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Agreement of Swiss-Adapted International and European Guidelines for the Assessment of Global Vascular Risk and for Lipid Lowering Interventions

Michel Romanens · Franz Ackermann · Michael Abay · Thomas Szucs · Matthias Schwenkglenks

Abstract
Background The Swiss national guidelines for the prevention of cardiovascular events have been published in 2005 by the Swiss Society of Cardiology (SGK) and the working group on lipids and atherosclerosis (AGLA). An agreement for global cardiovascular risk assessment and indications for cholesterol lowering among the international (IAS-AGLA) and the European (ESC score) guidelines is unknown.
Material and methods Subjects aged ≥45 years were recruited using newspaper announcements for the participation in our free of charge cardiovascular prevention program of the Vascular Risk Foundation (Varifo). The data served to calculate cardiovascular 10 year risk and to compare IAS-AGLA und ESC score with respect to risk and lipid lowering indications.
Results The primary prevention group included 713 subjects aged 55±6 years of which 47% were women. The mean 10-year risk ± standard deviation was low (IAS-AGLA: 3.9%±4.4% for myocardial infarction; ESC score: 1.7%±1.8% for cardiovascular death). In those subjects qualifying for a lipid lowering intervention, according to the IAS-AGLA score or the ESC score, the percentage of agreement between both scores was only 18% (kappa value 0.31 [95%CI: 0.22–0.39], $p<0.0001$).
Conclusions Our study shows, that the agreement for the available Swiss guidelines (IAS-AGLA, ESC score) for initiation of a lipid lowering therapy is low in our primary prevention group of subjects aged 45–65 years. According to the PROCAM study, about 30% of myocardial infarctions occur in persons with an intermediate risk. Therefore an improved risk stratification strategy is necessary.

Key words Primary prevention · Myocardial infarction · Guidelines

Introduction

In June 2005, the working group on lipids and atherosclerosis (AGLA) of the Swiss Society of Cardiology (SGK) published guidelines for the prevention of atherosclerosis [1]. In these guidelines no recommendation in favour or against one of the two available guidelines (IAS-AGLA or ESC score) was expressed [1]. For the German part of Switzerland the agreement in risk stratification and indication for cholesterol lowering is unknown when adhering to either the PROCAM-based IAS-AGLA score or the ESC score.

The goal of this work was therefore to study the agreement of these two Swiss-adapted risk assessment algorithms and guidelines for cholesterol lowering in a large primary prevention group of subjects.

M. Romanens (✉)
Ziegelfeldstrasse 1,
4600 Olten, Switzerland
e-mail: info@kardiolab.ch

F. Ackermann
4600 Olten, Switzerland

M. Abay
8001 Zurich, Switzerland

T. Szucs
Institute of Social- and Preventive Medicine, University of Zurich,
Zurich, Switzerland

M. Schwenkglenks
ECPM Research, c/o ECPM Executive Office,
4031 Basel, Switzerland

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Methods

Subject recruitment

Between May and December 2005, subjects were asked to participate in the Cordicare I cardiovascular risk assessment study of the Vascular Risk Foundation (Varifo) using radio and newspaper announcements. The check-up performed was free of charge for all interested subjects aged 45 years or more. All subjects had to give their written consent. The study was approved by the ethics commission of the canton of Solothurn.

Measurements

Participants completed a standardized questionnaire on the presence of major independent cardiovascular risk factors and known diseases (cardiovascular, cancer) as well as the use of medication. Afterwards, blood pressure was measured in a standard fashion and a single blood sample was taken for measurements of total cholesterol, triglycerides, HDL-cholesterol and glucose.

Risk calculations

For the assessment of 10-year cardiovascular risk, we used our internet-based risk calculator (Fig. 1, http://scopri.ch/riskalgorithms.htm), which uses published risk factor coefficients. (Table 1) [2, 3]. The IAS-AGLA score calculates the 10-year risk of non-lethal or lethal MI and uses correction factors for Switzerland according to the AGLA 2005 recommendations (Table 2) [1]. High risk was defined as a 10-year risk of ≥20%, intermediate risk as a 10-year risk of 10–19%. The ESC score expresses the 10-year risk of death from vascular causes and was calculated using the algorithm for low risk populations as recommended for Switzerland [3]. High risk was defined as a 10-year risk of ≥5.0%. Intermediate risk was defined by our

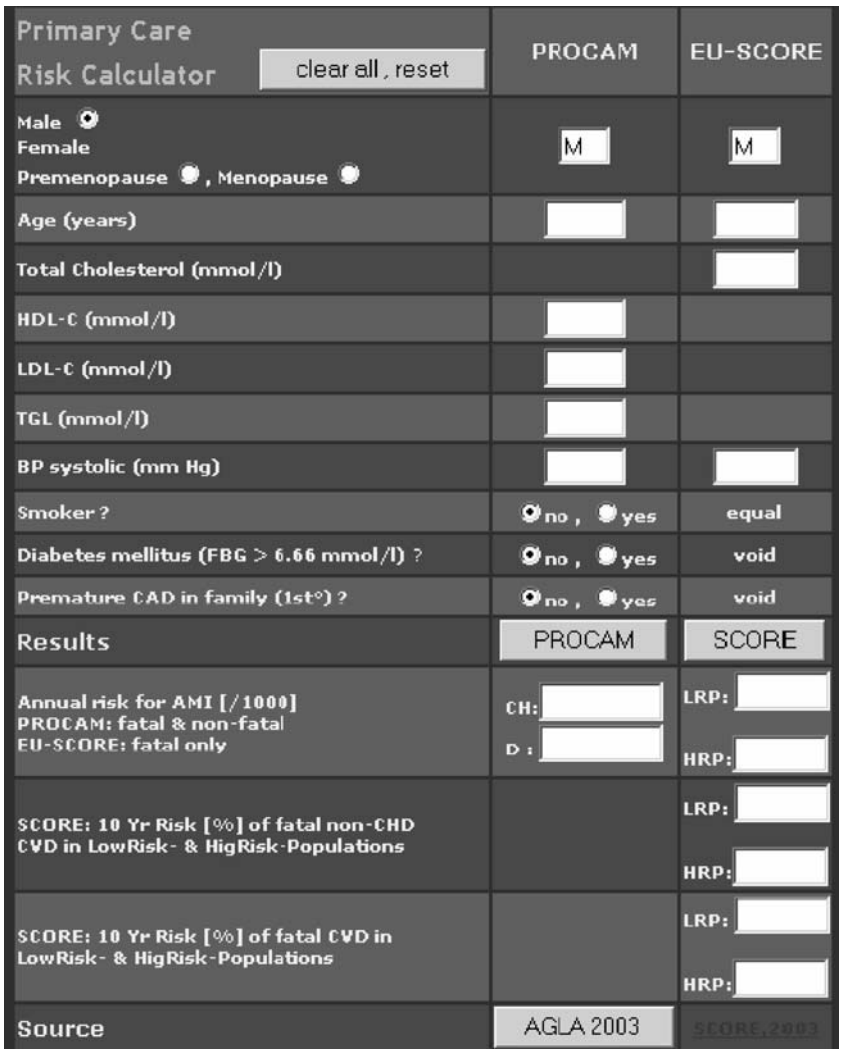

Fig. 1 Internet based risk calculator (http://scopri.ch/riskalgorithms.htm)

Table 1 Swiss adapted risk factors and correction factors for the IAS-AGLA risk algorithm

y=−8.9769	Risk factors	Minimal- and maximal values
+	0.103×age	(35−65 years)
+	0.010×systolic blood pressure	(100−225 mmHg)
+	0.5026×LDL-cholesterol	(1.94−6.48 mmol/l)
−	1.2372×HDL-cholesterol	(0.65−1.94 mmol/l)
+	0.317×log(TGL x 88.57)	(0.57−4.56 mmol/l)
+	0.658×current smoking	x (0=no, 1=yes)
+	0.399×diabetes mellitus	x (0=no, 1=yes)
+	0.382×premature CAD in family	x (0=no, 1=yes)
Corrections for the German part of Switzerland according to the AGLA guidelines 2005 [1]		
Man → ×0.7		
Woman, postmenopausal → ×0.7		
Woman, premenopausal → ×0.25×0.7		

Calculation of probabilities (P) for coronary artery disease (CAD) in percent in 10 years was performed using the formula: $P = 100 \times (1 - 0.9369^{a})$ for $a = \exp(y)$.

study group (for the purpose of better comparability) as a risk of 2.0–4.9% [2, 3].

Guidelines for LDL- and total cholesterol lowering interventions

The indication for treatment of the risk factor cholesterol and LDL-cholesterol was defined using the official AGLA-guidelines (Table 2 [1–3]).

Exclusion of subjects

Subjects were excluded from analysis if any of the following criteria was present: (a) history of cardiovascular event or known diabetes mellitus (diabetes mellitus is viewed as a coronary risk equivalent); (b) triglyceride values >4.5 mmol/l (because of uncertainties to calculate LDL-cholesterol based on the Friedewald formula); (c) age above 65 years (because risk calculators are validated only up to the age of 65 years).

Table 2 Cut-off levels for LDL-cholesterol lowering in primary care—recommendations SGK/AGLA 2005 [1–3]

Intervention is recommended if
IAS-AGLA score
Risk<10% and LDL-cholesterol>4.9 mmol/l
Risk<10% and LDL-cholesterol>4.1 mmol/l and ≥1 additional risk factor is present
Risk 10-19% and LDL-cholesterol>3.4 mmol/l
Risk≥20% and LDL-cholesterol>2.6 mmol/l
ESC score
Risk 0.0–5.0% and cholesterol>8.0 mmol/l or LDL-cholesterol>6.0 mmol/l
Risk>5.0% and cholesterol>5.0 mmol/l or LDL-cholesterol>3.0 mmol/l

Statistical analysis

Data are described statistically using standard methods. For the calculation of agreement between IAS-AGLA and ESC score we performed Kappa-statistics using Analyse-Software Analyse-It, Ltd, Version 2.02. Differences among groups for binary or categorical variables we used the χ^2-test. For all statistical tests, a two-tailed level of significance of $p \leq 0.05$ was chosen.

Results

Overall, we could include 1,040 subjects in this study. For several reasons, we excluded 327 subjects from further analysis: 201 subjects were aged more than 65 years, 60 subjects had known vascular disease, 40 had a history of diabetes, nine subjects had triglycerides over 4.5 mmol/l and in 14 subjects, we could not obtain a complete set of data. Therefore, 713 subjects were left for further analysis (primary prevention group).

Characteristics of study subjects

Mean age was 55±6 years of which 47% were women (Table 3). Current smoking was found in 16% and premature familial CAD in 18% of participating subjects. The mean values of other major independent risk factors were within the normal range except for total cholesterol (5.8 mmol/l). Only a few subjects had very high cholesterol

Table 3 Clinical and laboratory characteristics of subjects

	N	Percent
Number of subjects/%	713	100
Age (mean+SD) in years	55±6	
Men	376	53
Current smoker	111	16
Premature familial coronary artery disease	130	18
cholesterol mean+SD) in mmol/l	5.8±1.1	
HDL-cholesterol (mean+SD) in mmol/l	1.66±0.44	
LDL-cholesterol (mean+SD) in mmol/l	3.4±1.0	
Triglyceride (mean+SD) in mmol/l	1.5±0.8	
Systolic blood pressure (+SD) in mmHg	131±14	
cholesterol>8.0 mmol/l	15	2
HDL-cholesterol<1.00 mmol/l	27	4
LDL-cholesterol>6.0 mmol/l	3	0.4
Systolic blood pressure>140 mmHg	159	22
ESC score (mean+SD) in %	1.7±1.8	
IAS-AGLA (mean+SD) in %	3.9±4.4	
Body-mass-index (kg/m^2)	26±4	
On a statin therapy	41	6

(>8.0 mmol/l) or very high LDL-cholesterol values (>6.0 mmol/l); 2% and 0.4% respectively. An elevated blood pressure (systolic blood pressure>140 mmHg) was found in 22% of subjects. Mean body mass-index was slightly elevated (BMI 26±4). Both the IAS-AGLA score and the ESC score indicated a low average cardiovascular risk in our subjects (IAS-AGLA-10-years risk: 3.9%±4.4%; ESC score 10-year risk: 1.7%±1.8%).

Agreement of risk between IAS-AGLA and ESC score

The vast majority of subjects exhibited a low 10-year risk for vascular events (Table 4). Using IAS-AGLA 91.4% of subjects had a low risk, using ESC score 70.3% of subjects had a low risk. Agreement between IAS-AGLA and ESC score with respect to low risk was found in 69.3% of subjects. Based upon IAS-AGLA criteria, we found 8.3% of subjects at intermediate risk, with ESC score we found 25.2% of subjects at intermediate risk. Both with IAS-AGLA and ESC score, the numbers of high risk subjects was low: IAS-AGLA identified 8 (0.3%) high risk subjects, ESC score identified 32 (4.5%) high risk subjects, agreement for high risk was found however only in 2 (0.3%) of subjects. the Kappa-value was 0.22 (95% CI: 0.16–0.28, $p<0.0001$).

Table 4 Agreement of 10-year risk categories between IAS-AGLA and ESC score

IAS-AGLA	ESC score			
	Low	Intermediate	High	Total
Absolute values				
Low	494	145	13	652
Intermediate	6	30	17	53
High	1	5	2	8
Total	501	180	32	713
Percent values				
Low	69.3	20.3	1.8	91.4
Intermediate	0.8	4.2	2.4	7.4
High	0.1	0.7	0.3	1.1
Total	70.2	25.2	4.5	99.9

Kappa value: 0.22 (95% confidence interval: 0.16–0.28) $p<0.0001$

Agreement for cholesterol lowering between IAS-AGLA and ESC score

Using IAS-AGLA criteria, 19% of subjects qualified for a cholesterol lowering intervention, using ESC score this was found in 6% of subjects (Tables 5 and 6, Fig. 2). In 570 (80%), both guidelines agreed not to lower cholesterol or LDL-cholesterol. In 32 (5%) of subjects, both guidelines were in agreement with respect to lower cholesterol or LDL-cholesterol. However, in 111 (15%) we found no agreement for cholesterol lowering. The Kappa-value was 0.31 (95%CI: 0.22–0.39, $p<0.0001$).

In subjects with high risk, IAS-AGLA would recommend to lower cholesterol in all subjects N=8, 100%), and ESC score would recommend to lower cholesterol in 28 (88%) of subjects ($p=0.293$). In subjects with intermediate risk, IAS-AGLA would lower cholesterol in 46 subjects (87%), ESC score would lower cholesterol only in 5 (3%) of subjects (χ^2 169.03, $p<0.0001$). In subjects with low risk, IAS-AGLA would lower cholesterol in 12% of subjects, according to ESC score guidelines, this would be warranted in 1% of subjects (χ^2 48.86, $p<0.0001$).

Discussion

Our study shows for the first time in the German part of Switzerland, that cardiovascular risk assessment and pri-

Table 5 Absolute values: agreement for the indication to lower cholesterol or LDL-cholesterol between IAS-AGLA and ESC score

IAS-AGLA (*N*)	ESC score		
	No	Yes	Total
No	570	8	578
Yes	103	32	135
Total	673	40	713

Kappa value 0.31 (95% confidence interval: 0.22–0.39, $p<0.0001$)

Table 6 Percent values: agreement for the indication to lower cholesterol or LDL-cholesterol between IAS-AGLA and ESC score

IAS-AGLA (%)	ESC score		
	No	Yes	Total
No	80	1	81
Yes	14	4	19
Total	94	6	100

mary prevention of vascular events based upon the International (IAS-PROCAM [2]) and the European (ESC score [3]) guidelines exhibit quite substantial differences. Our findings are relevant, because our results go beyond the well known differences between risk assessments tools for myocardial infarction, in that they show, that discordance is also quite pronounced for treatment decisions. Therefore we urge other countries to check if their national guidelines propose two or more risk assessment tools and if these may lead to discrepant treatment decisions.

For comparison, we used the current Swiss guidelines with correction factors as proposed by the Working Group of Lipids and Atherosclerosis of the Swiss Society of Cardiology [1]. We found a rather high agreement with respect to risk stratification in 69% of subjects (Table 4) and regarding the cholesterol lowering in 80% of subjects (Tables 5 and 6). This agreement occurred however to a vast extent in low risk subjects, who generally would not qualify for a more intense primary prevention strategy. This is in accordance with the known low risk of the Swiss population for vascular events [4]. However, at the population level, a precise identification of high risk subjects would be quite useful. Our data show, that in most of the subjects who are deemed to be at high cardiovascular risk or might qualify for cholesterol lowering interventions, there is a low agreement between the two guidelines (Tables 5 and 6). Agreement for high cardiovascular risk was found in only two subjects using both IAS-AGLA and ESC score risk assessment tools. Furthermore, IAS-AGLA qualified six subjects as having high risk not identified as such by ESC score, on the other side, ESC score found 30 high risk subjects not identified as such by IAS-AGLA. The same problem occurred with respect to lower cholesterol ndication: agreement in 32 subjects, disagreement in 112 subjects. However, disagreement for cholesterol lowering interventions is mainly due to the chosen cut offs for LDL-Cholesterol lowering between the two guidelines.

Although our subjects do not represent a random sample of the local population, the distribution into the risk categories "low, high, and intermediate" is similar to the risk distribution published for the PROCAM cohort [2, 5]. Considering the higher level of cardiovascular risk in Germany when compared to Switzerland, the mean IAS-AGLA-based risk of 3.9% compares well with the mean IAS-PROCAM-based risk of 4.9% [5]. However, the validity of our conclusions is not hampered by an eventual selection bias, since the question of agreement of between IAS-AGLA and ESC score can be answered independently of the representativity of the population sample under investigation. We acknowledge the limitation that we cannot provide outcome data on our rather small sample with too short a duration for follow-up.

Accurate detection and treatment of subjects with elevated cardiovascular risk is important in primary care. Compared to the Swiss Lipid Guidelines published in 1999 [6], calculation of global cardiovascular risk for risk stratification is now recommended [1–3]. According to the Swiss Guidelines 2005, both IAS-AGLA and ESC score are recommended for initial risk stratification and lipid lowering guidelines. Both IAS-AGLA and ESC score have however a relatively low sensitivity (around 30%) with a high specificity (around 90%). Therefore, about two thirds of subjects who suffer an acute myocardial infarction or vascular death within the next 10 years are initially categorized as intermediate or even low cardiovascular risk [2, 3]. This shortcoming in sensitivity may be overcome with the following strategies A, B or C:

A: By changing the test calibration defining a lower cut-off for the definition of high risk (e.g. 15% instead of 20% 10-year risk), or

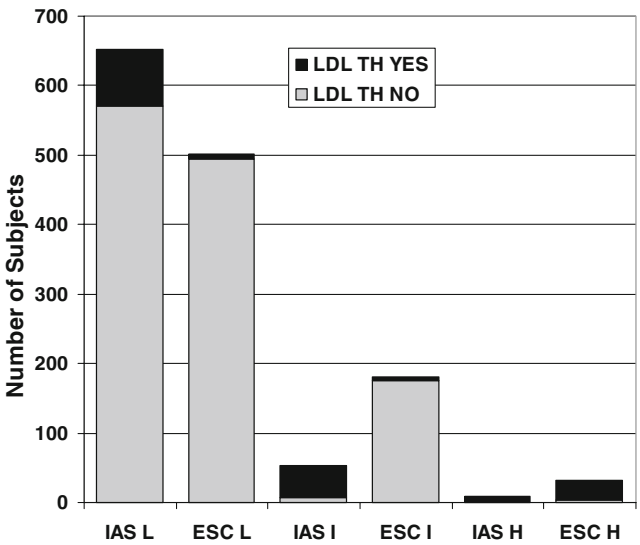

Fig. 2 Absolute distribution for the indication to lower cholesterol for different risk groups according to IAS-AGLA and ESC score. *IAS* IAS-AGLA, *ESC* European Society of Cardiology score, *L* low risk, *I* intermediate risk, *H* high risk

B: By more aggressive cholesterol reducing interventions also in intermediate risk subjects [2], or
C: By adding a sequential test in the intermediate risk subjects allowing further risk stratification and eventually changing a subjects risk category, e.g. by calculating posterior probabilities [7–9].

Our data show that based on the IAS-AGLA recommendations, 46 of 53 (87%) subjects having intermediate risk would receive a cholesterol lowering therapy. Using ESC based recommendations, only five of 180 (3%) subjects with intermediate risk would receive a cholesterol lowering therapy (Fig. 2). According to the PROCAM study, around one third of myocardial infarctions occur in intermediate risk patients [2]. Therefore, a strategy using the recommendations of IAS-AGLA may improve cardiovascular prevention both on an individual as well as on a population level.

However, these risk calculators have not been validated in a Swiss German cohort and may therefore be misleading. Sequential testing in intermediate risk subjects with additional tests such as atherosclerosis imaging or biological marker of risk such as high-sensitivity c-reactive protein (strategy C), may help to overcome the problem of decreased sensitivity of the risk calculators.

Conclusions

Our study shows for the first time, that the IAS-AGLA and the ESC score recommendations in subjects aged 45 to 65 years yield important differences both for the risk category allocation as well as for the indication to lower cholesterol in primary care. Since according to the PROCAM cohort, about 30% of myocardial infarctions occur in the intermediate risk group, the difference of the two guidelines with respect to medical intervention (IAS-AGLA would treat 87% of intermediate risk subjects, ESC score would treat 3% of subjects with lipid lowering drugs), a strategy which aims at optimizing risk stratification in the intermediate risk group appears necessary. Further, the question, which additional test may be best used for additional risk stratification, is still open to debate. The Taskforce on Atherosclerosis Imaging of the AGLA (Swiss atherosclerosis) has recognized this problem and is currently discussing new risk models for Switzerland.

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Conflicts of interest None

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