



Vascular ultrasound for cardiovascular risk stratification in asymptomatic patients with type-2 diabetes

Angeladine Kenne Malaha, Julien Magne, Lucile Jarlan, Katia Mansour,
Melissa Ait-Ouatet, Sophie Galinat, Marie-Pierre Teissier, Philippe Lacroix,
Ileana Desormais, Victor Aboyans

► To cite this version:

Angeladine Kenne Malaha, Julien Magne, Lucile Jarlan, Katia Mansour, Melissa Ait-Ouatet, et al..
Vascular ultrasound for cardiovascular risk stratification in asymptomatic patients with type-2 dia-
betes. Primary Care Diabetes, 2021, 10.1016/j.pcd.2021.04.006 . hal-03227780

HAL Id: hal-03227780

<https://unilim.hal.science/hal-03227780>

Submitted on 2 Aug 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

VASCULAR ULTRASOUND FOR CARDIOVASCULAR RISK STRATIFICATION IN ASYMPTOMATIC PATIENTS WITH TYPE-2 DIABETES.

Angeladine KENNE MALAHA¹, Julien MAGNE^{1,2}, Lucile JARLAN², Katia
MANSOUR¹, Melissa AIT-OUATET¹, Sophie GALINAT³, Marie-Pierre TEISSIER^{1,3},
Philippe LACROIX^{1,4}, Ileana DESORMAIS^{1,4}, Victor ABOYANS^{*1,2}

1 INSERM, Univ. Limoges, CHU Limoges, IRD, U1094 Tropical Neuroepidemiology,
Institute of Epidemiology and Tropical Neurology, GEIST, Limoges, France

2 Department of Cardiology. Dupuytren University Hospital, Limoges, France

3 Department of Endocrinology, Dupuytren University Hospital, Limoges, France

4 Department of Vascular Medicine & Surgery. Dupuytren University Hospital,
Limoges, France

*Corresponding Author:

Pr. Victor Aboyans, MD, PhD, FESC

Department of Cardiology,

Dupuytren University Hospital

Limoges, France

Phone : +33 555 056 310

Mail : victor.aboyans@unilim.fr

1 **ABSTRACT**

2 Aims- To identify new independent vascular markers to predict cardiovascular events
3 in patients with type-2 diabetes (T2D), and their incremental value compared to the
4 Swedish National Diabetes Register (NDR) risk score.

5 Methods- A retrospective cohort study was conducted on 1332 asymptomatic
6 patients with T2D, free from prior CV event, assessed for a cardiovascular work-up,
7 including Duplex ultrasonography to detect plaque on carotid and femoral arteries.
8 The extent of atherosclerosis was rated as atherosclerosis burden score (ABS).

9 Patients were followed up to 5 years and the occurrence of cardiovascular events
10 recorded.

11 Results- A total of 82 patients (6.2%) experienced a cardiovascular event, including
12 34 (2.6%) myocardial infarction, 18 (1.4%) cardiac revascularisation and 17 (1.3%)
13 stroke. The independent determinants of these events were male sex (HR = 1.81
14 [1.13 – 2.88], p=0.013) and ABS ≥ 2 (HR = 1.98 [1.21–3.25], p=0.007). The NDR risk
15 score performed poorly to predict cardiovascular events (area under the curve = 0.56
16 [0.49–0.63], p=0.11), whereas screening for atherosclerotic plaques provided
17 significant incremental prognostic value over the NDR score (model χ^2 increase:
18 +231%, p=0.002).

19 Conclusion- Duplex ultrasonography to screen for atherosclerotic plaques improve
20 the estimation of cardiovascular prognosis on top of clinical data and could be
21 routinely used to improve cardiovascular risk stratification.

22 **Key words:** Type-2 diabetes; cardiovascular diseases; primary prevention;
23 atherosclerosis burden score, ultrasound, plaque, carotid, femoral.

1. INTRODUCTION

In 2017, 425 million individuals worldwide had diabetes, including 58 million in Europe [1] and most of those patients have type-2 diabetes (T2D)[2]. Type-2 diabetes and cardiovascular diseases (CVDs) develop alongside. Over half of deaths and the majority of morbidity cases in people with T2D are related to CVDs. Thus, the guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed by the European Society of Cardiology (ESC) request physicians to jointly manage these conditions [3].

According to the recent ESC guidelines [3], the choice of antidiabetic therapy strategy depends on the patient's cardiovascular risk. Several risk scores such as the Swedish National Diabetes Register (NDR) risk score have been specifically developed for patients with T2D [4,5]. ESC guidelines classify patients with subclinical atherosclerosis as at very-high risk of CVDs. Several markers issued from peripheral vascular or coronary imaging are proposed to identify subclinical atherosclerosis, but with low level of recommendation and evidence [3]. It is suggested that atherosclerosis burden score (ABS), i.e. the sum of the plaques in carotid and femoral arterial bifurcations, is better than common carotid intima-media thickness, carotid mean/maximal thickness, and carotid/femoral plaque scores for the detection of presence and extension of coronary artery disease in non-diabetic populations [6]. Vascular ultrasound is a non-invasive and harmless technique to detect subclinical atherosclerosis, but it's incremental value on top of regular risk scores for patients with T2D has been poorly assessed [6,7].

In this study, we aimed at identifying independent vascular markers to predict cardiovascular events, and assessing their incremental prognostic value over the clinical NDR score in patients with T2D.

2. METHODS

2.1. STUDY DESIGN

We retrospectively analysed the data of patients with T2D referred to our centre from January 2007 to December 2016 for cardiovascular work-up. This was an open cohort with consecutive recruitment of patients in primary prevention, i.e. free of any clinical atherosclerotic disease. Patients with a history of CVD (i.e. with clinical history of coronary, cerebrovascular or peripheral artery disease) and those with cardiovascular symptoms during assessment were excluded.

A vascular nurse collected information on sociodemographic characteristics, risk factors, anthropometrics and current medication of each patient using standardized questionnaires and checked with the patient's record. The most recent biological tests results were also collected from the electronic database of the hospital. This was followed by a standard 12-lead electrocardiogram and 4-limbs blood pressure measurements using conventional Doppler method, to determine the ankle-brachial index (ABI) [8].

Patients were then assessed by Duplex ultrasound for atherosclerotic plaques detection. [Plaques were defined as intimal calcified lesions >1 mm and/or >50% increased thickness compared to adjacent intimal wall. All echographies were performed using a Philipps® IE33 ultrasound machine \(Philipps®, Eindhoven, The Netherlands\) , using a 8-12 MHz linear vascular ultrasound probe.](#) ABS was assessed, ranging from 0 to 4 according to the number of location with plaques at the level of carotid and femoral bifurcations. Distal flows at the ankle arteries levels were also recorded. Following this initial work-up, the cardiovascular specialist was free to decide for any additional cardiovascular imaging tests or treatments if

necessary. (See Appendix A for the variables included in the study with their description)

A 5-year follow-up period was considered, with last evaluation in June 30th, 2019. The primary source of follow-up data were the patients' medical records. In absence of any information, general practitioners were contacted to collect vital status and the occurrence of any cardiovascular event including:

- Cardiovascular death
- Ischaemic or haemorrhagic stroke and transient ischaemic accident
- Acute coronary syndromes
- Cardiac revascularisation: including percutaneous coronary intervention and coronary artery bypass grafting

The primary outcome was composite of cardiovascular death and non-fatal events as afore mentioned. This outcome was consistent with those from Swedish NDR score proposed to assess the 5-year cardiovascular risk in patients with T2D (13). Our dataset had enough variables and information available to compute this score for 76% of the study participants. The risk score equation used to derived the NDR score was retrieved from previous publication [9] (see Appendix B). Deaths from non-cardiovascular causes, lost to follow-up and follow-up durations under 5 years were recorded and analysed as censored data.

2.2. STATISTICS

Characteristics of our study population were described using means \pm standard deviation and frequencies (percentages) for qualitative variables. Bivariate analyses were performed with the Chi² or Fisher exact tests where applicable for categorical variables, whereas *t* tests were used for continuous ones.

Calibration and discrimination characteristics were estimated to evaluate the ability of score to predict cardiovascular events in our population. We computed the difference between the rate of events predicted by the score and the percentage of events observed during the follow-up. Sensitivity, specificity, and receiver operating characteristic (ROC) curve were obtained and area under the curve (AUC) evaluated. We considered patients at low, intermediate and high risk of CVD events those with a risk score respectively $< 10\%$, $10-19\%$ and $\geq 20\%$.

Independent markers of cardiovascular events were assessed using Cox proportion hazard (PH) models. We plotted log-minus-log survival curves and visually inspected the proportionality of the hazard. Univariate models were performed for each independent variable. Subsequent multivariate analysis with backward stepwise models were used incorporating variables with a univariate p value < 0.20 . However, selection of variables was carefully performed to avoid collinearity. In the final model, the age variable was forced with the variables of the last step.

A final Cox PH model including NDR risk score and independent variables identified was performed to assess incremental value in term of cardiovascular events prediction. Improvement was quantified using the models' χ^2 value.

Statistical significance was set at p value < 0.05 for all analyses.

2.3. Ethical considerations

This is an observational study on a cohort of patients managed according to the standards of care at the moment of their management. According to French law on that period, no ethical committee authorization was required.

3. RESULTS

From 2007 to 2016, 1,873 patients with diabetes attended cardiovascular screening and prevention consultations for the first time. Among them 1,332 (71%) asymptomatic T2D patients in primary prevention were considered for our study as all variables for calculation of the NDR score were available. The flowchart of patients' selection is presented in Appendix C.

3.1. GENERAL CHARACTERISTICS

Baseline characteristics of the population and results of vascular explorations and further cardiac ischemic tests are given in Table 1. Overall, mean age in the study population was 59.5 ± 10.7 years and 658 patients (49.4%) were male. Based on clinical, ECG and vascular imaging data, 470 (35.3%) patients received a prescription for an ischemic stress test at the end of the visit, with 58 (14.8%) positive results. Those patients were secondarily referred for coronary angiography. The outcome of the population was relatively good (92.1 ± 0.9 % of cardiovascular event-free survival at 5 years). Over an average follow-up duration of 3.7 ± 1.7 years, the primary composite outcome occurred in 82 (6.2%) patients and mean time-to-event duration was 2 ± 1.5 years. During the overall follow-up period, the occurrence of the different cardiovascular events in the population was as follows: myocardial infarction 34 cases (2.6%), coronary revascularisation 18 cases (1.4%), stroke/transient ischemic attack 17 cases (1.3%), unstable angina, 8 cases (0.6%) and cardiovascular death 5 cases (0.4%). Patients with cardiovascular events were more frequently male ($p=0.003$), with smoking history ($p=0.048$), and with higher triglycerides levels ($p=0.004$) (Table 1).

3.2. SWEDISH NDR RISK SCORE ASSESSMENT

The average estimated 5-year risk of any cardiovascular event using the NDR risk score was $16.8 \pm 12.5\%$. Figure 1 displays calibration and discrimination of NDR risk score. Calibration analysis (A) showed that the score overestimated the risk of events, with a difference between predicted and observed percentages of events of 1%, 7% and 24% in low-, intermediate- and high-risk groups, respectively. The ROC curve displayed a non-significant area under the curve of 0.561 [0.489 – 0.633], $p=0.11$ (B). The most accurate risk cut-off value was identified at 15% but was associated with limited sensitivity and specificity (52.4% and 55.5% respectively) (C).

3.3. INDEPENDENT MARKERS OF CARDIOVASCULAR EVENTS.

The cox regression models are presented in Table 2. Variables identified as independent markers of cardiovascular events were male sex and an $ABS \geq 2$. Figure 2 shows the outcomes of the patients according to sex and ABS score. Cox proportional-hazard models were used to evaluate the prediction of cardiovascular events by the NDR risk score when used alone or associated to the atheroma plaque screening. Figure 3 displays the χ^2 of those models that were all significant ($p<0.01$) and suggests that considering the presence of atheroma plaques is significant to predict cardiovascular events in T2D patients. In fact, it improved the NDR prediction model by 231% ($p=0.002$).

4. DISCUSSION

Our study reveals that in patients with T2D in primary prevention and managed with a dedicated cardiovascular work up: (1) the outcome of the population is relatively good, (2) a risk score merely based on clinical data has poor ability to predict CV

outcomes, (3) atherosclerosis burden (i.e. carotid and femoral atherosclerosis) is a strong determinant of cardiovascular events, and (4) it provides incremental prognostic value over a clinical score (here the Swedish NDR score).

The 5-year occurrence of cardiovascular events is 6.2% in the present series and is lower than the rates reported in a previous study from our country. Indeed, Sosner et al. reported a rate of 19.3% for major adverse cardiovascular events over a 65 month follow-up period [10]. This marked difference may be in part explained by difference in inclusion/non-inclusion criteria between that study and ours. Of note, they included patients who already had clinical history of CVD, and excluded those with a T2D history of less than 2 years. However, patients with previous CVD are already at very high risk and should benefit from optimal preventive measures. In this regard, we focused on patients free of disease in order to assess the interest of screening for subclinical atherosclerotic disease. In addition, exclusion of patients with T2D history of less than 2 years could be seen as arbitrary and this disease is known to be often already present for long before being diagnosed [3].

Atheroma plaques were present in more than half (55.7%) of our study population with carotid plaques present in 42.2% and femoral plaques in 43.4% of patients; almost one out of 4 patients (28.7%) had both carotid and femoral plaques. A study by De Kreutzenberg et al., in the T2D population identified very high rates of carotid plaques (81.8%) and demonstrated a strong relationship between the presence of plaque and the occurrence of major adverse cardiovascular events. Furthermore, they found a graded relationship between increased plaque calcification and reduced event-free survival [11]. Shore et al. also demonstrated that in patients with T2D and no manifest CVD, the presence and severity of carotid plaque were the most significant risk factor of further cardiovascular events [12].

It is generally accepted that the usual risk scores (e.g. the European SCORE) are not well adapted for the diabetic population, and several attempts have been made to propose specific scores for this population [9,13–15]. A study by Leeuw et al. evaluated cardiovascular risk scores in the T2D population. They found that some models are designed for the prediction of cardiovascular diseases, whereas others are specifically made to predict coronary heart diseases. Additionally, the target time of risk evaluation varies; most models predict a 5-year risk, whereas few predict a 10-year risk or a 4-year risk [5]. Some scores were designed decades ago, so do not take into account recent advances in risk management [5] and require updating. We selected *a posteriori* the Swedish NDR score as we had all the variables needed to estimate the risk in most patients of our database. Although the Swedish NDR score presented excellent calibration and discrimination characteristics within the original population, those indicators appeared to be quite poor in our study with an overestimation of the patients' risk. These results are consistent with those of previous studies found in the literature, where generally, external validation of scores in diabetic patients presented deceiving results [5,16,17]. This stems mainly from the differences in the designs of derivation and validation studies, inclusion criteria, methods of variables definition / collection and, definition / collection of the outcomes, leading to the use of proxies, which, despite sensitivity analyses and approvals, are not reliable.

ABS improved the prognostic prediction on top of the NDR score. Even though evidence in the literature has demonstrated the importance of subclinical atherosclerosis in patients' risk management as well as in the prediction of cardiovascular outcomes, no study had evaluated their benefit over the classical risk

assessment tools yet. Moreover, we did not find any study taking into consideration that factor in their prediction models or in a final risk equation.

Identifying markers of cardiovascular events in T2D population is of great importance in clinical practice. It offers practitioners simple and accessible features to estimate for better management of their patients. The ABS derives from vascular ultrasonography, a non-invasive and painless test. It is cheap, easy and rapid enough to be performed in routine as compared to non-contrast-enhanced computed tomography that is a radiant and heavy investigation to measure coronary artery calcification. In fact, in the Progression of Early Subclinical Atherosclerosis study (PESA) study, Fernandez-Friera et al., found that among study participants with no coronary artery calcification, nearly 60% had plaques at other vascular sites [18]. Additionally, a recent study by Katakami et al. on 3,263 participants recommended to add carotid ultrasonography measures to conventional risk factors while evaluating cardiovascular risk [19]. Hence, the identification of plaques at the carotid and/or femoral level enables to identify a subgroup of diabetic patients at higher risk than initially supposed, with need for intensified therapies as suggested recently by the ESC guidelines [3].

Our study has some limitations. First, we only studied one risk score, i.e. the NDR risk score, due to the availability of all variables for its calculation. However, the aim of our study was not a validation or comparison of different risk scores, but rather, to define the incremental value of plaque identification on top of a clinical risk score. Further investigations may be needed to develop and validate new risk stratification strategies considering plaque screening. Another limitation is inherent to the in-clinic nature of the study as the physicians were free to adjust treatments and decide coronary screening strategies following the assessment, and we cannot rule out the

possibility that the presence of carotid/femoral plaques would have led to intensified screening strategies and preventive measures. If so, our results are rather conservative. We did not find ABI as a predictive marker of cardiovascular events in our study, which contrasts with other reports [20,21]. While the ABI is recognized as valid predictive marker of cardiovascular events in the general population [8], its poorer sensitivity and specificity among patients with diabetes may be explained by a poorer ability of ABI to identify atherosclerosis[22].

5. CONCLUSION

Our study shows that carotid and femoral plaques identified by vascular ultrasound have an incremental predictive value to identify patients with T2D at higher risk of cardiovascular events. Whereas Swedish NDR score depicted limited prognosis performance in our series, the ABS score improves risk stratification. Consequently, screening for subclinical atherosclerosis with carotid/femoral ultrasound imaging and ABS score could be implemented in the routine management of T2D patients in primary prevention. Randomized trials are necessary to compare different preventive strategies after the identification of a high burden of atherosclerosis in these patients.

Availability of data and materials

Datasets analysed during the current study are available from the corresponding author upon request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interest

262 AKM – none
263 JM – none
264 LJ – none
265 KM – none
266 MAO – none
267 SG – none
268 MPT – none
269 PL – none
270 ID - none
271 VA – Amgen, Bayer, BMS/Pfizer alliance, Boehringer Ingelheim.

272 **Authors' contributions**

273 VA and JM designed and coordinated the study. SG, MPT, ID, PL and VA conducted
274 patients' consultations and examinations. AKM, LJ, KM and MAO collected data.
275 AKM and JM performed statistical analyses and drafted the manuscript. All the
276 authors revised and have approved the final version of the manuscript.

- 278 [1] International Diabetes Federation., IDF Diabetes Atlas, 8th ed., International
279 Diabetes Federation, Brussels, Belgium, 2017.
- 280 [2] G. Roglic, World Health Organization, eds., Global report on diabetes, World
281 Health Organization, Geneva, Switzerland, 2016.
- 282 [3] F. Cosentino, P.J. Grant, V. Aboyans, C.J. Bailey, A. Ceriello, V. Delgado, M.
283 Federici, G. Filippatos, D.E. Grobbee, T.B. Hansen, H.V. Huikuri, I. Johansson,
284 P. Jüni, M. Lettino, N. Marx, L.G. Mellbin, C.J. Östgren, B. Rocca, M. Roffi, N.
285 Sattar, P.M. Seferović, M. Sousa-Uva, P. Valensi, D.C. Wheeler, ESC Scientific
286 Document Group, 2019 ESC Guidelines on diabetes, pre-diabetes, and
287 cardiovascular diseases developed in collaboration with the EASD, *Eur. Heart J.*
288 41 (2020) 255–323. <https://doi.org/10.1093/eurheartj/ehz486>.
- 289 [4] S. van Dieren, J.W.J. Beulens, A.P. Kengne, L.M. Peelen, G.E.H.M. Rutten, M.
290 Woodward, Y.T. van der Schouw, K.G.M. Moons, Prediction models for the risk
291 of cardiovascular disease in patients with type 2 diabetes: a systematic review,
292 *Heart.* 98 (2012) 360–369. <https://doi.org/10.1136/heartjnl-2011-300734>.
- 293 [5] J. van der Leeuw, S. van Dieren, J.W.J. Beulens, H. Boeing, A.M.W.
294 Spijkerman, Y. van der Graaf, D.L. van der A, U. Nöthlings, F.L.J. Visseren,
295 G.E.H.M. Rutten, K.G.M. Moons, Y.T. van der Schouw, L.M. Peelen, The
296 validation of cardiovascular risk scores for patients with type 2 diabetes mellitus,
297 *Heart.* 101 (2015) 222–229. <https://doi.org/10.1136/heartjnl-2014-306068>.
- 298 [6] P. Yerly, P. Marquès-Vidal, R. Owlya, E. Eeckhout, L. Kappenberger, R. Darioli,
299 M. Depairon, The Atherosclerosis Burden Score (ABS): a Convenient
300 Ultrasound-Based Score of Peripheral Atherosclerosis for Coronary Artery
301 Disease Prediction, *J Cardiovasc. Transl. Res.* 8 (2015) 138–147.
302 <https://doi.org/10.1007/s12265-015-9617-5>.
- 303 [7] N. Katakami, M. Takahara, H. Kaneto, K. Sakamoto, K. Yoshiuchi, Y. Irie, F.
304 Kubo, T. Katsura, Y. Yamasaki, K. Kosugi, I. Shimomura, Ultrasonic tissue
305 characterization of carotid plaque improves the prediction of cardiovascular
306 events in diabetic patients: a pilot study, *Diabetes Care.* 35 (2012) 2640–2646.
307 <https://doi.org/10.2337/dc12-0331>.
- 308 [8] V. Aboyans, M.H. Criqui, P. Abraham, M.A. Allison, M.A. Creager, C. Diehm,
309 F.G.R. Fowkes, W.R. Hiatt, B. Jönsson, P. Lacroix, B. Marin, M.M. McDermott,
310 L. Norgren, R.L. Pande, P.-M. Preux, H.E.J. Stoffers, D. Treat-Jacobson,
311 American Heart Association Council on Peripheral Vascular Disease, Council
312 on Epidemiology and Prevention, Council on Clinical Cardiology, Council on
313 Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention,
314 and Council on Cardiovascular Surgery and Anesthesia, Measurement and
315 interpretation of the ankle-brachial index: a scientific statement from the
316 American Heart Association, *Circulation.* 126 (2012) 2890–2909.
317 <https://doi.org/10.1161/CIR.0b013e318276fbcf>.
- 318 [9] J. Cederholm, K. Eeg-Olofsson, B. Eliasson, B. Zethelius, P.M. Nilsson, S.
319 Gudbjörnsdóttir, Swedish National Diabetes Register, Risk prediction of
320 cardiovascular disease in type 2 diabetes: a risk equation from the Swedish
321 National Diabetes Register, *Diabetes Care.* 31 (2008) 2038–2043.
322 <https://doi.org/10.2337/dc08-0662>.
- 323 [10] P. Sosner, C. Hulin-Delmotte, P.-J. Saulnier, S. Cabasson, E. Gand, F.
324 Torremocha, X. Piguel, A. Miot, R. Maréchaud, D. Herpin, S. Ragot, S. Hadjadj,

- SURDIAGENE Study Group, Cardiovascular prognosis in patients with type 2 diabetes: contribution of heart and kidney subclinical damage, *Am. Heart J.* 169 (2015) 108–114.e7. <https://doi.org/10.1016/j.ahj.2014.09.012>.
- [11] S.V. De Kreutzenberg, G.P. Fadini, S. Guzzinati, M. Mazzucato, A. Volpi, A. Coracina, A. Avogaro, Carotid plaque calcification predicts future cardiovascular events in type 2 diabetes, *Diabetes Care.* 38 (2015) 1937–1944. <https://doi.org/10.2337/dc15-0327>.
- [12] A.C. Shore, H.M. Colhoun, A. Natali, C. Palombo, F. Khan, G. Östling, K. Aizawa, C. Kennbäck, F. Casanova, M. Persson, K. Gooding, P.E. Gates, H. Looker, F. Dove, J. Belch, S. Pinnola, E. Venturi, M. Kozakova, I. Goncalves, J. Kravic, H. Björkbacka, J. Nilsson, SUMMIT Consortium, Use of Vascular Assessments and Novel Biomarkers to Predict Cardiovascular Events in Type 2 Diabetes: The SUMMIT VIP Study, *Diabetes Care.* 41 (2018) 2212–2219. <https://doi.org/10.2337/dc18-0185>.
- [13] A.P. Kengne, A. Patel, M. Marre, F. Travert, M. Lievre, S. Zoungas, J. Chalmers, S. Colagiuri, D.E. Grobbee, P. Hamet, S. Heller, B. Neal, M. Woodward, ADVANCE Collaborative Group, Contemporary model for cardiovascular risk prediction in people with type 2 diabetes, *Eur. J. Cardiovasc. Prev. Rehabil. Off. J. Eur. Soc. Cardiol. Work. Groups Epidemiol. Prev. Card. Rehabil. Exerc. Physiol.* 18 (2011) 393–398. <https://doi.org/10.1177/1741826710394270>.
- [14] R.J. Stevens, V. Kothari, A.I. Adler, I.M. Stratton, R.R. Holman, The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56), *Clin. Sci.* 101 (2001) 671–679. <https://doi.org/10.1042/cs1010671>.
- [15] W.A. Davis, M.W. Knuiman, T.M.E. Davis, An Australian cardiovascular risk equation for type 2 diabetes: the Fremantle Diabetes Study, *Intern. Med. J.* 40 (2010) 286–292. <https://doi.org/10.1111/j.1445-5994.2009.01958.x>.
- [16] A.P. Kengne, A. Patel, S. Colagiuri, S. Heller, P. Hamet, M. Marre, C.Y. Pan, S. Zoungas, D.E. Grobbee, B. Neal, J. Chalmers, M. Woodward, for the ADVANCE Collaborative Group, The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) Study, *Diabetologia.* 53 (2010) 821–831. <https://doi.org/10.1007/s00125-010-1681-4>.
- [17] S.H. Read, M. van Diepen, H.M. Colhoun, N. Halbesma, R.S. Lindsay, J.A. McKnight, D.A. McAllister, E.R. Pearson, J.R. Petrie, S. Philip, N. Sattar, M. Woodward, S.H. Wild, Scottish Diabetes Research Network Epidemiology Group, Performance of Cardiovascular Disease Risk Scores in People Diagnosed With Type 2 Diabetes: External Validation Using Data From the National Scottish Diabetes Register, *Diabetes Care.* 41 (2018) 2010–2018. <https://doi.org/10.2337/dc18-0578>.
- [18] L. Fernández-Friera, J.L. Peñalvo, A. Fernández-Ortiz, B. Ibañez, B. López-Melgar, M. Laclaustra, B. Oliva, A. Mocoroa, J. Mendiguren, V. Martínez de Vega, L. García, J. Molina, J. Sánchez-González, G. Guzmán, J.C. Alonso-Farto, E. Guallar, F. Civeira, H. Sillesen, S. Pocock, J.M. Ordovás, G. Sanz, L.J. Jiménez-Borreguero, V. Fuster, Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study, *Circulation.*

- 131 (2015) 2104–2113.
<https://doi.org/10.1161/CIRCULATIONAHA.114.014310>.
- [19] N. Katakami, T. Mita, M. Gosho, M. Takahara, Y. Irie, T. Yasuda, T.-A. Matsuoka, T. Osonoi, H. Watada, I. Shimomura, Clinical Utility of Carotid Ultrasonography in the Prediction of Cardiovascular Events in Patients with Diabetes: A Combined Analysis of Data Obtained in Five Longitudinal Studies, *J. Atheroscler. Thromb.* 25 (2018) 1053–1066. <https://doi.org/10.5551/jat.43141>.
- [20] S. Hyun, N.I. Forbang, M.A. Allison, J.O. Denenberg, M.H. Criqui, J.H. Ix, Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus, *J. Vasc. Surg.* 60 (2014) 390–395. <https://doi.org/10.1016/j.jvs.2014.02.008>.
- [21] V. Aboyans, P. Lacroix, M.-H. Tran, C. Salamagne, S. Galinat, F. Archambeaud, M.H. Criqui, M. Laskar, The prognosis of diabetic patients with high ankle-brachial index depends on the coexistence of occlusive peripheral artery disease, *J. Vasc. Surg.* 53 (2011) 984–991. <https://doi.org/10.1016/j.jvs.2010.10.054>.
- [22] A.F. AbuRahma, E. Adams, J. AbuRahma, L.A. Mata, L.S. Dean, C. Caron, J. Sloan, Critical analysis and limitations of resting ankle-brachial index in the diagnosis of symptomatic peripheral arterial disease patients and the role of diabetes mellitus and chronic kidney disease, *J. Vasc. Surg.* 71 (2020) 937–945. <https://doi.org/10.1016/j.jvs.2019.05.050>.

395 **Table 1:** Baseline characteristics of the study population and vascular explorations
396 findings.

Variables	Whole cohort (n=1,332)	No CVD event (n=1,250, 93.8%)	CVD events (n=82, 6.2%)	p value
Demographics and clinical data				
Age, years	59.5±10.7	59.4±10.7	61.3±10.5	0.11
Male sex, n (%)	658 (49.4)	604 (48.3)	54 (65.9)	0.003
BMI, kg/m ²	32.4±7.4	32.5±7.6	31.2±5.3	0.14
SBP, mmHg	135±18	134±18	136±18	0.51
DBP, mmHg	74±10	74±10	73±9	0.31
Pulse pressure, mmHg	61±14	61±14	65±15	0.06
Atrial fibrillation, n (%)	32 (2.4)	28 (2.2)	4 (4.9)	0.13
Risk factors				
Diabetes duration, years	9.1±8.5	9.0±8.4	10.1±9.2	0.30
Smoking status, n (%)				
Non-smokers	629 (47.7)	601 (48.5)	28 (34.6)	0.048
Current smokers	271 (20.5)	249 (20.1)	22 (27.2)	
Past smokers	420 (31.8)	389 (31.4)	31 (38.3)	
Treated hypertension, n (%)	829 (62.5)	773 (62.1)	56 (69.1)	0.24
Diabetic retinopathy, n (%)	86 (12.6)	80 (12.5)	6 (13.6)	0.83
Family history of CVD, n (%)	319 (25.6)	301 (25.7)	18 (22.8)	0.56
Biology				
HbA1c, n (%)				
< 6.5	225 (20.2)	213 (20.1)	12 (22.2)	0.58
6.5 – 8.9	611 (54.8)	585 (55.2)	26 (48.1)	
≥ 9.0	278 (25.0)	262 (24.7)	16 (29.6)	
e-GFR, mg/L/1.73m ²	107±128	109±135	91±28	0.30
Total cholesterol, mg/L	1.83±0.45	1.83±0.45	1.94±0.47	0.07
HDL cholesterol, mg/L	0.46±0.14	0.46±0.14	0.45±0.20	0.54
LDL cholesterol, mg/L	1.03±0.36	1.03±0.36	1.11±0.38	0.10
Triglycerides, mg/L	1.73±1.07	1.71±1.05	2.11±1.37	0.004

Treatments

Lipid lowering drugs, n (%)	850 (66.3)	792 (65.8)	58 (72.5)	0.22
Antihypertensive drugs, n (%)	876 (68.3)	818 (68.0)	58 (72.5)	0.40
Antithrombotic agents, n (%)	329 (25.6)	300 (24.9)	29 (36.3)	0.03

Vascular explorations

Ankle brachial index, n (%)				
≤ 0.89	84 (6.5)	77 (6.3)	7 (8.6)	0.71
0.90 – 1.39	1024 (79.0)	962 (79.2)	62 (76.5)	
≥ 1.40 or not compressible	188 (14.5)	176 (14.5)	12 (14.8)	
Carotid plaque, n (%)				
Absent	765 (57.8)	729 (58.7)	36 (43.9)	0.001
Unilateral	174 (13.1)	167 (13.4)	7 (8.5)	
Bilateral	385 (29.1)	346 (27.9)	39 (47.6)	
Femoral vessels plaque, n (%)				
Absent	729 (56.6)	692 (57.2)	37 (46.8)	0.059
Unilateral	129 (10.0)	123 (10.2)	6 (7.6)	
Bilateral	430 (33.4)	394 (32.6)	36 (45.6)	
Plaque territory, n (%)				
None	588 (44.3)	562 (45.2)	26 (31.7)	0.06
Femoral only	179 (13.5)	169 (13.6)	10 (12.2)	
Carotid only	179 (13.5)	165 (13.3)	14 (17.1)	
Both femoral and carotid	380 (28.7)	348 (28.0)	32 (39.0)	
ABS, n (%)				
0 or 1	735 (55.4)	707 (56.8)	28 (34.1)	<0.001
2 or more	591 (44.6)	537 (43.2)	54 (65.9)	
Abnormal distal flows, n (%)	106 (8.7)	102 (8.9)	4 (5.3)	0.27

Ischaemia testing

Ischaemia test prescribed, n (%)	470 (35.3)	422 (33.8)	48 (58.5)	<0.001
Abnormal test result, n (%)	58 (14.8)	41 (11.7)	17 (40.5)	<0.001

397 ABS: atherosclerosis burden score; BMI: body mass index; CVD: cardiovascular
398 diseases; DBP: diastolic blood pressure; e-GFR: estimated glomerular filtration rate;
399 HBA1c: glycated haemoglobin; SBP: systolic blood pressure;

400 **Table 2:** Cox proportional hazard model to predict cardiovascular events.

Variables	N	uHR [95% CI]	mHR [95% CI]	<i>p</i> value
Age, per 10 years	1,332	1.20 [0.97 – 1.48]	1.08 [0.86 – 1.36]	0.49
Male sex	1,332	2.04 [1.29 – 3.22]	1.81 [1.13 – 2.88]	0.01
BMI, per kg/m ²	1,332	0.97 [0.94 – 1.01]	-	-
Atrial fibrillation	1,332	2.13 [0.78 – 5.82]	-	-
Pulse pressure, per 10 mmHg	1,293	1.15 [0.995 – 1.34]	-	-
Diabetes duration, per 10 years	1,254	1.12 [0.87 – 1.43]	-	-
Smoking status ever	1,320	1.67 [1.06 – 2.65]	-	-
ABS ≥2	1,326	2.35 [1.49 – 3.72]	1.98 [1.21 – 3.25]	0.007

401 Hazard ratio in univariate (uHR) and multivariate (mHR) models. ABS:
 402 atherosclerosis burden score: BMI: body mass index

403 **FIGURE CAPTIONS**

404 Figure 1: Swedish national diabetes risk score characteristics.

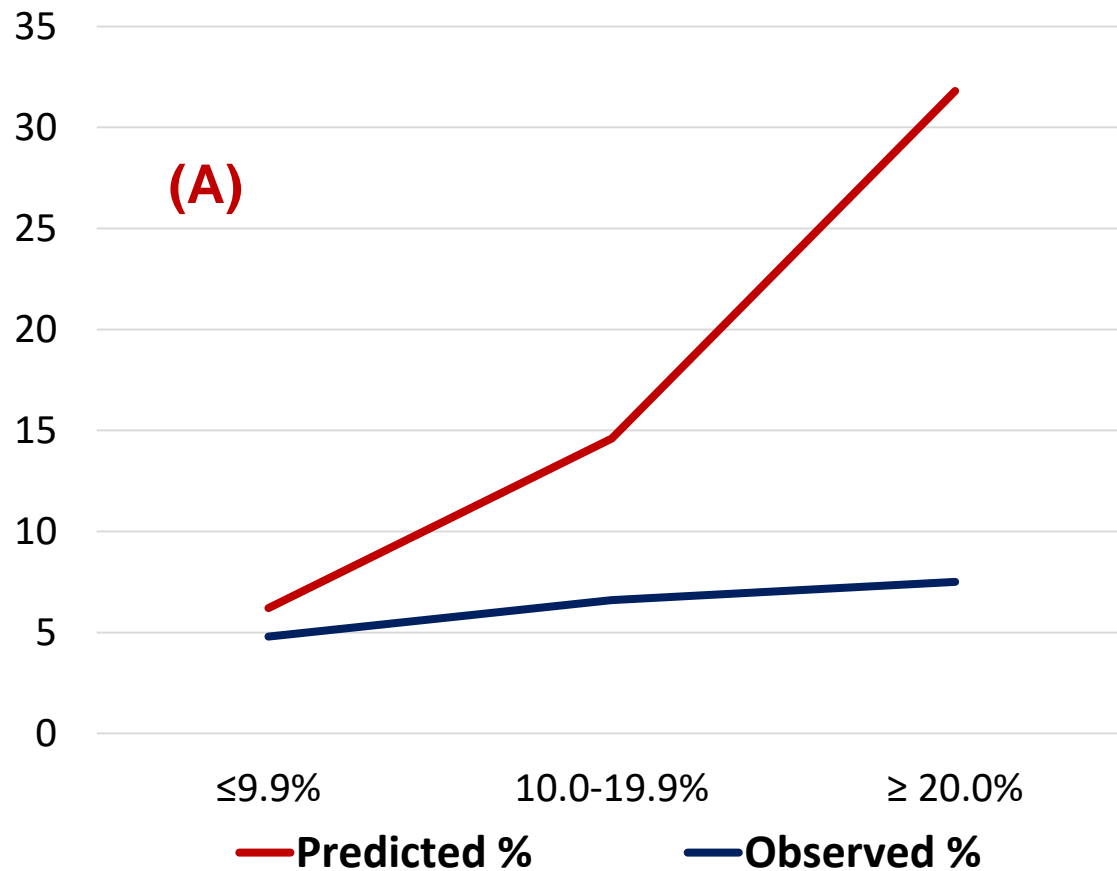
405 A) Calibration: predicted and observed cardiovascular events

406 B) Discrimination: prediction of cardiovascular events

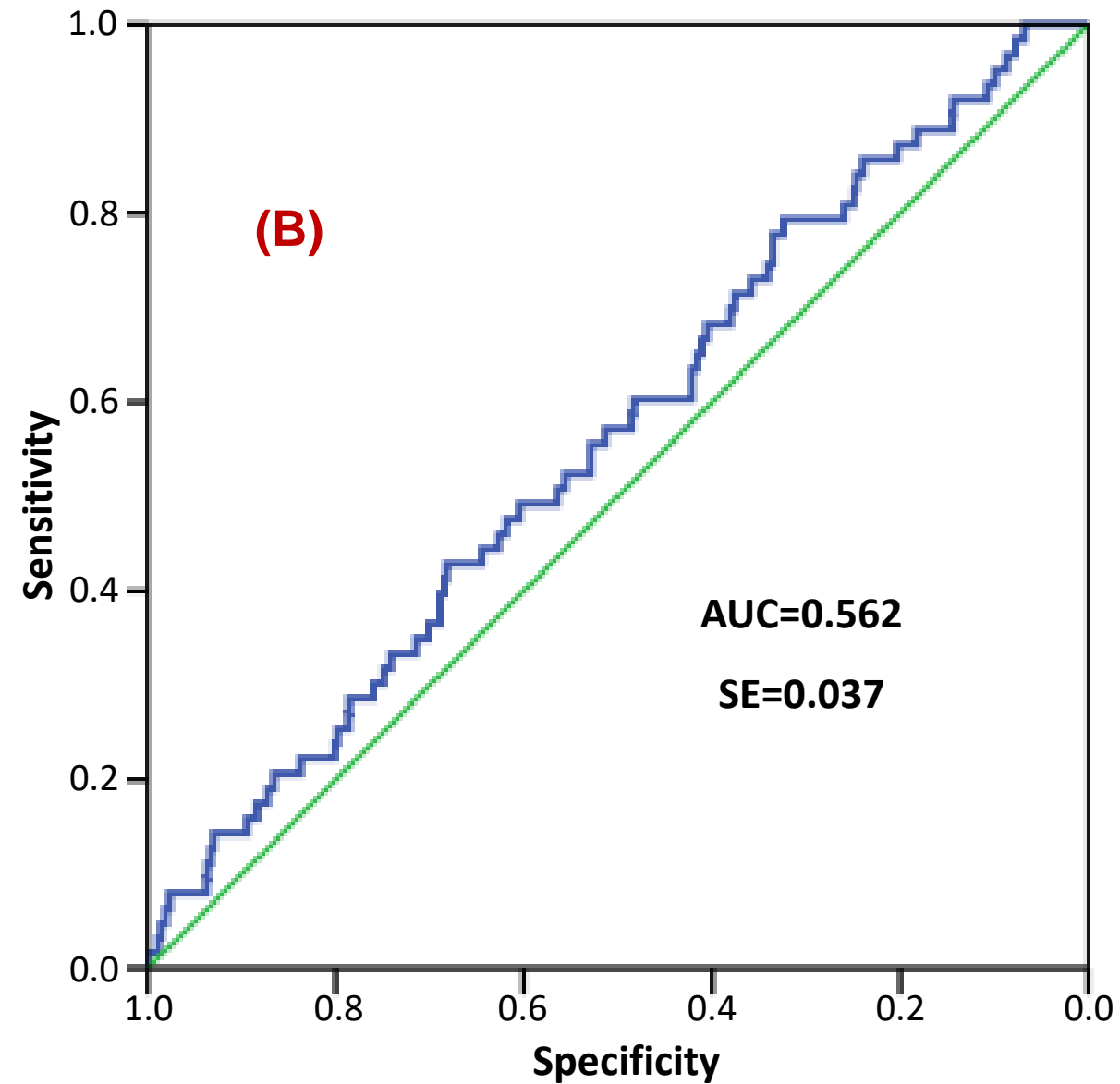
407 C) Discrimination: patient's classification performances

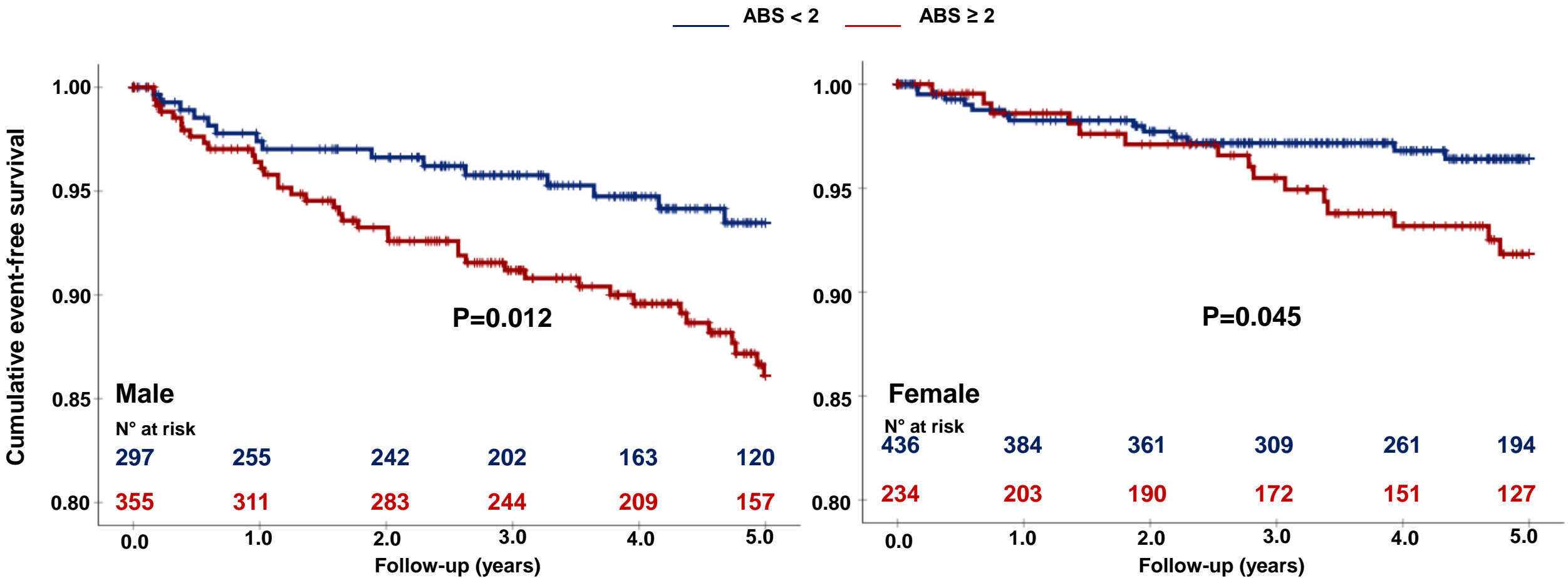
408 Figure 2: Outcomes of the patients according to gender and ABS score.

409 Figure 3: Improvement of risk prediction with vascular ultrasonography



Risk cut-offs	Sensitivity	Specificity
$\geq 5\%$	0.921	0.132
$\geq 10\%$	0.714	0.373
$\geq 15\%$	0.524	0.555
$\geq 20\%$	0.365	0.701





Cox proportional hazard model's χ^2

