-RC2 was performed in the remaining patients of the complete BOA trial cohort ($N = 2{,}650 - 482 = 2{,}168$), the validation cohort.
Results: The primary outcome event occurred in 67% (321/454) of the derivation cohort and in 66% (1,371/2,083) of the validation cohort during a median follow up of 6.6 years. The BOA-RC2 included the following determinants: age, critical limb ischaemia, diabetes, and a prior vascular intervention. The performance of the BOA-RC2 was good with a Brier score of 0.19, an area under the curve of 0.73, and a Hosmer—Lemeshow statistic of $p = .9$.
Conclusions: The BOA-RC2 proves to be fit for the prediction of mortality and major ischaemic events in patients after peripheral bypass surgery. The BOA-RC2 can be used to adequately inform the patient about his/her risk of future events in an illustrative manner and stress the necessity of preventative measures, such as lifestyle adjustments, screening for risk factors, and drug treatments. In the future, the BOA-RC2 may be of interest to identify patients at high risk of mortality and ischaemic events for clinical research on new therapeutic options.

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INTRODUCTION

Infrainguinal bypass surgery is a commonly accepted treatment for critical limb ischaemia, a grave manifestation of peripheral arterial disease (PAD).[1] Compared with patients with coronary artery disease or cerebrovascular disease, patients with PAD have the highest risk of vascular death and the second highest risk of myocardial infarction and stroke.[2,3]

Personal risk profiles might help the physician to offer individualized patient care and improve clinical decision making for optimal secondary prevention. To this end, a prediction model was derived in 2009 to identify determinants and quantify the long-term risk of future ischaemic events in patients with PAD.[4] This initial model, the BOA Risk Chart (BOA-RC1), was based on a subset of participants of the Dutch Bypass Oral anticoagulants or Aspirin (BOA) trial, who received infrainguinal bypass surgery.[5] The primary outcome event of the BOA-RC1 was the composite of vascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, or major lower limb amputation.

In the present study, the aim was to further improve the chart's clinical and social—economical usefulness by first adjusting the primary outcome event and, second, validating this adjusted BOA Risk Chart (BOA-RC2). The primary outcome event now includes death by all causes instead of death by a vascular cause alone. Validation of the BOA-RC2 makes the model ready for external use. In addition, derivative charts of the BOA-RC2 were developed to show the risk at different time intervals (2, 5, and 10 years) in

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combination with a chart displaying the observed median time to event per risk category in the validation cohort, which makes the model more informative through time.

METHODS

Derivation cohort

The BOA-RC1 and BOA-RC2 were based on a predefined subgroup of patients from the Dutch BOA trial, referred to as the derivation cohort. Full details of the Dutch BOA trial and derivation of the BOA-RC1 have been published elsewhere.[4,5] In summary, the Dutch BOA trial included 2,650 patients after infrainguinal bypass surgery from 77 medical centres throughout the Netherlands between 1995 and 1998. Patients were randomly allocated to receive oral anticoagulation or aspirin to study the effects of oral anticoagulants and aspirin in preventing bypass occlusion, lower limb amputation, and ischaemic events.

The derivation cohort consisted of 482 patients (18%) from the Dutch BOA trial. These patients were included by six of the 77 participating medical centres that had been selected because they contributed a large proportion of patients in the Dutch BOA trial. The follow up data of these 482 patients were extended from 1998 to 2009 and collected from the vascular surgeon, general practitioner, patient, or relatives and acquaintances in a stepwise manner according the proven effective method of the LiLAC Study.[6]

The primary outcome event of the BOA-RC1 was the composite of vascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, or major lower limb amputation. Determinants of the primary outcome event were age, critical limb ischaemia, diabetes, and a prior vascular intervention.

To further optimize the clinical and social—economical usefulness of the BOA-RC1, it was decided to adjust the primary outcome event by substituting vascular mortality for all-cause mortality. Also, follow up data on lower limb amputation were not available in the National Registry of Hospital Discharge Diagnoses and were omitted from the adjusted primary outcome event. So, the adjusted primary outcome event for the BOA-RC2 was the composite of all cause death, non-fatal myocardial infarction, and non-fatal ischaemic stroke (whichever occurred first). Adjudication and classification of the outcome events has been described previously.[4] Briefly, a panel consisting of a vascular surgeon, a clinical epidemiologist, a neurologist, and a cardiologist adjudicated and classified the outcome events according to the pre-specified definitions (Supplementary Table 1).

Validation cohort

To BOA-RC2 was validated in the remaining patients of the complete cohort of the Dutch BOA trial ($N = 2{,}650 - 482 = 2{,}168$), referred to as the validation cohort. The long-term follow up data of the validation cohort were collected at the National Death Registry and the National Registry of Hospital Discharge Diagnoses from January 1995 to December 2007, using a validated probabilistic method.[7–9] In these databases, cause of death and the indications for hospitalization are coded according to the International Classification of Diseases, Ninth Revision (ICD-9).[10] Events used for the composite outcome event were all cause mortality, myocardial infarction (ICD-9 codes 410), and ischaemic cerebrovascular accidents (ICD-9 codes 433—434). The main diagnoses per code are displayed in Supplementary Table 2. Major limb amputation was not available in the National Registry of Hospital Discharge Diagnoses. This study was conducted in accordance to the Declaration of Helsinki and procedures were approved by the institutional review board of the UMC Utrecht. All patients gave written informed consent.

Statistical analyses

Continuous variables were summarized as means, and discrete variables were summarized as frequencies and percentages. Missing ankle—brachial index (ABI) data of 81 patients in the derivation cohort were imputed with multiple imputations. The cumulative risk of mortality and vascular events with 95% confidence intervals (CI) was estimated with Kaplan—Meier analysis and presented graphically as Kaplan—Meier curves. Differences between the derivation and validation cohort were analysed with the Student *t* test.

Derivation BOA-RC2

Derivation of the BOA-RC2 was performed in the previously described derivation cohort ($N = 482$) similarly to the BOA-RC1 derivation that has been described elsewhere.[4] In brief, risk factor assessment was performed with the Cox proportional hazards model and associated variables that yielded $p < .20$ in the univariate analysis were included in the multivariate analysis. Independent predictors of the primary outcome event ($p < .05$) were identified using backward stepwise elimination. The regression coefficients of the independent predictors were reduced with a uniform shrinkage factor.[11] Discriminatory performance of the model was assessed with area under receiver operator characteristic curves (AUC-ROC). In addition to the model derived from all patients in the derivation cohort, separate models for patients with critical limb ischaemia and intermittent claudication were compared.

The BOA-RC2 was developed based on all the independent predictors from the Cox proportional hazards model with the highest AUC-ROC and displayed the 10 year risks for the primary outcome event in patients with any combination of these predictors.

Derivative charts displaying 2 and 5 year risks for the primary outcome event were developed based on the model used for the BOA-RC2.

Validation BOA-RC2

The overall performance of the BOA-RC2 in the validation cohort was assessed by calculating the Brier score.[12] The discriminatory performance was assessed by calculating the

area under the ROC curve and its calibration was analysed by a calibration graph and the Hosmer—Lemeshow test.[13] In addition, a chart displaying the observed median time to event per risk category in the validation cohort was made. The validation analyses were done in SPSS version 14.0 and graphs were made in GraphPad Prism version 5.03.

RESULTS

Derivation cohort

The follow up data of the derivation cohort were complete in 94% of the 482 patients ($N = 454$). The median follow up was 6.6 years. The mean age of the derivation cohort was 69 years (SD 10). The patients' baseline characteristics are summarized in Table 1. The primary outcome event occurred in 66.7% ($N = 321$) of patients. The primary outcome event consisted of 242 deaths (50.2%), 44 myocardial infarctions (9.1%), and 35 strokes (7.3%). The primary outcome event occurred within the first 30 days of peripheral bypass surgery in seven patients (0.2%).

Validation cohort

The follow up data of the validation cohort were complete in 96% of the 2168 patients ($N = 2{,}083$). The median follow up was 6.6 years. The mean age of the validation cohort was 69 years (SD 10). The primary outcome event occurred in 65.8% ($N = 1{,}371$) of patients. The event free survival is shown in Fig. 1. The commonest primary outcome event was death (53.0%; $N = 1{,}105$) followed by myocardial infarction (7.6%; $N = 159$) and stroke (5.1%; $N = 107$). During the first 30 days the primary outcome event occurred in 35 patients (0.2%).

The patients' baseline characteristics of the total Dutch BOA study population and the validation cohort are summarized in Table 1. A larger proportion of patients had an ABI $\leq$0.6 in the validation cohort than the derivation cohort; the same is true for diabetes mellitus. Fewer patients had hyperlipidaemia, were smokers, or received a venous bypass in the validation cohort than the derivation cohort.

Table 1. Baseline characteristics among patients of the derivation cohort and the validation cohort.

Baseline characteristics	Derivation cohort ($N = 482$)	Validation cohort ($N = 2083$)
Demographic characteristics		
Male sex	313 (65%)	1331 (64%)
Age >69 years	274 (57%)	1124 (54%)
Age (mean, SD)	69 (10)	69 (10)
Medical history		
Angina pectoris	80 (17%)	346 (17%)
Myocardial infarction	75 (16%)	374 (18%)
TIA and/or stroke	49 (10%)	247 (12%)
ABI (mean, SD)	0.54 (0.39)	0.55 (0.33)
ABI $\leq$ 0.9	450 (93%)	1560 (94%)
ABI $\leq$ 0.6	288 (60%)	1136 (68%)*
Critical limb ischaemia	220 (46%)	1039 (50%)
Diabetes mellitus	109 (23%)	569 (27%)*
Hypertension	186 (39%)	815 (39%)
Hyperlipidaemia	101 (21%)	324 (16%)*
Smoking	289 (60%)	1103 (53%)*
Vascular intervention	213 (44%)	962 (46%)
Trial bypass		
Femorocrural/ pedal bypass	107 (22%)	409 (20%)
Venous bypass	313 (65%)	903 (43%)*
Trial medication		
Oral anticoagulants	239 (50%)	1043 (50%)

Note. Data are number (%) unless otherwise indicated. SD: standard deviation; TIA: transient ischaemic attack; ABI = ankle—brachial index.
*p-Value < .05.

BOA-RC2 derivation

Baseline characteristics associated with the primary outcome event in a univariate model were increasing age, diabetes, critical limb ischaemia, previous myocardial infarction, ABI $\leq$0.6, hypertension, hyperlipidaemia, previous vascular intervention and femorocrural or femoropedal bypass. Besides hyperlipidaemia, all these characteristics increased the risk of a primary outcome event.

The independent determinants of the primary outcome event were increasing age, diabetes, critical limb ischaemia, and a previous vascular intervention. The AUC-ROC curve of the prediction model for the primary outcome event was 0.78 (95% CI 0.73—0.82) (Table 2). The independent determinants for patients with critical limb ischaemia were age and diabetes; for patients with intermittent claudication the independent determinants were age and prior vascular events. Separate Cox regression models for patients with critical limb ischaemia and intermittent claudication did not

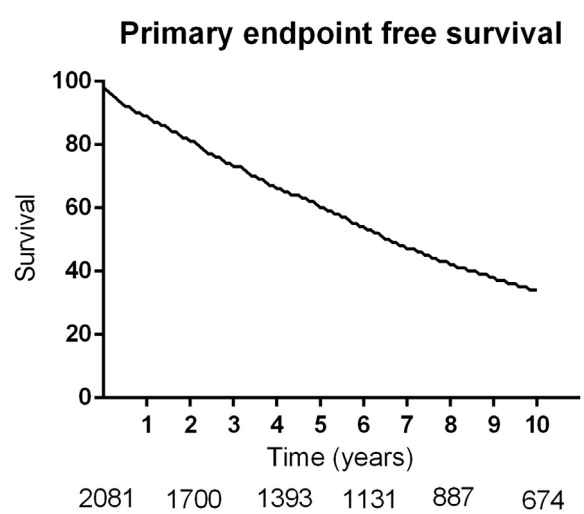

Figure 1. Kaplan—Meier curve of the composite primary outcome event free survival of the validation cohort ($N = 2083$). *Note.* y-axis: percentage of primary outcome event free survival of the validation cohort; x-axis: Time in years with the number of patients at risk per year.

Table 2. Indicator variables retained in Cox regression models for prediction of the primary outcome event.

	All patients HR[a] (95% CI)	CLI HR[a] (95% CI)	IC HR[a] (95% CI)
Demographic facts			
Age[b]	1.06 (1.05—1.07)	1.05 (1.03—1.86)	1.07 (1.04—1.09)
Medical history			
Critical limb ischaemia	1.5 (1.2—1.8)	—	—
Diabetes mellitus	1.4 (1.1—1.7)	1.4 (1.0—1.9)	—
Vascular intervention	1.3 (1.1—1.7)	—	1.5 (1.1—2.1)
ROC-AUC (95% CI)	0.78 (0.73—0.82)	0.76 (0.69—0.84)	0.75 (0.69—0.81)

CLI = critical limb ischaemia; IC = intermittent claudication; ROC-AUC = area under the receiver operator characteristic curve.
[a] Hazard ratio (HR) after shrinkage.
[b] Age was taken as a continuous variable with the HR representing the risk per year increase.

show a higher discriminatory performance (ROC-AUC, respectively 0.76, 0.75).

Fig. 2 systematically displays the 10 year predicted risks of the primary outcome event for each combination of the four independent determinants. These risks ranged from 28% for a patient younger than 65 years of age with intermittent claudication, no diabetes, and no prior vascular intervention to 97% for a patient older than 75 years of age with critical limb ischaemia, diabetes, and a prior vascular intervention. Comparable risk distribution was seen in the derivative charts displaying 2 and 5 year risks for the primary outcome.

BOA-RC2 validation

The overall performance of the BOA-RC2 in the validation cohort was fair with a Brier score of 0.19. The AUC-ROC analysis showed a fair to good discriminatory performance of the BOA-RC2 in the validation cohort with an area under the curve of 0.73 (95% CI 0.71—0.75) (Fig. 3). The BOA-RC2 predicted 1,395 primary outcome events in the validation cohort, while 1,372 primary outcome events were observed in the validation cohort. The Hosmer—Lemeshow statistic (chi-square 13.56; $p = .9$) showed great goodness of fit between expected and observed primary outcome events. Furthermore, the calibration curve showed similar numbers of expected and observed primary outcome events (Fig. 4), representing a good calibration of the BOA-RC2. The median time to event ranged from 10 years for young patients with intermittent claudication to 3 years for patients older than 75 years of age with critical limb ischaemia, diabetes, and a prior vascular intervention (Fig. 5).

DISCUSSION

Patients with PAD, especially critical limb ischaemia, are at high risk of secondary, usually fatal, ischaemic events. Therefore individual risk assessment of mortality or major ischaemic events in patients who require peripheral bypass surgery is essential to adequately inform the patient and apply patient specific preventative measures, such as lifestyle adjustments, screening, and drug treatments. Up to now, long-term data of major ischaemic events in PAD patients were scarce and even lacking for patients with severe PAD, preventing an accurate risk assessment of future ischaemic events. Therefore, all major ischaemic events of patients from the Dutch BOA trial during a 10 year follow up were collected. Ten years after peripheral bypass surgery, 66% of the patients had died, suffered a myocardial

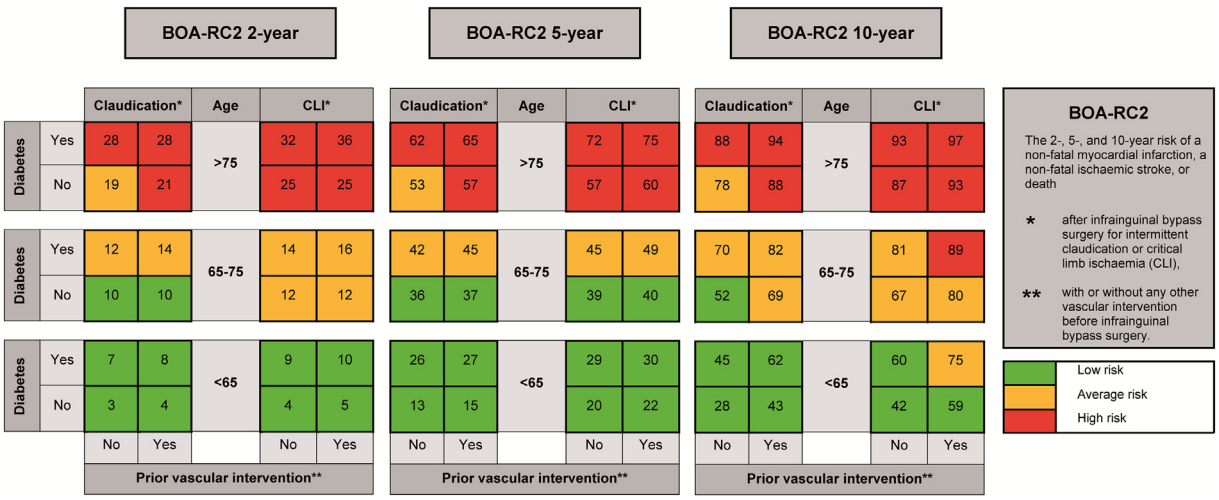

Figure 2. The BOA-RC2 with the 10 year risk of the composite primary outcome event for each combination of the four independent predictors and derived charts displaying 2 and 5 year risk. *Note*. Cut off points average risk: 10%, 40%, and 60%; high risk: 20%, 40%, and 85% for 2, 5, and 10 year risk respectively. CLI = critical limb ischaemia.

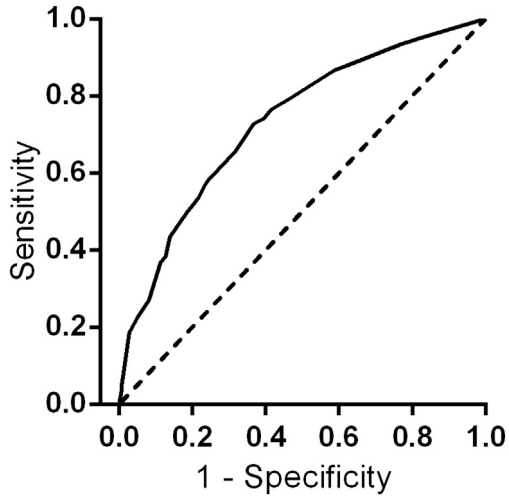

Figure 3. Discriminatory performance of the BOA-RC2 in the validation cohort. *Note*. Area under the curve: 73%, 95% CI 71—75%.

infarction, or an ischaemic stroke. Furthermore, the BOA-RC2 was derived in order to easily assess the individual long-term risk of mortality or major ischaemic events. The 10 year risks ranged from 28% for a patient younger than 65 years with intermittent claudication, no diabetes, and no prior vascular intervention up to 97% for a patient older than 75 years with critical limb ischaemia, diabetes, and a prior vascular intervention. To further aid clinical decision making derivative charts displaying the 2 and 5 year risk of death and major cardiovascular events and a chart displaying the observed median time to event per risk category in the validation cohort were produced (Figs. 2 and 5). As far as is known, the BOA-RC2 is the first validated risk chart that quantifies long-term risk of secondary cardiovascular events or death of patients with severe PAD.

Estimating a patient's 10 year risk with the BOA-RC2 is independent of current use of oral anticoagulants or aspirin and also of the type of bypass graft constructed, as these determinants did not contribute to the prediction model.

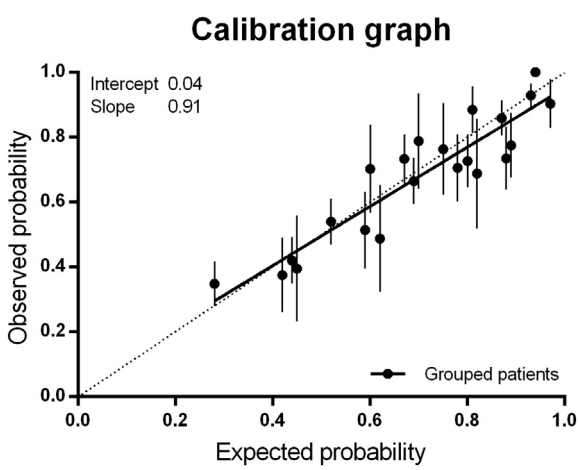

Figure 4. Calibration of the BOA-RC2 in the validation cohort. *Note*. Intercept of the calibration curve: 0.04. Slope of the calibration curve: 0.91.

Strengths and limitations

In accordance with the trend in current literature and the preference of health care financial management to report all cause mortality, the composite primary outcome event of the original BOA Risk Chart (BOA-RC1) was adjusted by including all cause mortality as opposed to vascular mortality alone. In addition, the outcome event vascular death has a more specific definition than all cause death, leaving more room for misinterpretation and subsequent erroneous coding. The straightforward outcome event all cause death is clear and more suitable for broad use.

Furthermore, the BOA-RC2 was derived from a population consisting of both patients with critical limb ischaemia and patients with severe claudication. Though patients at an advanced stage of PAD are at a higher risk of ischaemic events, separate Cox regression models for patients with critical limb ischaemia and claudication did not show a higher discriminatory performance (ROC-AUC, respectively 0.76, 0.75) than the BOA-RC2 (ROC-AUC 0.78). The lack of improvement in discriminatory power of the separate models is most likely caused by the fact that both researched stages of severe PAD share the same risk factors for future mortality and cardiovascular events. The BOA-RC2 showed a good calibration and discriminatory performance in the validation cohort. This emphasizes that the BOA-RC2 gives an accurate risk assessment and is appropriate for external use.

Unfortunately, follow up data on lower limb amputations, an important adverse event in patients with PAD, were missing and not included in the composite primary outcome event of the BOA-RC2. In the derivation cohort only 3% of the patients had a major amputation during 10 year follow up in addition to the 67% of patients that died, suffered a myocardial infarction, or an ischaemic stroke. Therefore, it is believed that this model would not dramatically improve with a primary outcome event that included major amputation. Further data on amputation risk can be found in previous manuscripts from the BOA study group.[4,5]

The determinants of the composite primary outcome event, such as a history of vascular intervention, most of which were performed in the legs, and critical limb ischaemia, are very specific for PAD and not just for atherosclerosis in general, such as age and diabetes. Therefore, it is believed that the BOA-RC2 remains exclusively for patients with PAD after peripheral bypass surgery despite excluding major limb amputations from the primary outcome event.

Furthermore, the larger part of the data in the derivation cohort was collected retrospectively, except for the first 2 years between 1995 and 1998, which were performed prospectively. To reduce the number of missed events to a minimum, the follow up data from 1998 to 2009 were collected in a step wise manner. It is believed that this method has proven to be effective, as the number of events recorded in the derivation cohort was very similar to the number of events recorded in the validation cohort by national registries. The long-term follow up data of the

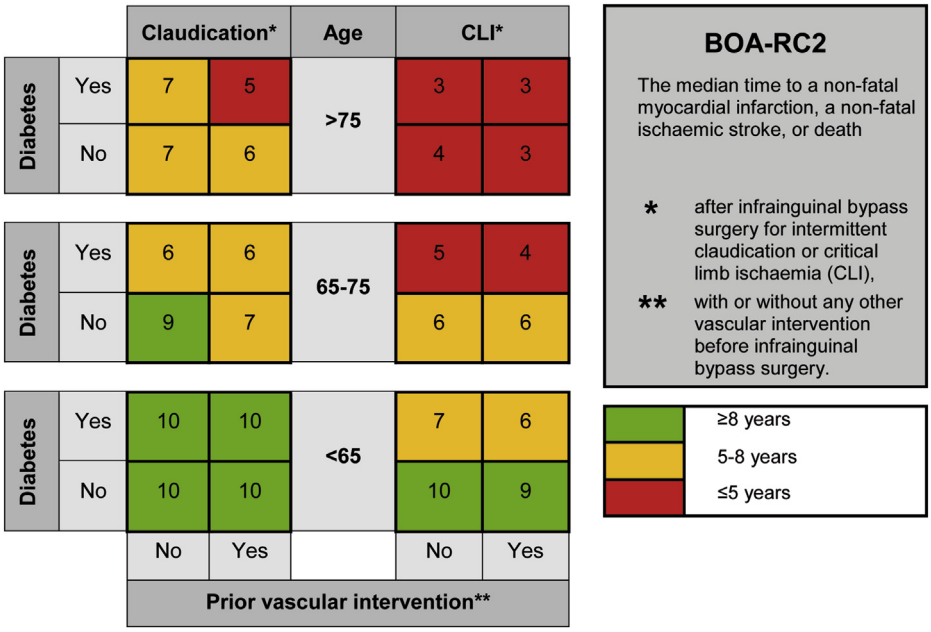

Figure 5. Observed median time to event for each combination of the four independent predictors of the patients in the validation cohort. CLI = critical limb ischaemia.

validation cohort from prospectively recorded national registries were nearly complete (96%).

Differences in patient characteristics such as ABI $\leq$0.6, diabetes, hyperlipidaemia, smoking, and venous bypass between the derivation and validation cohort were observed. These differences included one independent determinant incorporated in the BOA-RC2 (diabetes), but did not result in a difference in risk of the primary outcome event between the cohorts. Therefore, no calibration adjustment of the BOA-RC2 was required, which was confirmed by the results of the validation.

Undoubtedly, the application of secondary prevention management has improved (e.g. increased use of statins and platelet aggregation inhibition) since the onset of the BOA trial in 1995, reducing the risk of ischaemic events. Unfortunately, data on these changes in baseline medical history could not be collected, but the follow up data on ischaemic events were extended up to December 2007, with only a small percentage of missing events. In theory, these changes would reduce the BOA-RC2 calibration for the current patient, but should not affect its discriminatory performance.

For adequate risk estimation in a similar population, such as patients with PAD following endovascular interventions, validation studies of the BOA-RC2 in these populations are recommended. Furthermore, adjustment of the BOA-RC2 based on the setting of similar populations can improve the performance of the risk chart.[14]

CONCLUSION

The BOA-RC2 proves to be fit for the prediction of mortality and major ischaemic events in patients after peripheral bypass surgery. The BOA-RC2 can be applied to adequately inform the patient of his/her risk of future events in an illustrative manner and stress the necessity of preventative measures, such as lifestyle adjustments (e.g. physical exercise, smoking cessation), screening for risk factors (e.g. HbA1c and cholesterol levels; cardiac and cerebrovascular evaluation), and drug treatments (statins, antiplatelet therapy and blood pressure regulation). In the future, the BOA-RC2 may be of interest to identify patients at high risk of mortality and ischaemic events for clinical research on new therapeutic options.

COMPETING INTERESTS

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ejvs.2015.04.005.

REFERENCES

1 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;**33**(Suppl. 1):S1—75.

2 Achterberg S, Cramer MJ, Kappelle LJ, de Borst GJ, Visseren FL, van der Graaf Y, et al. Patients with coronary, cerebrovascular or peripheral arterial obstructive disease differ in risk for new vascular events and mortality: the SMART study. *Eur J Cardiovasc Prev Rehabil* 2010;**17**(4):424—30.

3 Steg PG, Bhatt DL, Wilson PW, D'Agostino Sr R, Ohman EM, Röther J, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *J Am Med Assoc* 2007;**297**(11):1197—206.

4 Van Hattum ES, Tangelder MJ, Lawson JA, Moll FL, Algra A. Long-term risk of vascular events after peripheral bypass surgery. A cohort study. *Thromb Haemost* 2012;**108**(3):543—53.
5 The Dutch BOA Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000;**355**(9201):346—51.
6 van Wijk I, Kappelle LJ, van Gijn J, Koudstaal PJ, Franke CL, Vermeulen M, et al. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet* 2005;**365**(9477):2098—104.
7 De Bruin A, Kardaun J, Gast A, De Bruin E, Van Sijl M, Verweij G. Record linkage of hospital discharge register with population register: experiences at Statistics Netherlands. *Stat J UN Econ Comm Eur* 2004;**21**:23—32.
8 Paas G, Veenhuizen K. *Research on the validity of the LMR*. Utrecht, The Netherlands: Prismant; 2002.
9 Reitsma JB, Kardaun JW, Gevers E, de BA, van der WJ, Bonsel GJ. Possibilities for anonymous follow up studies of patients in Dutch national medical registrations using the Municipal Population Register: a pilot study. *Ned Tijdschr Geneeskd* 2003;**147**(46):2286—90.
10 *World Health Organization. Online ICD9/ICD9CM codes*. Retrieved 4 March, 2014 from: http://icd9.chrisendres.com.
11 Van Houwelingen JC, Le CS. Predictive value of statistical models. *Stat Med* 1990;**9**(11):1303—25.
12 Brier G. Verification of forecasts expressed in terms of probability. *Mon Wea Rev* 1950;**78**:1—3.
13 Hosmer DW, Lemeshow S. *Applied logistic regression*. New York: Wiley; 1989.
14 Debraya T, Vergouwe Y, Koffijberg H, Nieboer D, Steverberg EW, Moons KG. A new framework to enhance the interpretation of external validation studies of clinical prediction models. *J Clin Epidemiol* 2015;**68**(3):279—89.