High sensitivity CRP is not a useful tool to further stratify subjects in primary care for their risk of myocardial infarction

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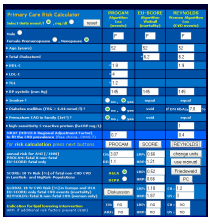
Introduction

Coronary risk charts have a high specificity (» 90%), but a relatively low sensitivity (» 30%), therefore, about 2/3 of subjects with future myocardial infarction are not categorized as having a high coronary risk. Additional risk stratifiers may be needed to increase the known low sensitivity of AGLA risk charts. For this study, we used high sensitivity C-reactive Protein (CRP) and atherosclerosis imaging of the carotid arteries and compared the results of different approaches to risk assessment in the same subject.

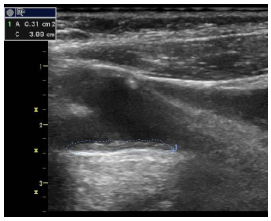
Methods

Healthy subjects aged 45 years or more were asked to participate in a free of charge cardiovascular risk assessment program (Cordicare II project). For the purpose to compare risk modification within the same subjects, we first calculated a reference value based on the 10 year risk derived from the AGLA risk calculator in subjects aged≥45 years. For a first comparison we used the REYNOLDS risk calculator, which includes CRP. This risk was calculated on our website: www.scopri.ch/riskalgorithms.htm. For a second comparison to AGLA. we used a posttest risk calculator based on the total plaque area of the carotid arteries (TPA). For calculation of posttest risk we used the known sensitivities and specificities for zero Plaque and gender specific tertiles of TPA published in the TROMSO study (Stroke 2007;38:2873). For computation of posttest risk, the Bayes formula was used (Kardiovaskuläre Medizin 2007;10:139). Our comparisons allowed us to measure the agreement between the different risk assessment tools and we used weighted kappa statistics for this purpose, categorizing subjects into low, intermediate, and high coronary risk. Finally, we were able to define the number of subjects qualifying for a lipid lowering medical intervention, based on the AGLA recommendations 2005.

Primary Care Risk Calculator



Atherosclerosis Imaging of Carotid Artery with www.tpainfo.ch Ultrasound to derive total plaque area



Calculator for posttest risk using the Tromso cohort

These results are derived from the TROMSO study, with 2989 men and 3237 women
Mean observation time 6.0 years, incident myocardial infarctions: N=295
Posttest Risk Calculations are exemplified for a AGLA risk of 10%

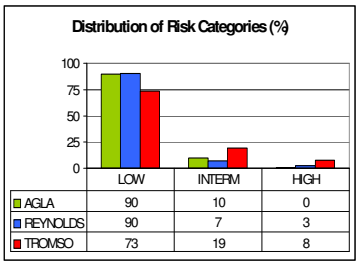
TPA MEN	TPA Zero		TPA WOMEN	TPA Zero	
0	PRETEST PROBABILITY	0.100	0	PRETEST PROBABILITY	0.100
	SENSITIVITY	0.690		SENSITIVITY	0.790
	SPECIFICITY	0.500		SPECIFICITY	0.570
	RESULT	0.064		RESULT	0.039
	TPA Tertile 1			**TPA Tertile 1**	
1 - 24	PRETEST PROBABILITY	0.100	1 - 18	PRETEST PROBABILITY	0.100
	SENSITIVITY	0.690		SENSITIVITY	0.790
	SPECIFICITY	0.500		SPECIFICITY	0.570
	RESULT	0.133		RESULT	0.170
	TPA Tertile 2			**TPA Tertile 2**	
25 - 49	PRETEST PROBABILITY	0.100	19 - 35	PRETEST PROBABILITY	0.100
	SENSITIVITY	0.550		SENSITIVITY	0.670
	SPECIFICITY	0.670		SPECIFICITY	0.730
	RESULT	0.156		RESULT	0.216
	TPA Tertile 3			**TPA Tertile 3**	
50 +	PRETEST PROBABILITY	0.100	36 +	PRETEST PROBABILITY	0.100
	SENSITIVITY	0.300		SENSITIVITY	0.410
	SPECIFICITY	0.840		SPECIFICITY	0.880
	RESULT	0.172		RESULT	0.275

Results (Table 1 and Figures):

A total of 213 subjects aged 59±9 (±1SD) were studied. There were 101 women (47%). Mean 10 year risk was 4.3±5.1% for AGLA, 4.8±5.1 for REY (p=0.099) and 15.0±7.7 for TROMSO (p<0.0001). While AGLA and REY categorized subjects as low in 90%, this was the case only in 73% of subjects with TROMSO (p<0.01, see distribution figure). REY and TROMSO shifted 13 and 49 subjects into a higher and 8 and 0 into a lower risk category .The indication for intensified LDL lowering was found with AGLA, REY and TROMSO in 26, 22 (p NS) and 55 cases (p=0.0007, see reclassification figure).

Table 1

	N	%	p
All	213	100	
Women	101	47.4	
Age + 1 SD (years)	59±9		
LDL <3.4 mmol/l and CRP > 2.0 mg/l	28	13.1	
AGLA Risk mean + 1 SD %	4.3±5.1		
LDL Intervention AGLA	26	12.2	
LDL Intervention REY	22	10.3	0.54
LDL Intervention TROMSO	**55**	**25.8**	**0.0003**



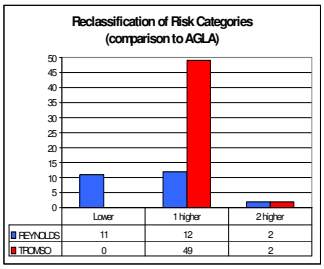


Table 2: Agreement for risk categories between AGLA and REYNOLDS (wKappa: 0.43, p<0.0001)

	REYNOLDS		
AGLA	LOW	INTERM	HIGH
LOW	181	8	2
INTERM	11	7	3
HIGH	0	0	1

L= low (0-9.9%), I = intermediate (10.0-19.9%), H= high (≥ 20.0%)

Table 3: Agreement for risk categories between AGLA and TROMSO (wKappa: 0.41, p<0.0001)

	TROMSO		
AGLA	LOW	INTERM	HIGH
LOW	156	34	1
INTERM	0	7	14
HIGH	0	0	1

Discussion

The key finding of our work is an underestimation of coronary risk when AGLA or REYNOLDS are compared to TROMSO, a posttest risk measure using AGLA as the pretest risk. As expected from the known low sensitivity of coronary risk charts, subclinical atherosclerosis derived risk reduced the percentage of low risk subjects from 90% to 73% with an increase of the mean estimated coronary risk from 5% (AGLA, REYNOLDS) to 15% (TROMSO, p<0.0001). Using the AGLA 2005 cutoffs for treatment goals of LDL-cholesterol in this population, we observed a significant increase of subject needing lipid lowering therapies (from 12% for AGLA to 26% for TROMSO, p=0.0003).

Although we did not use a random sample of our local population, we believe, that our results remain valid. Because we did not aim at defining the true prevalence of low risk but rather aimed at the question, if low risk is present, which additional risk modifier might significantly change the risk perception in a significant number of subjects, our approach can be justified.

Further, all our calculations were based on sex specific databases and risk calculations. Therefore, we can exclude a gender bias in our results.

The databases used were derived from large cohorts with sufficient time of observation, which is especially true for the TPA risk assessment tool, which was derived from 2898 men and 3237 women with an observation time of 6 years for incident myocardial infarction.

Conclusions

In our Swiss German population based middle-aged sample with a low mean coronary risk as determined by AGLA, the inclusion of hsCRP did not change significantly risk categories or LDL goals. However, using TPA, a significant number of subjects was shifted into higher risk categories with treatment implication for LDL-cholesterol. Therefore, the reliance on hsCRP as clinically important risk modifier in primary care has to be questioned, whereas TPA posttest risk calculations may increase the sensitivity of AGLA and have important impact on primary prevention of myocardial infarction and public health.