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What cardiovascular risk scores integrating biological data should be used in 2024 ?

A systematic review of the literature

INTRODUCTION

Cardio-neurovascular diseases (CNVD) are the leading cause of death worldwide. In 2019, they accounted for 17.9 million deaths[1]. Thanks to therapeutic advances, CVD-related mortality has fallen since the 1990s[1]. This diminution is unevenly distributed across the income brackets of the countries considered, to the benefit of high-income countries. The onset of CVD leads to chronic disease and a per- sonal and family socio-economic burden[1]. The decline in disability-adjusted years is also unequal between high-income and low-income countries[2]. In France in 2016, around 140,000 people died from MCNV[3]. French mortality from ischemic cardiopathy and neurovascular disease also fell between 2000 and 2016 in men (relative risk [RR] = 0.69 [0.67 - 0.71]) and in women (RR = 0.69 [0.67 - 0.71]). women (RR = 0.65 [0.62 - 0.69])[3].

In 2019 in France, 8.5 million people were receiving chronic vascular risk treatment[4]. Expenditure by the French health insurance system on MCNV reached 17.7 billion euros. The occurrence of CVD in an individual is influenced by the presence of cardiovascular risk factors (CVFs). The accumulation of CVFs in the same individual increases his or her risk. of MCNV in a non-linear fashion, as FCVs potentiate each other[9]. Nine modifiable CHDs are responsible for 90% of myocardial infarction mortality in any population[5]. These include lipid abnormalities, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors (depression and stress), high alcohol consumption, lack of fruit and vegetable intake and lack of regular physical activity.

Certain medicinal treatments have proved effective in secondary prevention[6]. Drug treatment of hypertension in primary prevention appears to be efficient[7]. Several meta-analyses have suggested the efficacy of statins in populations at high and moderate cardiovascular risk (CVR)[8,9]. However, the studies included in these meta-analyses included few low-risk patients, questioning the relevance of statin treatment for people with low CVR[10]. The cost to healthcare systems of treating large populations is a matter of debate in high-income countries[11]. They are unthinkable for lower -income countries. Non-medicinal measures such as smoking cessation, physical activity, alcohol reduction and salt reduction are also effective in the prevention of cardiovascular disease of MCNV.

Their implementation can be integrated in all countries, whatever their resources. To best estimate an individual's risk of developing CVD based on their FCV, cardiovascular risk scores (CVRS) were created. The Framingham cohort, created in 1948, led to the first multivariate logistic model in 1967[12]. This model

evolved into the Framingham score, published in 1998. Other SRCVs have been created to adapt to other populations. In Europe and France, the SCORE (Systematic Coronary Risk Estimation) index was created in 2003[13]. This SRCV exclusively evaluated the ten-year probability of death from MCNV.

SCORE2 was published in June 2021 to assess the risk of cardiovascular morbidity and mortality in European subjects aged 40 to 69, and SCORE2-OP for Europeans aged 70 and over[14]. Each SRCV has its limitations. For example, SCORE could not be used in people over 65, men under 40, women under 50, severe hypertensives (BP ≥ 180/110 mmHg), patients with familial hypercholesterolemia and chronic renal failure. It did not comply with international recommendations for assessing the SVR of diabetics[13]. In 2020, the French National Authority for Health (HAS) took the initiative of drawing up a recommendation for good practice in primary care management of global cardiovascular risk in primary and secondary prevention[15] .

This recommendation will address the choice of a cardiovascular risk calculation tool from among those available worldwide. The HAS guidance note highlighted the multiplicity of tools available and the inconnues concerning these tools, notably the heterogeneity of the CVFs they included, the uncertainties concerning their limits and their place in patient management[15]. There are two main two main types of CRVS: those that include clinical data, which can be used population screening without access to medical records, and those medical records, and those that integrate clinical and biological data (mainly lipid abnormalities) that can be abnormalities) that can be used in primary care, where this data is stored These are the biological SRCVs.

Another study looked at purely clinical scores to overall response to the HAS's questions is currently underway.

The aim of this systematic review of the literature was to identify the various biological CRVS used worldwide used worldwide in primary cardiovascular primary prevention target populations, parameters and performance.

METHOD

Systematic review of the literature reported according to PRISMA 2020 criteria, conducted on PubMed, Embase, Cochrane, Scopus and Google Scholar databases.

The research question was defined according to PICO criteria. The population was clinico-biological CVRS, the intervention was their use in primary prevention; there was no comparator; the outcomes sought were sensitivity, specificity, CVRS discrimination, biological data used and endpoints.

Eligibility criteria

The articles included had to concern a CRLS using biological data, on a population between 18 and 75 years of age and in a primary care setting. The method should be a literature review, a meta-analysis, a randomized controlled trial, a cohort study or a cross-sectional survival study. The presentation of the article had to follow the IMRaD format (Introduction, Method, Results and Discussion). Exclusion criteria were: no CV risk studied, writing in a language other than English or French, a full version of the article not found, a specific study population (children, pregnant women or over 75s), use in secondary prevention only, another type of publication.

Search strategy

A first search equation was created by two researchers on PubMed using MeSH terms. This equation was tested and monitored by evaluating the referencing of the first relevant articles retrieved. The equation chosen was "Cardiovascular diseases/prevention and control"[Mesh] AND "Primary prevention"[Mesh] AND "Risk assess- ment"[Mesh]. It was then adapted to each database (appendix 1, online).

Selection process

Rayyan Intelligent Systematic Reviews software was used to select references. The software automatically detected doublons. Two researchers then blindly selected articles by title and abstract, followed by full text. The quality of the selected articles was assessed using the CASP and AMSTAR grids, according to the study methods. When the blind was lifted, disagreements were resolved by consensus with the help of a third researcher. The data synthesis was organized into four sections. A first summary presented details of the scores found with the articles (Table 1). The second summary grouped data extracted from references according to scores: sensitivity, specificity. In the third section, data specific to SCORE were grouped together (table 2). When the information was area under the curve (AUC) and C-index values for all scores were presented on the fourth axis (figures 2 and 3). The AUC corresponds to the probability of an event being classified as positive by the test on the range of possible threshold values.

The C-index has the same probability, adapted to survival studies.

RESULTS

The database search was carried out in July 2021, with an update in September 2021, and retained 44 articles (Figure 3). There were 3 systemic literature reviews, 5 cohort meta-analyses, 35 studies of cohort and 1 randomized controlled trial. Nine studies were designed to create CRSVs. Ten evaluated a risk score in a given population. Twelve compared the performance of several scores in the same population. Three tested the addition of new parameters to existing scores. Six were recalibrations of scores for given populations. One review presented the characteristics of the scores, and another compared the performance of the scores tools using the Framin-

Score	Country	Ethnic origin	Age	Gender	Total cholesterol	HDL	LDL	Triglycerides	C-reactive protein	Diabetes	Systolic blood pressure	Diastolic blood pressure
WHO/ISH[16,17]	X		X	X	X					X	X	
GloboRisk[18-23]	X		X	X	X					X	X	
SCORE[13,19,20,24-33]	X		X	X	X	X					X	
SCORE2[14]	X		X	X	X	X					X	
DECODE[16]	X		X	X	X					X1,2	X	
Framingham[16,17,22,24,29,31,34,35]			X	X	X	X				X	X3	X
GVRS[46]		X	X	X	X	X				X1,2	X3	X
ACC/AHA Pooled Cohort Equation[17,22,24,27,31,32,35,37,38,45,52-55]		X	X	X	X	X				X	X3	
Reynolds risk score[16,31,35,56]			X	X	X	X			X	X1	X	
QRISK[16]			X	X	X	X					X[3]	
QRISK2[16,17,24]		X	X	X	X	X				X	X[3]	
ASSIGN[16]			X	X	X	X				X	X	
FINRISK[16]			X	X	X						X	
Copenhagen risk score[16]			X	X	X	X				X	X	
PROCAM[16,34,44]			X	X		X	X	X		X	X3	
CUORE risk score[16,39]			X	X	X	X				X	X3	
RISKARD[16]			X	X	X	X				X		
CAMUNI risk score[36]			X	X	X	X				X	X[3]	
Iberisk[25]			X	X	X3	X				X4	X3	X
EPOCH-JAPAN score[57]			X	X	X	X				X	X	
KRPM[45,55]			X	X	X	X				X	X3	

Table 1 -. Cardiovascular risk scores (CVRS), bibliographic references and clinico-biological parameters used to assess CV risk, *by score*

1: fasting blood glucose; 2: continuous variables; 3: plus current antihypertensive treatment; 4: HBA1C for women; 5: only in men; WHO/ISH: World Health Organization/ International Society of Hypertension; SCORE: Systematic COronary Risk Evaluation ; DECODE: Diabetes Epidemiology: COllaborative analysis of Diagnosis criteria in Europe; GVRS: Global Vascular Risk Score; ACC/AHA: American College of Cardiology and American Heart Association; ASSIGN: ASsessing cardiovascular risk using SIGN guidelines; FINRISK: FINland cardiovascular RISK study; PROCAM: PROspective CArdiovascular Münster; CAMUNI: CArdiovascular Monitoring UNIt; EPOCH-JAPAN: Evidence for cardiovascular Prevention from Observational CoHorts in Japan; KRPM: KoRean Prediction Model for atherosclerotic cardiovascular disease.

gham equation. The quality assessment of the articles is presented in Appendix 2 (online).

Twenty-one clinico-biologic SRCVs were identified. Twenty-eight parameters were used to calculate them. On average, SRCVs included 9 calculation parameters, with a minimum of 7 for FINRISK, WHO/ ISH, GloboRisk, SCORE and SCORE2 and a maximum of 15 for QRisk2 and Iberisk. Five parameters were age, sex, cholesterol, blood pressure and tobacco consumption. Seventeen were used exceptionally, with one or two scores. Details of the scores are shown in Table 1.

The most widely used statis-

Pressure average	Heart rate	Body mass index	Waist circumference	Chronic renal failure	Proteinuria	Rheumatoid arthritis	Atrial fibrillation	Obliterative arteriopathy of the limbs	Smoking	Alcohol consumption	Physical activity	Family history	Postal code	Social deprivation index	Manual labor
									X						
									X						
									X						
									X						
									X						
									X						
			X					X	X	X	X				
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		X							X			X	X		
		X		X		X	X		X			X	X		
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	X	X	X						X						
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X	X	X							X						
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		X		X					X	X5		X			X
					X				X						
									X						

tical tool for assessing CRVS was the C-index (14 articles), followed by the ratio of predicted to observed events (9 articles), then AUC (7 articles). Four articles presented sensibility and specificity data. The others presented concordance assessments, the number of subjects to be treated with statins, or no statistical data.

Of the 21 scores identified, 6 provided data on sensibility and specificity: GloboRisk, SCORE, Framingham, PCE and CAMUNI. These data were not available for the other 15 scores. SCORE had the most detail. Score sensitivities varied according to risk thresholds and populations. The full results are presented in Appendix 3 (online).

For SCORE, sensitivity ranged from 11% in low-risk autrian women to 97% in low-risk Swedish women. For these same categories, the specificities were 99% and 15% respectively. There was no correlation between the increase in cardiovascular risk and variations in SCORE sensitivities and specificities. Details of SCORE's sensitivities are shown in Table 2. Score discrimination was assessed for 12 scores by either AUC or C-index. The mean AUC of the scores was 0.75 and the mean C-index was 0.73.

The CSAs are shown in Figure 1 and C-indexes in figure 2. In France, only the SCORE and SCORE2 scores were evaluated. Sensitivity, specificity and AUC were available for SCORE, and C-index was available for SCORE2.

DISCUSSION

Main results

This systematic review identified 21 cardiovascular risk scores. Twelve were assessed for discrimination. Sensitivities and specificities were available for six scores and absent for fifteen. The five parameters present in all CVRS were age, sex, cholesterol, blood pressure and tobacco consumption. The mean area under the curve (AUC) for SRCV was 0.75 and the mean C-index was

Modified score	Population	Gender	Risk level	Sensitivity (%)	Specificity (%)	ASC
No	Russian	I	Low	90	40	
			Moderate	59-32	75-84	
			High	20	95	
	Swedish	I	Low	97	15	0,72
			Moderate	84-61	47-68	
			High	40	85	
	United Kingdom	I	Low	94	20	0,70
			Moderate	83-66	46-64	
			High	45	82	
Yes	English non-manual trades	I		61	77	
	English manual trades	I		57	69	
No	Scottish	I	Low	82	52	0,71
			Moderate	66-51	5-84	
			High	33	92	
	French	I	Low	51	82	0,71
			Moderate	20	96	
	Danish	M	All	24	86	0,76
		F				0,74
	Austrian	M	Low	59	78	
			Moderate	33	91	
		F	Low	23	94	
			Moderate	11	99	
	German	I	Low	80	82	
			Moderate	43	96	

Table 2 - SCORE sensitivities, specificities and areas under the curve (AUC)
F: feminine; I: undifferentiated; M: masculine.

0.73. In France, the only scores adapted to the population were SCORE and SCORE2, but there were no specificity or sensitivity data for SCORE2.

Comparison with literature

The statistical characteristics of CRSVs can be translated into clinical relevance. The AUC is a statistical tool based on Receiver Operating Characteristic (ROC) curves. ROC curves and their AUC enable the analysis of clinical performance of the scores. The clinical contribution of a score is nil for an AUC of 0.5, not very informative if 0.5 ≤ AUC < 0.7, moderately informative if 0.7 ≤ AUC < 0.9, very informative if 0.9 ≤ AUC < 1 and perfect if AUC = 1[58]. The informative C-index values are similar[59]. The mean AUC of the SRCVs included was 0.75 and the mean C-index 0.73, reflecting moderately informative scores. SCORE2, the new score recommended in France, has C-indexes ranging from 0.67 (0.65-0.68) to 0.81 (0.76-0.86) in Europe[14].

This SRCV is presented as a breakthrough in SCORE comparison, but their C-index difference of 0.01 (CI95 = 0.0085- 0.0115; p < 0.001) ultimately appears marginal. Details of the cohorts used to validate SCORE2 in France are surprising[14]. Two French cohorts were included in the model derivation. The DESIR cohort comprised 3,328 participants, 49% male, recruited on average in 1995. The PRIME cohort included 9,583 participants, all male, recruited on average in 1992. In comparison, 9 English cohorts were included in the SCORE2 validation, comprising 476,072 participants. For external validation, only the 1997 French EPIC -CVD cohort was included. This cohort was exclusively female and included 599 participants.

It has been established that the incidence and mortality of cardiovascular disease in France varies from one region to another[60] . It is likely that these three cohorts are not representative of the French population, and do not allow us to accurately estimate cardiovascular risk in France. This observation argues in favor of the development of cohorts in primary care, which the P4DP (platform for data in primary care) project, supported by the Collège national des généralistes enseignants, could help to consolidate[61].

Imaging scores were not included in this review. This score must be combined with an initial clinical RCV score. This score must be combined with an initial clinical SVR score. A 2022 meta-analysis evaluated its value in the general population[62]. The pooled gain in C-index with the addition of the calcium score was 0.036 (CI95= 0.020-0.052); very few of the participants reclassified into risk groups had a cardiovascular event within 10 years. This meta-analysis suggests an unfavorable cost-effectiveness balance for calcium scoring.

Strengths and limitations of the review

This systematic review was rigorously conducted. Several databases were searched, and articles were selected on a double-blind basis. The Rayyan® web application enabled automatic detection of duplicates, secured blinding and unblinding, and ensured traceability of decisions, inclusion and exclusion criteria. The review was reported according to PRISMA criteria. Several search equations were tested before the final equation was constructed. However, it was impossible to construct the search equation using MeSH terms. To date, there is no MeSH indexing of cardiovascular scores. Authors of similar reviews have encountered the

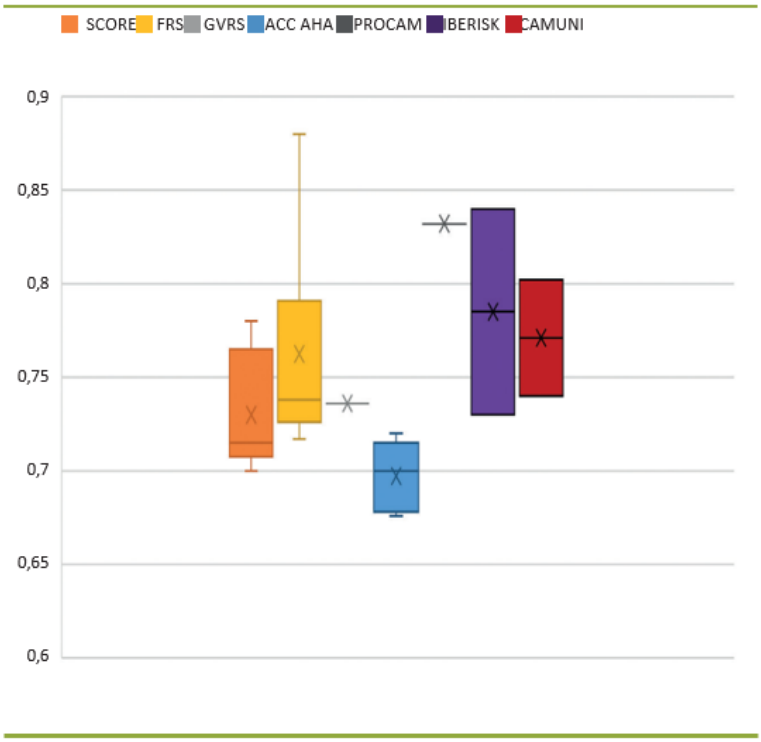

Figure 1 - Distribution of areas under the curve (AUC) by score presenting this data

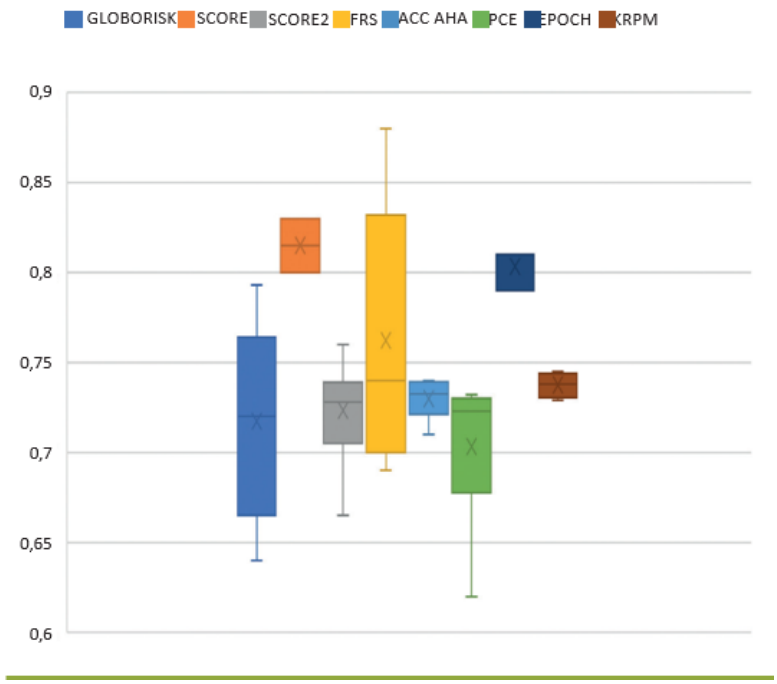

Figure 2 - Distribution of C-indexes by score presenting this data

same difficulty. The creators of the WHO/ISH score used the terms "cardiovascular disease", "risk score", "risk equation", "risk algorithm", and "risk prediction "[63] in their review. A systematic review published in the British Medical Journal in 2012 had constructed score equations as "Framingham OR FRS OR Framingham risk score OR NCEP ATP III OR National Cholesterol Education Program Adult Treatment Panel III "[64]. Repeating this equation in 2023 identified 19,570 articles.

The use of non-indexed generic terms may have limited the identification of relevant publications, and necessitated reading a large number of references to select around 1.2%. The synthesis of the results of this review required several approaches, due to the heterogeneity of the studies. A similar recent review reached the same conclusion[65].

Outlook

In this review, 6 studies were recalibration studies. Scores developed for a given population do not retain their discriminatory properties in another population[66]. Consequently, outside the context of research in France, it is difficult for clinicians to use scores other than SCORE and SCORE2. In France, the sensitivity and specificity of SCORE by risk level are known, but not for SCORE2. The WHO/ISH score, intended for moderate- and low-income countries, was calibrated on the same French cohorts as SCORE, and includes a non-laboratory test variant which could be an alternative to scores with a biological component[63].

Overall, SRCVs have low sensitivity and high specificity. For the clinician, this makes them diagnostic tests rather than screening tests whose objective is drug prescription[67]. The Copenhague cohort approach, which evaluates the entire prevention strategy (from score achievement to statin survival), is particularly relevant, as it studies the efficacy of the entire prevention strategy, from the diagnostic stage to the benefits of drug prescription[24,52]. The sensitivity and specificity values of the scores mean that the French clinician is currently more likely to exclude a high-risk individual (low sensitivity) than to wrongly classify a low-risk individual in a higher category (high specificity). Faced with a SRCV that appears abnormally low, it is permissible to reclassify a patient as higher risk and treat him or her as

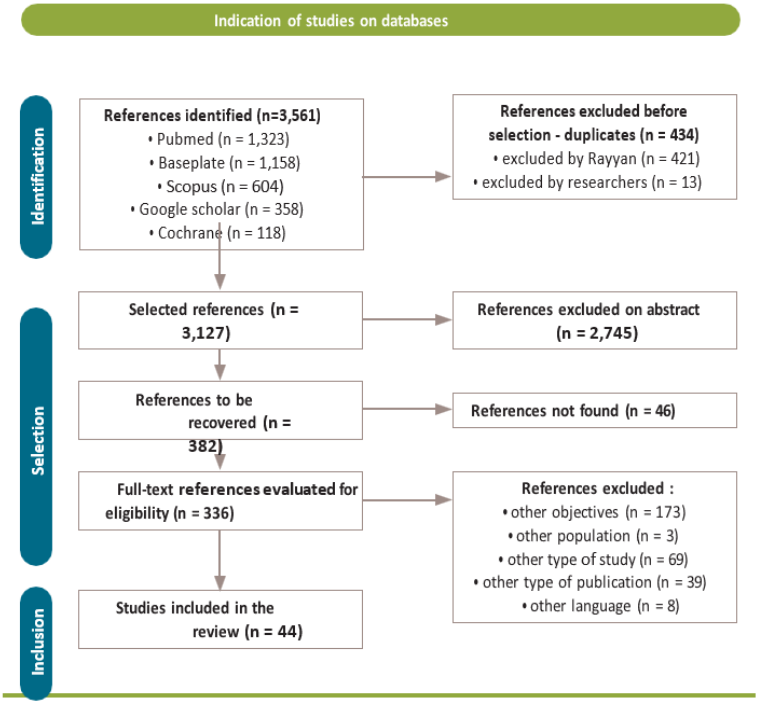

Figure 3 - Flow chart of selected studies, PRISMA 2020

Summary

Context. Cardiovascular diseases (CVD) are the leading cause of death. In 2019, they caused 17.9 million deaths worldwide. In 2016, 140,000 people died of CVD in France. Cardiovascular risk scores (CVRS) were created to estimate the individual risk of developing a CVD. *Objective.* The aims of this review were to list the different CVRS using biological date (laboratory CVRS) used in primary cardiovascular pre- vention worldwide, and to know their targeted population, parameters and performance.

Methods. A systematic review was conducted on PubMed, Embase, Cochrane, Scopus, and Google Scholar. References were included if they tested a laboratory CVRS, if their population was aged 18 to 75 years old, if the study was a literature review, a meta-analysis, a randomised control trial, a cohort study or a cross-sectional survival study, and if the article had an IMRAD format. The article quality was assessed using CASP or AMSTAR standards. The Rayyan Intelligent Systematic Reviews application was used.

Results. The search was conducted in July 2021 and updated in Sep- tember 2021. Forty-four articles were included and 21 biological CVRS were identified. Sensitivity and specificity were available for six scores. The mean area under the curve (AUC) of score was 0.75 and the mean C-index was 0.73. For France, the only CVRS assessed were SCORE and SCORE2.

Conclusion. SCORE and SCORE2 are the only applicable CVRS in clinical practice in France. SCORE2 is presented as a breakthrough compared to SCORE but this seems marginal due to its unknown sensi- tivities and specificities. Limitations of CVRS should be addressed during initial medical training.

Keywords: primary prevention; cardiovascular diseases; risk assessment.

such. A patient identified as high risk will most likely benefit from the recommended drug interventions.

In 2021, French health insurance reimbursed €13,532,084 for outpatient statin prescriptions[68]. Since 2016, remuneration based on public health objectives (Rosp) has included the performance of SRCVs by contracted practitioners. The generalization of decisions based on SRCVs would probably reduce these expenses. In addition, French health insurance reimbursed 33,809,718 tests for lipid abnormalities in 2023, which corresponds to an annual lipid check-up for every French adult over 40[69]. The frequency of these assessments is questionable, and SRCV is not the answer. It would be interesting if future recommendations on cardiovascular risk assessment were to address this issue.

SCORE2 and SCORE2-OP are rank A knowledge in the the Livret de suivi des apprentissages (LiSA) for students in the second cycle of medical studies in France. However, the limitations of these tools are not addressed in medical education. They could be the subject of specific discussions during their internship with their university-approved practitioners. The choice of an SRCV for clinical practice in general medicine thus offers a practical exercise in critical reading of articles, with direct consequences for patient care in primary prevention.

The appendices can be viewed online at: www.exercer.fr

Links of interest : the authors have declared that they have no conflicts of interest concerning the data published in this article. The links of interest of each of the article's authors can be consulted online at www.transparence.gouv.fr.

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