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THESE

préparée sous la direction du Docteur **Julien Vaucher**

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Hadrien BEURET

Médecin diplômé de la Confédération Suisse
Originaire de Soubey (Jura)

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Comparison of Swiss and European Risk Algorithms for Cardiovascular Prevention in Switzerland

Lausanne, le 19 mai 2020

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Comparaison des Algorithmes de Prévention Cardiovasculaire Suisse et Européen dans une Cohorte Suisse

Contexte : En Suisse, la prévention cardiovasculaire est basée sur des recommandations émanant de deux sociétés savantes différentes : 1) le Groupe de travail Lipides et Athérosclérose (GSLA) » ; et 2) la Société Européenne de Cardiologie (ESC). Chacune fournit un score de risque cardiovasculaire (PROCAM pour le GSLA et SCORE pour l'ESC), ainsi qu'un algorithme de prise en charge, guidant les mesures de prévention en fonction du risque cardiovasculaire estimé.

But : Notre but premier était de déterminer lequel, entre l'algorithme du GSLA et celui de l'ESC, était le plus performant pour prédire la survenue d'événements cardiovasculaires athérosclérotiques (ECVA), ainsi que leur propension respective à recommander la prescription de statines dans la population suisse. Notre deuxième but était de valider pour la Suisse les scores de risque du GSLA et de l'ESC, couramment utilisés en prévention primaire.

Méthode : Les données sont basées sur une étude populationnelle prospective, la cohorte « CoLaus ». L'échantillon initial comprenait 6'733 personnes, âgées de 35 à 75 ans (54% de femmes), qui furent suivies durant 10 ans. Nous avons calculé les performances de discrimination et de calibration des algorithmes du GSLA et de l'ESC, et ainsi déterminé leurs capacités à prédire la survenue d'événements cardiovasculaires.

Résultats : Des 6'733 participants de l'échantillon initial, 5'529 avaient des données complètes et furent inclus dans nos analyses. L'âge moyen (déviation standard, DS) était de 52.4 (10.6) ans. Durant un suivi moyen (DS) de 10.2 (1.7) ans, 370 (6.7%) participants présentèrent un ECVA. La sensibilité des algorithmes du GSLA et de l'ESC pour la prédiction d'ECVA étaient respectivement de 51.6% (IC 95%, 46.4-56.8) et de 58.6% (53.4-63.7). Les performances de discrimination et de calibration étaient similaires entre les algorithmes du GSLA et de l'ESC, avec des valeurs d'air sous la courbe de 0.78 (95% CI, 0.76-0.80) et de 0.79 (0.76-0.81), et des scores de Brier de 0.059 et de 0.041, respectivement. Parmi les 370 individus ayant présentés un ECVA, seulement 278 (75%) étaient éligibles pour un traitement par statine au début du suivi. Les performances prédictives des scores de risque du GSLA et de l'ESC étaient également similaires et bonnes, validant leur usage pour la population suisse en prévention cardiovasculaire primaire.

Conclusion : Les algorithmes du GSLA et de l'ESC présentent des facultés similaires pour prédire la survenue d'événements cardiovasculaires en Suisse. Un quart des événements cardiovasculaires ont lieu chez des personnes identifiées à bas risque selon les recommandations actuelles, soulignant le besoin de développer des méthodes complémentaires pour améliorer les stratégies de prévention cardiovasculaire.

Comparison of Swiss and European risk algorithms for cardiovascular prevention in Switzerland

Hadrien Beuret[1], Nadine Hausler[1], David Nanchen[2],
Marie Méan[1,3], Pedro Marques-Vidal[1,3] and Julien Vaucher[1,3]

Abstract

Background: In Switzerland, two distinct algorithms are recommended for cardiovascular prevention: (a) Arbeitsgruppe Lipide und Atherosklerose (AGLA); and (b) European Society of Cardiology (ESC). We validated and determined which algorithm better predicts incident atherosclerotic cardiovascular disease and assessed statin eligibility in Switzerland.

Design: A prospective population-based cohort.

Methods: We employed longitudinal data of the CoLaus study involving 6733 individuals, aged 35–75 years, with a 10-year follow-up. Using discrimination and calibration, we evaluated the predictive performance of the AGLA and ESC algorithms for the prediction of atherosclerotic cardiovascular disease.

Results: From the 6733 initial participants, 5529 were analysed with complete baseline and follow-up data. Mean age (SD) was 52.4 (10.6) years and 54% were women. During an average follow-up (SD) of 10.2 years (1.7), 370 (6.7%) participants developed an incident atherosclerotic cardiovascular disease. The sensitivity of AGLA and ESC algorithms to predict atherosclerotic cardiovascular disease was 51.6% (95% confidence interval (CI) 46.4–56.8) and 58.6% (53.4–63.7), respectively. Discrimination and calibration were similar between the AGLA and ESC algorithms, with area under the receiver operating characteristic curve values of 0.78 (95% CI 0.76–0.80) and 0.79 (0.76–0.81), and Brier scores of 0.059 and 0.041, respectively. Among 370 individuals developing incident atherosclerotic cardiovascular disease, only 278 (75%) were eligible for statin therapy at baseline, including 210 (57%) according to both algorithms, 4 (1%) to AGLA only and 64 (17%) to ESC only.

Conclusion: AGLA and ESC algorithms presented similar accuracy to predict atherosclerotic cardiovascular disease in Switzerland. A quarter of adults developing atherosclerotic cardiovascular disease were not identified by preventive algorithms to be eligible for statin therapy.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for more than 17 million deaths annually.[1] In Switzerland, CVD also represents a health and economic burden, with about one third of all deaths attributable to CVD,[2,3] and annual direct costs corresponding to 16% of total health expenditures.[2,4]

Prevention of CVD is based on the use of different cardiovascular risk scores that were developed to assess the cumulative effect of cardiovascular risk factors.

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These scores are recommended to identify patients who would benefit the most from preventive measures, including the use of statins.[5–13] In Switzerland, cardiovascular prevention is based on two different guidelines: (a) the International Atherosclerosis Society guidelines (IAS), adopted by the Swiss Atherosclerosis Association (in German Arbeitsgruppe Lipide und Atherosklerose; AGLA);[6,7,14] and (b) the 2016 guidelines of the European Society of Cardiology (ESC).[5,10,15] Both guidelines propose risk algorithms and corresponding risk scores, using the AGLA score (based on the PROCAM score recalibrated for Switzerland) and the Systematic COronary Risk Estimation (ESC-SCORE), recalibrated for Switzerland, respectively (see Supplementary Table 1). Algorithms allow risk prediction in all patients, including those at very high risk (see Supplementary Figures 1 and 2). It is noteworthy that the AGLA and ESC algorithms differ in risk factors or thresholds of risk factors for identifying individuals at high or very high cardiovascular risk. Furthermore, the AGLA score predicts fatal and non-fatal incident coronary events whereas the ESC-SCORE estimates fatal CVD events (see Supplementary Table 1). Currently, it remains unknown which of the two algorithms and scores perform best in Switzerland. Establishing which one has a better predictive accuracy is important because implementation of preventive algorithms can greatly impact the incidence of CVD as well as the number of drugs used at large scale.

Using data of a prospective and population-based Swiss cohort, the CoLaus study,[16] our first aim was to compare AGLA and ESC algorithms and validate AGLA and ESC risk prediction models (i.e. AGLA score and ESC-SCORE) for the estimation of cardiovascular risk. Second, we compared statin eligibility according to the AGLA and ESC risk algorithms, based on participants' cardiovascular risk profile and low-density lipoprotein (LDL) cholesterol levels.

Methods

Study population

The CoLaus study (www.colaus-psycolaus.ch) is a Swiss population-based prospective cohort.[16] Between 2003 and 2006, 6733 subjects (age range 35–75 years, 54% women) were recruited from a random sample of the population of Lausanne, located in the French-speaking part of Switzerland. The participation rate amounted to 41%. The study was approved by the institutional ethics committee of the University of Lausanne and all participants provided written informed consent. Participants were invited to attend the outpatient clinic at the University Hospital of Lausanne in the morning after an overnight fasting

for baseline clinical assessment, questionnaire completion and blood sample collection. Periodic surveys of the whole cohort were conducted over a 13-year follow-up. Relevant medical records of participants who declared to have presented with a CVD and/or CVD-related procedure during their lifetime were collected. Information on cause of death was also prospectively collected during the study period (see clinical data collection in the Supplementary material).

Algorithms analysis

The AGLA and ESC risk algorithms are detailed in Supplementary Figures 1 and 2.[10,12]

Participant selection. Participants were eligible for analysis if complete information regarding variables of interest (such as blood pressure, lipid and glycaemic values, or smoking status) were available. Furthermore, those refusing to partake in the 10-year follow-up were excluded from analysis (see Supplementary Figure 3).

Outcomes and adjudication of cardiovascular events. As the AGLA and ESC algorithms were designed to predict different cardiovascular outcomes (see Supplementary Table 1), the prediction performance of the two algorithms was compared using a common set of clinical cardiovascular outcomes, namely atherosclerotic cardiovascular disease (ASCVD), as already performed[17] and recommended by the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) cardiovascular preventive guidelines.[9,18,19] We defined incident ASCVD as an episode of: (a) acute myocardial infarction; (b) sudden cardiac death; (c) symptomatic coronary artery disease with greater than 50% stenosis (treated by percutaneous coronary intervention or coronary artery bypass graft); and (d) fatal and non-fatal ischaemic stroke (including transient ischaemic attack). Peripheral artery disease was not included in ASCVD as this outcome was not collected in the CoLaus study.

The occurrence of an incident ASCVD was prospectively collected during the follow-up period. Participants experiencing an ASCVD were censored for the rest of the study period, preventing double counting of participants developing additional ASCVD. All cardiovascular events were independently adjudicated based on largely established recommendations and definitions (see Supplementary material). Myocardial infarction was adjudicated by two independent cardiologists, stroke by one neurologist, and deaths by two internists.

Statistical analysis

Participants' characteristics were described according to incident ASCVD. Categorical variables were

summarised as number of subjects with column percentages, and continuous variables as means with standard deviation (SD). Pearson chi-square (for categorical variables) or analysis of variance (ANOVA) (for continuous variables) were used to evaluate differences in subjects' baseline characteristics according to the occurrence of ASCVD.

Performance of risk algorithms. To examine performance of the whole AGLA and ESC algorithms, we included people at high and very high cardiovascular risk at baseline, comprising those with pre-existing cardiovascular disease (CVD) or equivalent (see Supplementary Table 1 and Supplementary Figures 1 and 2). This approach holds the potential to represent a better assessment of the entire risk algorithms and of their public health impact.

We assessed the predictive accuracy of the AGLA and ESC algorithms to assign individuals who developed ASCVD correctly into the high/very high risk category, with regard to low/intermediate categories of risk. For individuals requiring a risk estimation based on the computation of score (i.e. without prevalent ASCVD or equivalent condition; see Supplementary Figures 1 and 2), we systematically used recalibrated versions of the AGLA score and ESC-SCORE.[5–7,14,15] Discrimination and calibration were computed. Discrimination was expressed as area under the receiver operating characteristic (AUROC) curve and tested how well both algorithms distinguished high/very high risk subjects from those at low and intermediate risk. Calibration refers to the agreement between the predicted and observed rate of ASCVD and was assessed by the Brier score and Hosmer–Lemeshow statistic. In addition, goodness of fit was assessed with Akaike information criterion (AIC) and Bayesian information criterion (BIC). We derived calibration plots of the AGLA and ESC algorithms from Cox prediction models (using Stata command 'stmp2', fitting flexible parametric survival models), with partition of participants into 10 deciles of risk. Calibration plots were drawn using Stata command 'pmcalplot'.

As transient ischaemic attacks, not necessarily related to atherosclerosis, represented 41% of ischaemic strokes, we conducted an additional test by removing them from the analysis. We also performed a sensitivity analysis by excluding participants under statin therapy at baseline and reaching LDL-cholesterol targets.

Risk prediction model analysis. We additionally validated the AGLA and ESC risk prediction models (i.e. AGLA score and ESC-SCORE) using each score-specific cardiovascular outcome (i.e. 10-year risk of major coronary events and cardiovascular death, respectively) after the exclusion of high and very high risk individuals (see Supplementary Figures 1, 2 and 3). Detailed risk prediction model analysis is described in the Supplementary material.

Eligibility for statin therapy. We determined the number of participants eligible for statin treatment according to the AGLA and ESC algorithms, based on cardiovascular risk estimation and LDL-cholesterol levels.[10,12] Participants were considered as eligible for statin therapy when LDL-cholesterol levels were equal to or higher than the recommended targets for each category of risk (see Supplementary Figures 1 and 2).[10,12] Overlap between eligibility for statin therapy and incident ASCVD was presented as a Venn diagram. It is noteworthy that treating physicians were not implicated in any step of the study and the prescription of lipid-lowering therapy was left to their discretion.

All statistical analyses were performed using Stata 15.1 (Stata Corp, College Station, TX, USA).

Results

From the 6733 participants of the initial CoLaus study, 166 (2.5%) were excluded because of missing information on variables of interest, and 1038 (15.4%) refused to partake in the 10-year follow-up (see Supplementary Figure 3). Thus, 5529 participants (54.3% women) were available for the analyses.

The mean age of participants was 52.4 years (SD 10.6) and the mean follow-up was 10.2 years (SD 1.7) (Table 1). A total of 511 (9.2%) participants were on statin therapy at baseline and 166 (2.9%) had prior ASCVD. The AGLA and ESC algorithms, respectively, classified 19.3% and 21.4% of participants into the high or very high risk categories (Table 2).

During the 10.2 years follow-up, 370 (6.7%) participants developed an incident ASCVD, comprising 94 acute myocardial infarctions or sudden cardiac deaths, 151 symptomatic coronary artery diseases treated by revascularisation, 125 fatal and non-fatal ischaemic strokes, including 51 transient ischaemic attacks. Among the 222 participants who died during the study period, 27 (12%) of them died from ASCVD. Individuals who developed ASCVD were on average 10 years older, more likely to be men, have diabetes and be a smoker, and had higher blood pressure compared with participants without incident ASCVD (Table 1).

Performance of risk algorithms (n = 5529)

Sensitivity of the AGLA and ESC algorithms to predict ASCVD were 51.6% (95% confidence interval (CI) 46.4–56.8) and 58.6% (95% CI 53.4–63.7), respectively. The negative predictive values (95% CI) were 96.0%

Table 1. Participant characteristics at baseline, in risk algorithm analysis, by incident ASCVD (n = 5529).

	Incident ASCVD			
	All	No	Yes	P value
N (%)	5529	5159 (93.3)	370 (6.7)	
Age (years)	52.4 ± 10.6	51.8 ± 10.4	61.1 ± 9.6	<0.001
Male	2526 (45.7%)	2274 (44.1%)	252 (68.1%)	<0.001
Parental history of MI	308 (5.6%)	283 (5.5%)	25 (6.9%)	0.303
Smoking status				<0.001
Never	2262 (40.9%)	2162 (41.9%)	100 (27.0%)	
Former	1836 (33.2%)	1677 (32.5%)	159 (43.0%)	
Current	1431 (25.9%)	1320 (25.6%)	111 (30.0%)	
Blood pressure (mm Hg)				
Systolic	127.2 ± 17.6	126.4 ± 17.2	139.3 ± 19.1	<0.001
Diastolic	79.0 ± 10.8	78.7 ± 10.7	82.9 ± 11.8	<0.001
Lipids (mmol/L)				
Total cholesterol	5.5 ± 1.0	5.5 ± 1.0	5.6 ± 1.0	0.394
HDL-cholesterol	1.6 ± 0.4	1.7 ± 0.4	1.5 ± 0.4	<0.001
LDL-cholesterol	3.3 ± 0.9	3.3 ± 0.9	3.4 ± 0.9	0.047
Triglycerides	1.3 ± 0.7	1.3 ± 0.7	1.6 ± 0.8	<0.001
Glucose (mmol/L)	5.5 ± 1.0	5.5 ± 0.9	6.0 ± 1.8	<0.001
Diabetes mellitus (%)	389 (7.0%)	316 (6.1%)	73 (19.7%)	<0.001
eGFR (CKD-EPI) (ml/min/1.73 m^2)	85.7 ± 15.0	86.1 ± 14.9	80.2 ± 16.1	<0.001
Prevalent chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	228 (4.1%)	196 (3.8%)	32 (8.7%)	<0.001
Prevalent ASCVD	162 (2.9%)	92 (1.8%)	70 (18.9%)	<0.001
Statin therapy	511 (9.2)	406 (7.9%)	105 (28.4%)	<0.001

Results express the number of participants (%) or mean ± SD. Percentages are expressed by row. *P* values were derived using Pearson chi-square or analysis of variance when appropriate.
ASCVD: atherosclerotic cardiovascular disease; MI: myocardial infarction; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; SD: standard deviation.

Table 2. Distribution of risk categories at baseline in risk algorithm analysis, by incident ASCVD.

		ASCVD	
Risk categories	Total	No	Yes
N	5529 (100%)	5159 (93.3%)	370 (6.7%)
AGLA			
Low (<10%)	4229 (76.5%)	4087 (96.6%)	142 (3.4%)
Intermediate (≥10 to <20%)	231 (4.2%)	194 (84.0%)	37 (16.0%)
High (≥20%)	550 (9.9%)	486 (88.4%)	64 (11.6%)
Very high	519 (9.4%)	392 (75.5%)	127 (24.5%)
ESC			
Low (<1%)	3190 (57.7%)	3134 (98.2%)	56 (1.8%)
Intermediate (≥1 to <5%)	1153 (20.9%)	1056 (91.6%)	97 (8.4%)
High (5 to <10%)	592 (10.7%)	522 (88.2%)	70 (11.8%)
Very high (≥10%)	594 (10.7%)	447 (75.3%)	147 (24.7%)

Individuals were classified into four risk categories according to the predicted 10-year risk of major coronary event for the AGLA algorithm and cardiovascular death for the ESC algorithm.
High and very high risk criteria are detailed in Supplementary Figures 1 and 2.
ASCVD: atherosclerotic cardiovascular disease; AGLA: Arbeitsgruppe Lipide und Atherosklerose; ESC: European Society of Cardiology.

Table 3. Performance of the AGLA and ESC risk algorithms to identify incident ASCVD (*n* = 5529).

	AGLA (95% CI)	ESC (95% CI)
Sensitivity	51.6% (46.4–56.8)	58.6% (53.4–63.7)
Specificity	83.0% (81.9–84.0)	81.2% (80.1–82.3)
Positive predictive value	17.9% (15.6–20.3)	18.3% (16.1–20.6)
Negative predictive value	96.0% (95.4–96.5)	96.5% (95.9–97.0)
Discrimination		
AUROC	0.78 (0.76–0.80)	0.79 (0.76–0.81)
Calibration		
Brier	0.059	0.041
Hosmer–Lemeshow (*P* value)	<0.001	<0.001
Model fit		
AIC	5813	5763
BIC	5820	5770

The AGLA and ESC risk algorithms were dichotomised into high/very high versus low/intermediate categories of risk.
ASCVD: atherosclerotic cardiovascular disease; AGLA: Arbeitsgruppe Lipide und Atherosklerose score; ESC: European Society of Cardiology; CI: confidence interval; AUROC: area under the receiver operating characteristic; AIC: Akaike information criterion; BIC: Bayesian information criterion.

(95.4–96.5) for AGLA and 96.5% (95.9–97.0) for ESC (Table 3). Discrimination was comparable for the AGLA and ESC algorithms, with AUROC (95% CI) of 0.78 (0.76–0.80) and 0.79 (0.76–0.81) (see Table 3 and Supplementary Figure 4).

Calibration of the AGLA and ESC algorithms was also comparable with Brier scores of 0,059 and 0,041 for AGLA and ESC, respectively (Table 3). The Hosmer–Lemeshow statistic showed *P* values of less than 0.001 for both algorithms. For both AGLA and ESC algorithms, calibrations plots showed a tendency to overpredict ASCVD in the lower deciles of risk, and an underprediction in intermediate to high deciles of risk (Figure 1).

The predictive performances of the AGLA and ESC algorithms remained consistent after removing transient ischemic attacks from the analysis (see Supplementary Table 2). The results also remained similar after the exclusion of participants under statin therapy at baseline and reaching LDL-cholesterol targets (see Supplementary Table 3).

Risk prediction models analysis (n = 4254 for AGLA score and 4479 for ESC-SCORE)

Patient characteristics and distribution of risk categories for the risk prediction model analysis are presented in Supplementary Tables 4 and 5. The AGLA score and ESC-SCORE presented valid predictive performances with very high negative predictive values (99.1% and 99.8%, respectively) and good discrimination (AUROC, 0.80 and 0.87, respectively) (see Supplementary Table 6). The ESC-SCORE presented a

marginally higher discrimination and sensitivity for its specific outcome (CVD death).

Eligibility for statins (n = 5529)

According to the AGLA and ESC algorithms, 1206 (21.8%) and 1917 (34.7%) participants were eligible for statin therapy, respectively. There was a substantial overlap between the AGLA and ESC algorithms, with 1074 participants eligible for statins according to both algorithms (Figure 2). Concerning the 370 individuals who developed ASCVD, 210 (57%) were eligible for statins according to both algorithms, 274 (74%) according to the ESC algorithm, 214 (58%) according to the AGLA algorithm. However, 92 (25%) adults who developed ASCVD were not eligible for statins according to the algorithms.

Discussion

Using a contemporary population-based cohort with a 10-year follow-up, our findings showed that the AGLA and ESC algorithms had similar accuracy to predict a 10-year risk of ASCVD in the Swiss population. We also validated the AGLA and ESC risk prediction models in Switzerland (i.e. AGLA and ESC scores) for cardiovascular primary prevention. Full compliance with algorithms for statin therapy would result in a higher number of statin prescriptions based on the ESC risk algorithm compared to AGLA's. However, neither of the two risk algorithms advocated statin use for a quarter of adults who developed ASCVD. This implied that cardiovascular prevention should be refined, through the use
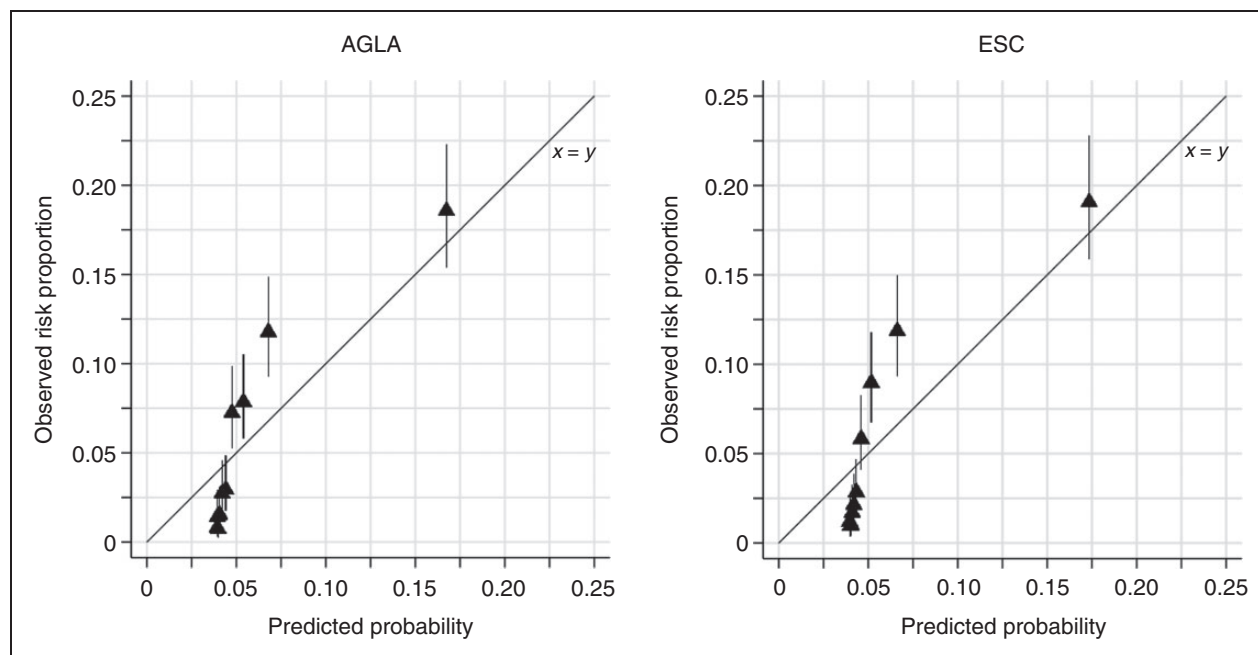
Figure 1. Predicted and observed ASCVD by algorithms. Calibration plots of cardiovascular risk score-specific Cox prediction model in the algorithms analysis (*n* = 5529). Observed ASCVD in the algorithms analysis was calculated using Kaplan–Meier estimates. Participants are divided into 10 deciles of risk represented by triangles. Vertical bars indicate 95% confidence intervals. ASCVD: atherosclerotic cardiovascular disease; AGLA: Arbeitsgruppe Lipide und Atherosklerose score; ESC: European Society of Cardiology.
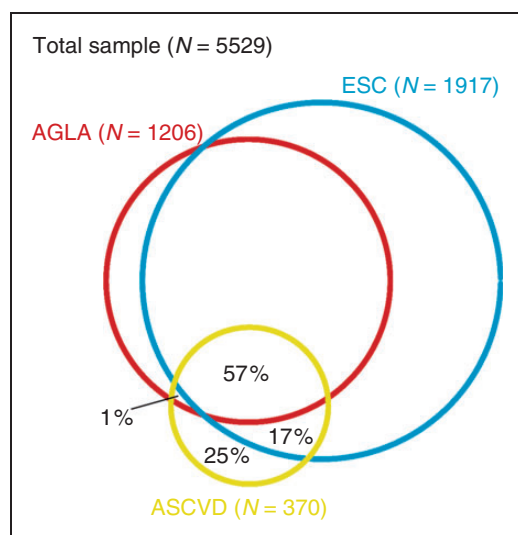

Figure 2. Statin eligibility according to the AGLA and ESC risk algorithms and incident ASCVD. The red and blue circles represent the proportional number of participants eligible to statin according to the AGLA and ESC algorithms, respectively. The yellow circle represents the participants who developed an ASCVD during the 10-year follow-up. ASCVD: atherosclerotic cardiovascular disease; AGLA: Arbeitsgruppe Lipide und Atherosklerose; ESC: European Society of Cardiology.

of complementary approaches (for example, genome-wide polygenic genetic risk scores or blood markers, such as lipoprotein (a)).

In Switzerland, cardiovascular prevention is based on the AGLA and ESC algorithms and their corresponding risk scores (AGLA score and ESC-SCORE). These scores have been developed in several European populations and recalibrated for Switzerland.[5–7,10,14,15] Switzerland is considered as a low cardiovascular risk country, with a prevalence of cardiovascular risk factors and disease rates similar to France, Italy, Germany, Spain, Portugal, the United Kingdom and The Netherlands.[20,21] Our results showed that both algorithms were comparable and that the AGLA score and ESC-SCORE are valid for use in Switzerland.[8,22] Previous studies,[8,22] comparing the ESC-SCORE in different European populations, have shown similar discrimination ability as in our study, with AUROC values ranging from 0.65 to 0.85, compared to 0.87 (95% CI 0.81–0.94) in our study. For the PROCAM score (used to derive the Swiss AGLA score), AUROCs were lower, ranging from 0.61 to 0.74 in European populations,[8,22] compared to 0.80 (95% CI 0.74–0.86) in our Swiss population. Overall, our results also confirmed findings from a recent

meta-analysis showing that the performance of scores can be equalised after adequate recalibration.[17]

Only a third of individuals experiencing major coronary events or dying from cardiovascular causes were classified at high or very high risk according to the AGLA-score and ESC-SCORE, respectively. Another Swiss study found similar results by retrospectively assessing the risk estimation and statin eligibility among 3172 patients hospitalised for a first episode of acute coronary syndrome.[23] Only 35% and 37% of subjects were identified as high risk according to the AGLA score and ESC-SCORE, respectively. Furthermore, we reported that 22% and 35% of participants would be eligible for statin treatment according to the AGLA and ESC algorithms, which is very close to the results found in a recent European meta-analysis of existing cardiovascular guidelines.[17] However, we found that among the 370 individuals who developed an incident ASCVD over the 10-year follow-up period, a quarter of them were not eligible for statin therapy by neither of the two algorithms. This study thus adds to previous evidence that current cardiovascular risk scores and algorithms fail to identify a substantial number of individuals at high cardiovascular risk.[14,23–25] This illustrates the paradox that at a population level many ASCVDs occur in people assumed to be at low cardiovascular risk,[10,25] simply because they are much more numerous. This also highlights the need to study alternative cardiovascular prevention strategies by integrating complementary approaches (for example, genome-wide polygenic genetic risk scores)[26] or additional risk markers, such as coronary artery calcium score or lipoprotein(a) levels.[10,18,19,25,27]

Our study has several limitations. First there was a relatively small number of certain incident ASCVDs, such as cardiovascular deaths. This could have limited the precision of some of our analyses, especially the risk prediction models analysis. Nevertheless, the algorithms analysis included 370 events, which is comparable to other studies.[28] Second, population-based studies may be affected by a 'healthy volunteer' selection bias,[29] which could have reduced our ability to capture actual cardiovascular risk in the Swiss population. However, the cardiovascular event rate was comparable to previous studies conducted in similar settings in other European cohorts.[28,30] Third, our study was purely observational and it is possible that a more intensive preventive strategy would have translated into a larger reduction of ASCVD. Fourth, our findings are related to the French-speaking part of Switzerland and might not be generalisable to other regions. Nevertheless, the prevalence of cardiovascular risk factors is relatively homogeneous in Switzerland[31,32] and the incidence of ASCVD in the region where the CoLaus study (that is, Canton de Vaud) was conducted

is similar to that in Switzerland. This reasonably allows extrapolating our results to the whole country.[33] Fifth, peripheral artery disease was not included in the definition of ASCVD. As neither the AGLA nor ESC risk algorithms included this outcome in their original equations, this minimises the risk that its exclusion reduced the predictive performance of the equations.

Our study also has strengths. First, we used the unique population-based cohort with a 10-year follow-up for cardiovascular events in Switzerland. Second, ASCVDs were prospectively collected and independently adjudicated according to recent recommendations and definitions, minimising the risk of misclassification.

Conclusion

Our findings, relying on contemporary and longitudinal data of more than 5500 Swiss individuals, showed that the AGLA and ESC cardiovascular preventive algorithms had similar accuracy to predict ASCVD and that both the AGLA and ESC scores were valid for use in primary prevention of CVD in Switzerland. However, our results confirmed that a significant proportion of individuals developing CVD are not identified as at high risk by current algorithms, highlighting the need for additional approaches to improve the performance of cardiovascular prevention strategies.

Author contribution

HB contributed to the design of the study, performed statistical analyses, interpreted the results and wrote the first draft of the manuscript. NH performed the statistical analyses, interpreted the results, wrote part of the article and revised the manuscript for important intellectual content. DN contributed to the design of the study, interpreted the results and revised the manuscript for important intellectual content. MM interpreted the results and revised the manuscript for important intellectual content. PMV collected data, contributed to the design of the study, interpreted the results and revised the manuscript for important intellectual content. JV conceived the original idea of the study, collected data, performed statistical analyses, interpreted the results and revised the manuscript for important intellectual content. JV had full access to the data and is the guarantor of the study. All authors discussed the design and results of the study, and contributed to the final manuscript.

Previous presentations of intermediate results

- 04.2019: EuroPrevent 2019, Lisbon (ESC Preventive Cardiology Congress)
- 06.2019: Swiss Society of General Internal Medicine Congress 2019

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