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

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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.

24

1. INTRODUCTION

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

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

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

49

2. METHODS

50

2.1. STUDY DESIGN

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

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

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

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

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

- 79 – Cardiovascular death
- 80 – Ischaemic or haemorrhagic stroke and transient ischaemic accident
- 81 – Acute coronary syndromes
- 82 – Cardiac revascularisation: including percutaneous coronary intervention and
83 coronary artery bypass grafting

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

92 **2.2. STATISTICS**

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

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

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

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

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

115 **2.3. Ethical considerations**

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

119 **3. RESULTS**

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

125 **3.1. GENERAL CHARACTERISTICS**

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

142 **3.2. SWEDISH NDR RISK SCORE ASSESSMENT**

143 The average estimated 5-year risk of any cardiovascular event using the NDR risk
144 score was $16.8 \pm 12.5\%$. Figure 1 displays calibration and discrimination of NDR risk
145 score. Calibration analysis (A) showed that the score overestimated the risk of
146 events, with a difference between predicted and observed percentages of events of
147 1%, 7% and 24% in low-, intermediate- and high-risk groups, respectively. The ROC
148 curve displayed a non-significant area under the curve of 0.561 [0.489 – 0.633],
149 $p=0.11$ (B). The most accurate risk cut-off value was identified at 15% but was
150 associated with limited sensitivity and specificity (52.4% and 55.5% respectively) (C).

151 **3.3. INDEPENDENT MARKERS OF CARDIOVASCULAR EVENTS.**

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

161 **4. DISCUSSION**

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

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

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

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

190 It is generally accepted that the usual risk scores (e.g. the European SCORE) are
191 not well adapted for the diabetic population, and several attempts have been made
192 to propose specific scores for this population [9,13–15]. A study by Leeuw et al.
193 evaluated cardiovascular risk scores in the T2D population. They found that some
194 models are designed for the prediction of cardiovascular diseases, whereas others
195 are specifically made to predict coronary heart diseases. Additionally, the target time
196 of risk evaluation varies; most models predict a 5-year risk, whereas few predict a
197 10-year risk or a 4-year risk [5]. Some scores were designed decades ago, so do not
198 take into account recent advances in risk management [5] and require updating. We
199 selected *a posteriori* the Swedish NDR score as we had all the variables needed to
200 estimate the risk in most patients of our database. Although the Swedish NDR score
201 presented excellent calibration and discrimination characteristics within the original
202 population, those indicators appeared to be quite poor in our study with an
203 overestimation of the patients' risk. These results are consistent with those of
204 previous studies found in the literature, where generally, external validation of scores
205 in diabetic patients presented deceiving results [5,16,17]. This stems mainly from the
206 differences in the designs of derivation and validation studies, inclusion criteria,
207 methods of variables definition / collection and, definition / collection of the
208 outcomes, leading to the use of proxies, which, despite sensitivity analyses and
209 approvals, are not reliable.

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

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

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

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

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

246 **5. CONCLUSION**

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

255 **Availability of data and materials**

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

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261 **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
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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,

- 325 SURDIAGENE Study Group, Cardiovascular prognosis in patients with type 2
326 diabetes: contribution of heart and kidney subclinical damage, *Am. Heart J.* 169
327 (2015) 108-114.e7. <https://doi.org/10.1016/j.ahj.2014.09.012>.
- 328 [11] S.V. De Kreutzenberg, G.P. Fadini, S. Guzzinati, M. Mazzucato, A. Volpi, A.
329 Coracina, A. Avogaro, Carotid plaque calcification predicts future cardiovascular
330 events in type 2 diabetes, *Diabetes Care.* 38 (2015) 1937–1944.
331 <https://doi.org/10.2337/dc15-0327>.
- 332 [12] A.C. Shore, H.M. Colhoun, A. Natali, C. Palombo, F. Khan, G. Östling, K.
333 Aizawa, C. Kennbäck, F. Casanova, M. Persson, K. Gooding, P.E. Gates, H.
334 Looker, F. Dove, J. Belch, S. Pinnola, E. Venturi, M. Kozakova, I. Goncalves, J.
335 Kravic, H. Björkbacka, J. Nilsson, SUMMIT Consortium, Use of Vascular
336 Assessments and Novel Biomarkers to Predict Cardiovascular Events in Type 2
337 Diabetes: The SUMMIT VIP Study, *Diabetes Care.* 41 (2018) 2212–2219.
338 <https://doi.org/10.2337/dc18-0185>.
- 339 [13] A.P. Kengne, A. Patel, M. Marre, F. Travert, M. Lievre, S. Zoungas, J.
340 Chalmers, S. Colagiuri, D.E. Grobbee, P. Hamet, S. Heller, B. Neal, M.
341 Woodward, ADVANCE Collaborative Group, Contemporary model for
342 cardiovascular risk prediction in people with type 2 diabetes, *Eur. J. Cardiovasc.*
343 *Prev. Rehabil. Off. J. Eur. Soc. Cardiol. Work. Groups Epidemiol. Prev. Card.*
344 *Rehabil. Exerc. Physiol.* 18 (2011) 393–398.
345 <https://doi.org/10.1177/1741826710394270>.
- 346 [14] R.J. Stevens, V. Kothari, A.I. Adler, I.M. Stratton, R.R. Holman, The UKPDS risk
347 engine: a model for the risk of coronary heart disease in Type II diabetes
348 (UKPDS 56), *Clin. Sci.* 101 (2001) 671–679. <https://doi.org/10.1042/cs1010671>.
- 349 [15] W.A. Davis, M.W. Knuiman, T.M.E. Davis, An Australian cardiovascular risk
350 equation for type 2 diabetes: the Fremantle Diabetes Study, *Intern. Med. J.* 40
351 (2010) 286–292. <https://doi.org/10.1111/j.1445-5994.2009.01958.x>.
- 352 [16] A.P. Kengne, A. Patel, S. Colagiuri, S. Heller, P. Hamet, M. Marre, C.Y. Pan, S.
353 Zoungas, D.E. Grobbee, B. Neal, J. Chalmers, M. Woodward, for the
354 ADVANCE Collaborative Group, The Framingham and UK Prospective
355 Diabetes Study (UKPDS) risk equations do not reliably estimate the probability
356 of cardiovascular events in a large ethnically diverse sample of patients with
357 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-
358 MR Controlled Evaluation (ADVANCE) Study, *Diabetologia.* 53 (2010) 821–831.
359 <https://doi.org/10.1007/s00125-010-1681-4>.
- 360 [17] S.H. Read, M. van Diepen, H.M. Colhoun, N. Halbesma, R.S. Lindsay, J.A.
361 McKnight, D.A. McAllister, E.R. Pearson, J.R. Petrie, S. Philip, N. Sattar, M.
362 Woodward, S.H. Wild, Scottish Diabetes Research Network Epidemiology
363 Group, Performance of Cardiovascular Disease Risk Scores in People
364 Diagnosed With Type 2 Diabetes: External Validation Using Data From the
365 National Scottish Diabetes Register, *Diabetes Care.* 41 (2018) 2010–2018.
366 <https://doi.org/10.2337/dc18-0578>.
- 367 [18] L. Fernández-Friera, J.L. Peñalvo, A. Fernández-Ortiz, B. Ibañez, B. López-
368 Melgar, M. Laclaustra, B. Oliva, A. Moco-roa, J. Mendiguren, V. Martínez de
369 Vega, L. García, J. Molina, J. Sánchez-González, G. Guzmán, J.C. Alonso-
370 Farto, E. Guallar, F. Civeira, H. Sillesen, S. Pocock, J.M. Ordovás, G. Sanz, L.J.
371 Jiménez-Borreguero, V. Fuster, Prevalence, Vascular Distribution, and
372 Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort:
373 The PESA (Progression of Early Subclinical Atherosclerosis) Study, *Circulation.*

- 374 131 (2015) 2104–2113.
375 <https://doi.org/10.1161/CIRCULATIONAHA.114.014310>.
- 376 [19] N. Katakami, T. Mita, M. Gosho, M. Takahara, Y. Irie, T. Yasuda, T.-A.
377 Matsuoka, T. Osonoi, H. Watada, I. Shimomura, Clinical Utility of Carotid
378 Ultrasonography in the Prediction of Cardiovascular Events in Patients with
379 Diabetes: A Combined Analysis of Data Obtained in Five Longitudinal Studies,
380 *J. Atheroscler. Thromb.* 25 (2018) 1053–1066. <https://doi.org/10.5551/jat.43141>.
- 381 [20] S. Hyun, N.I. Forbang, M.A. Allison, J.O. Denenberg, M.H. Criqui, J.H. Ix, Ankle-
382 brachial index, toe-brachial index, and cardiovascular mortality in persons with
383 and without diabetes mellitus, *J. Vasc. Surg.* 60 (2014) 390–395.
384 <https://doi.org/10.1016/j.jvs.2014.02.008>.
- 385 [21] V. Aboyans, P. Lacroix, M.-H. Tran, C. Salamagne, S. Galinat, F.
386 Archambeaud, M.H. Criqui, M. Laskar, The prognosis of diabetic patients with
387 high ankle-brachial index depends on the coexistence of occlusive peripheral
388 artery disease, *J. Vasc. Surg.* 53 (2011) 984–991.
389 <https://doi.org/10.1016/j.jvs.2010.10.054>.
- 390 [22] A.F. AbuRahma, E. Adams, J. AbuRahma, L.A. Mata, L.S. Dean, C. Caron, J.
391 Sloan, Critical analysis and limitations of resting ankle-brachial index in the
392 diagnosis of symptomatic peripheral arterial disease patients and the role of
393 diabetes mellitus and chronic kidney disease, *J. Vasc. Surg.* 71 (2020) 937–
394 945. <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)	
Current smokers	271 (20.5)	249 (20.1)	22 (27.2)	0.048
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)	
6.5 – 8.9	611 (54.8)	585 (55.2)	26 (48.1)	0.58
≥ 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)	
0.90 – 1.39	1024 (79.0)	962 (79.2)	62 (76.5)	0.71
≥ 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)	
Unilateral	174 (13.1)	167 (13.4)	7 (8.5)	0.001
Bilateral	385 (29.1)	346 (27.9)	39 (47.6)	
Femoral vessels plaque, n (%)				
Absent	729 (56.6)	692 (57.2)	37 (46.8)	
Unilateral	129 (10.0)	123 (10.2)	6 (7.6)	0.059
Bilateral	430 (33.4)	394 (32.6)	36 (45.6)	
Plaque territory, n (%)				
None	588 (44.3)	562 (45.2)	26 (31.7)	
Femoral only	179 (13.5)	169 (13.6)	10 (12.2)	0.06
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.

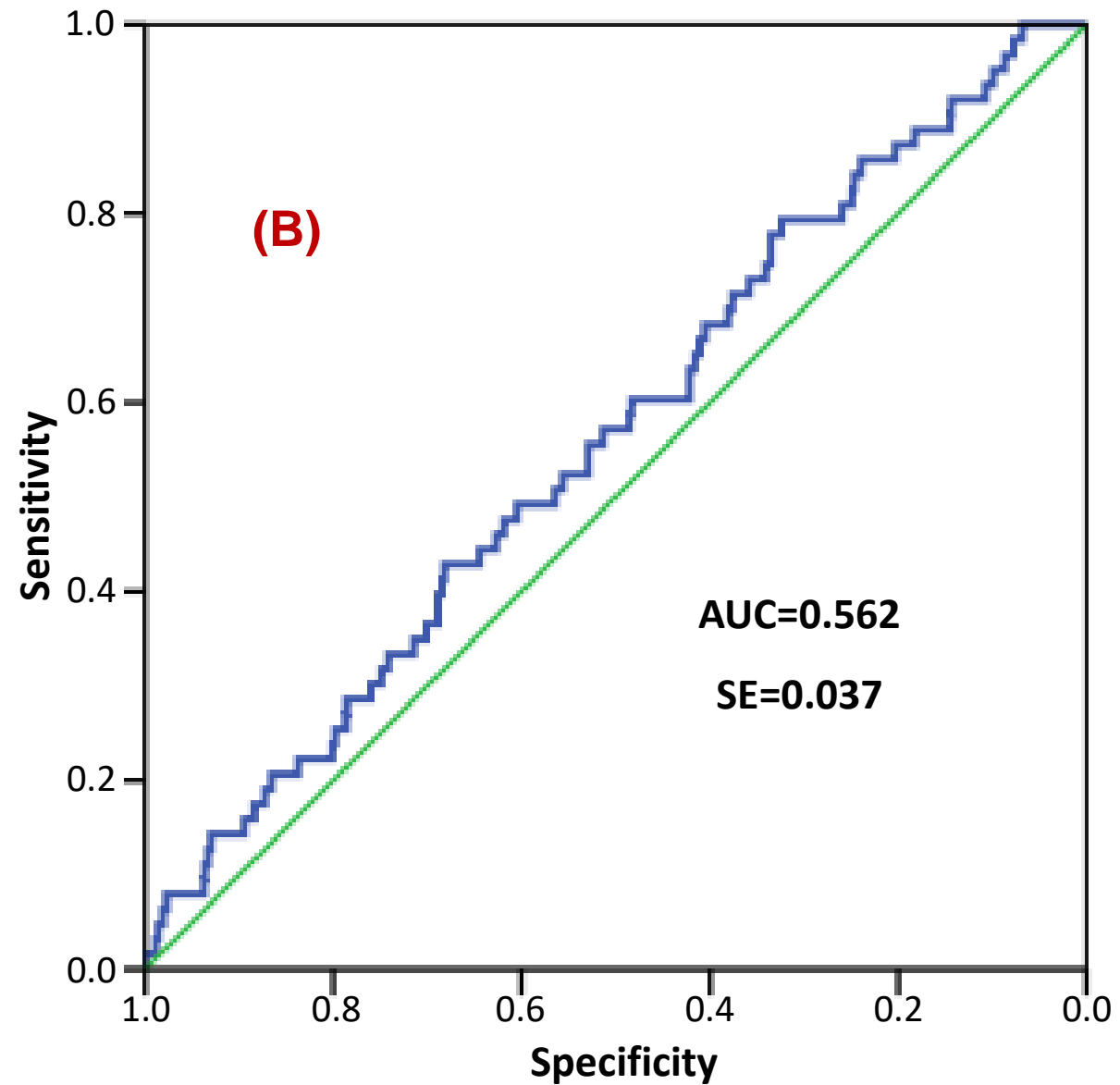
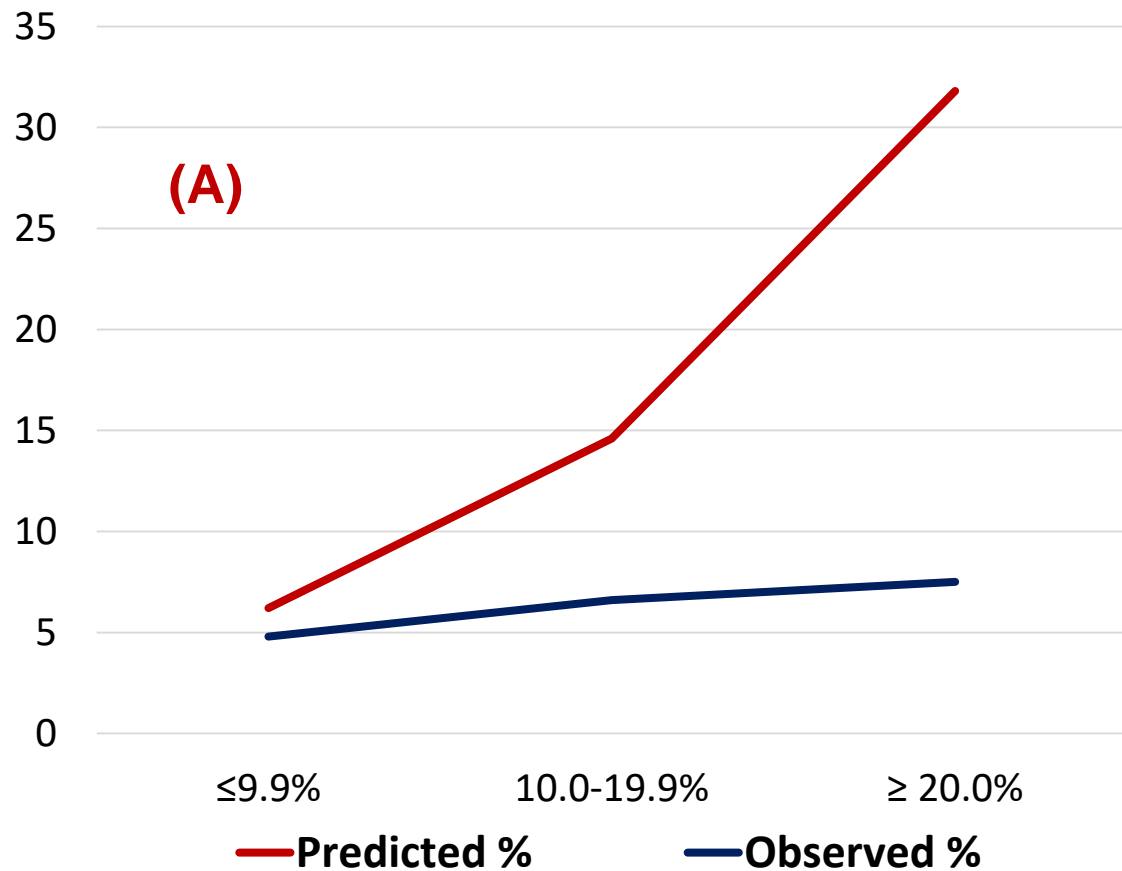
405 A) Calibration: predicted and observed cardiovascular events

406 B) Discrimination: prediction of cardiovascular events

407 C) Discrimination: patient's classification performances

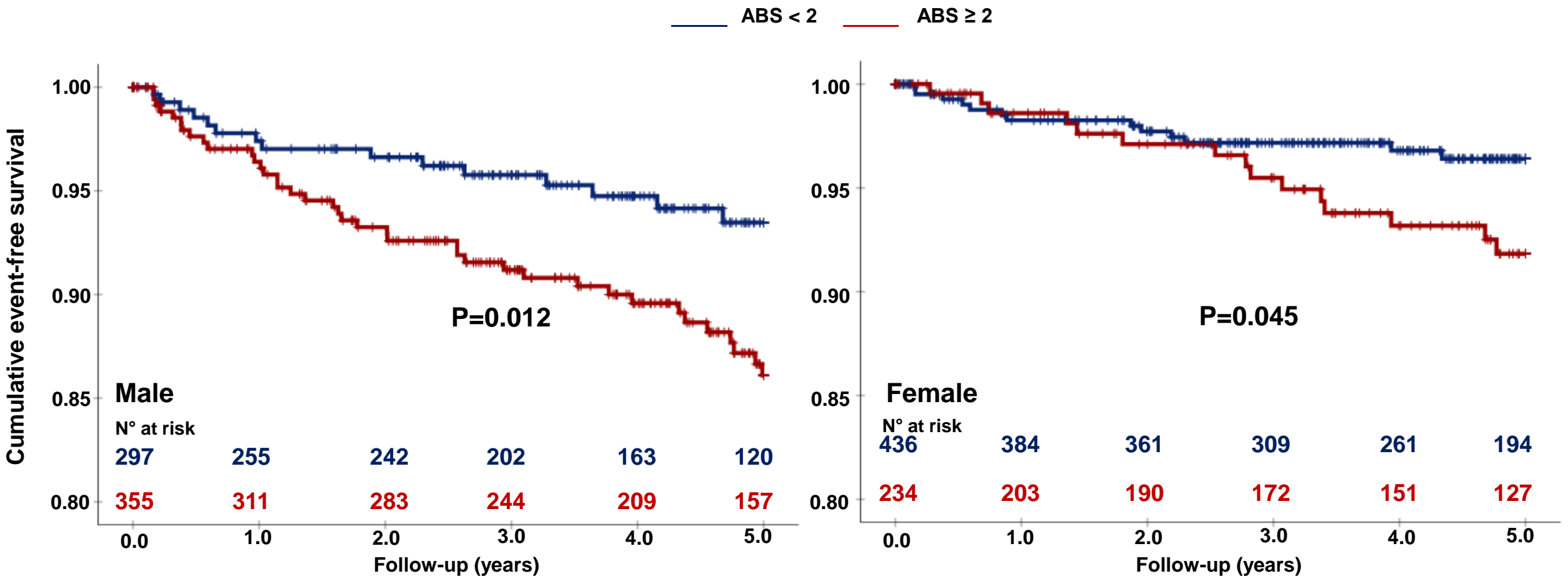
408 Figure 2: Outcomes of the patients according to gender and ABS score.

409 Figure 3: Improvement of risk prediction with vascular ultrasonography



(C)

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



Cox proportional hazard model's χ^2

