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RESEARCH LETTER
Risk Prediction/Assessment & Stratification

Prior myocardial infarction, coronary artery disease extent, diabetes mellitus, and CERT2 score for risk stratification in stable coronary artery disease

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Introduction

In the 2019 European Society of Cardiology (ESC) guideline for chronic coronary syndrome (CCS), 3% annual cardiac mortality was set as a limit for very high risk, which should prompt more aggressive medical treatment.[1] The guideline recommended methods for identifying high risk include, e.g. exercise electrocardiography, single-photon emission computed tomography or positron emission tomography perfusion imaging, stress echocardiography, cardiac magnetic resonance, coronary tomography angiography or invasive coronary angiography (ICA), and invasive functional testing.[1]

We and others have earlier demonstrated that distinct serum ceramide lipids predict CVD death in patients with CHD beyond LDL-cholesterol, and thus ceramides are being suggested as potential markers of residual risk.[2–5] Thus, we hypothesized that combining knowledge on disease extent obtained from ICA, disease severity [history of previous myocardial infarctions (MIs)], plaque vulnerability-related biomarker (ceramide- and phospholipid-based risk score CERT2), and risk increasing medical condition (diabetes mellitus type 2, DM2) would provide sufficient risk granulation, as recommended imaging methods, such as stress echocardiography or MRI, may be expensive and not always available. To this end, we tested risk stratification with the above-mentioned risk factors in two independent cohorts (COROGENE, LURIC) of patients referred for coronary angiography due to suspected coronary artery disease (CAD) and developed a new risk chart based on the results to aid clinical risk assessment in subjects with stable CHD, minor coronary atherosclerosis as well as no angiographic findings.

Methods

The Genetic Predisposition of Coronary Artery Disease (COROGENE) study is a prospective, cohort study of Finnish patients referred for ICA to the Helsinki University Central Hospital between June 2006 and March 2008.[6] The trial was approved by the ethics committee of Helsinki University Hospital (Approval number: Dnro 205/E0/2007). The Ludwigshafen Risk and Cardiovascular Health (LURIC) study comprises 3316 patients referred to the Cardiac Center Ludwigshafen (Germany) for ICA between July 1997 and January 2000.[7] The study protocol was approved by the ethics committee of the 'Landesärztekammer Rheinland-Pfalz' [#837.255.97(1394)]. Both studies were conducted in accordance with the Declaration of Helsinki and written informed consent was collected in all patients.

For evaluation in the present study, the patients both in both cohorts were assigned to groups based on the ICA findings as follows: (i) patients without angiographic CAD, (ii) patients without significant CAD (<50% stenosis), (iii) patients with one-vessel disease (≥50% stenosis in one major coronary artery), and (iv) patients with multivessel disease (≥50% stenosis in two or more major coronary arteries). Angiograms were performed on these patients for diagnostic reasons at baseline (baseline characteristics are shown in Supplementary material online, *Table S1*). Patients with acute coronary syndromes at baseline or recorded MIs during the preceding year were excluded from the analyses of the current

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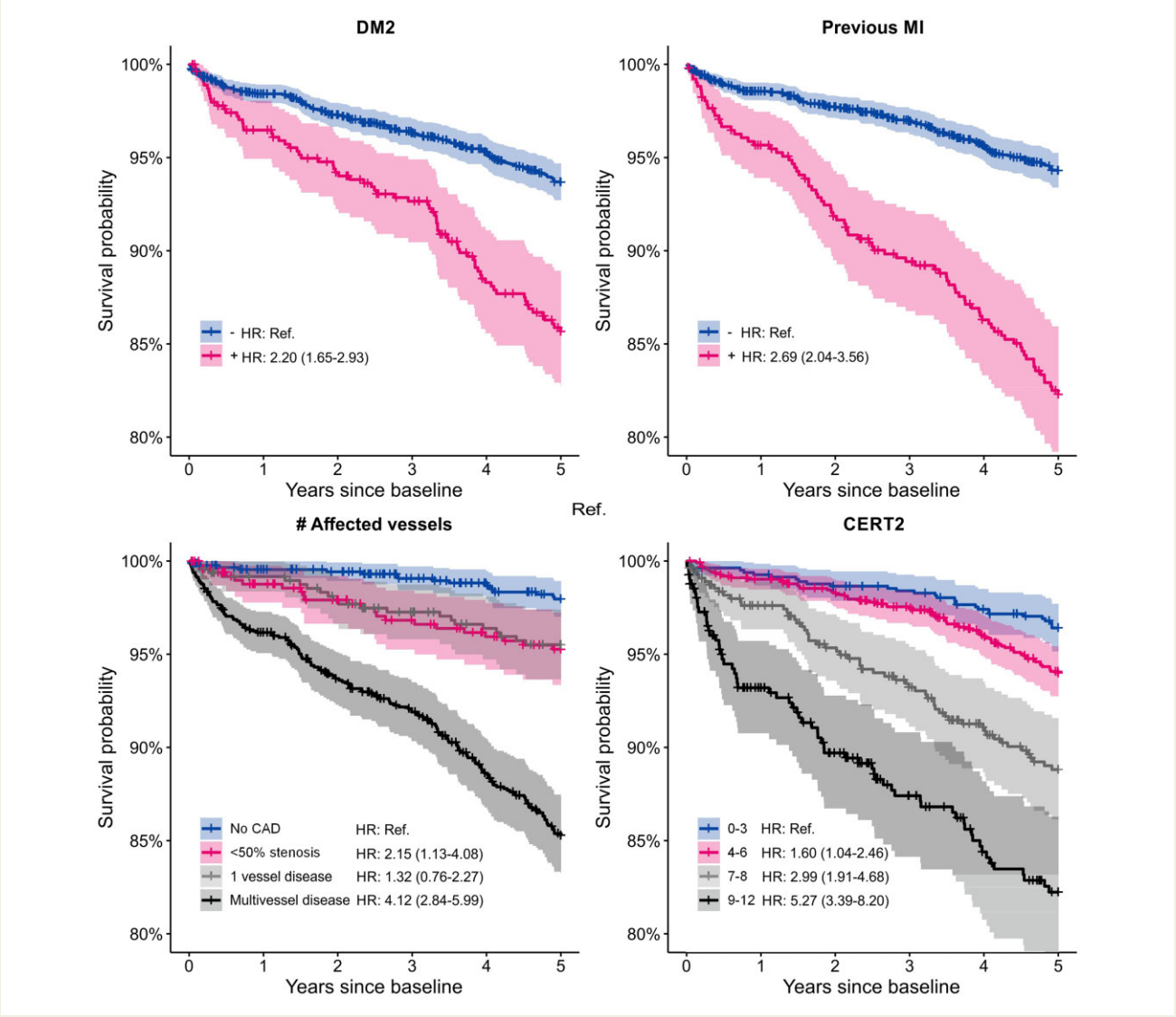

Figure 1 Kaplan–Meier curves and hazard ratios for diabetes mellitus type 2 (+/−), previous myocardial infarction (+/−), number of affected vessels (1–3), and CERT2 categories (0–3; 4–6; 7–8; 9–12 points) in the COROGENE study. CAD, coronary artery disease; DM2, diabetes mellitus type 2; HR, hazard ratio; MI, myocardial infarction.

study to focus on stabilized CCS patients, leaving 3017 and 1653 study subjects in COROGENE and LURIC, respectively. Details of the liquid chromatography–tandem mass spectrometry methods to analyse CERT2 risk score components and calculations are described in Supplementary material online, *Methods*.

Results

Kaplan–Maier curves and hazard ratios were used to investigate the effects of the risk factors (DM2, prior MI, disease extent, CERT2) in the COROGENE cohort (*Figure 1* and Supplementary material online, *Table S3*) for CVD death risk. A risk prediction chart based on the COROGENE data, following the concept of the European SCORE system used in primary prevention, was built (*Table 1*). This model revealed a wide range of CVD death risk in subjects referred to angiography due to suspected CAD (*Table 1*). Subjects without prior MI, angiographic CAD, DM2, and belonging to the lowest CERT2 risk group had only 0.1% risk of 1 year CVD death, whereas the highest risk patients had almost 14% predicted risk. When looking at the relative risk chart, there was more than 100-fold difference in risk between patients at highest vs. lowest risk (*Table 1*). Comparable risk charts were obtained for the LURIC study (Supplementary material online, *Table S4*). Linkage between absolute CVD death rates and different risk factor categories are shown in Supplementary material online, *Table S5*.

Discussion

The data of the present study confirms that CVD mortality risk in stable CHD patients is variable and high-risk patient identification is

Table 1 Predicted absolute and relative 1-year risk of CVD death in the COROGENE study

Absolute risk of 1 year CVD death (%)									
Prior MI	Disease extent	No diabetes				Diabetes			
Yes	Multivessel	1.6	2.7	4.9	9.1	3.0	4.9	8.3	13.8
	1 vessel	0.6	1.0	1.8	3.8	1.1	1.8	3.4	6.7
	<50% stenosis	0.5	0.9	1.8	3.6	1.0	1.8	3.3	6.4
	none	0.3	0.4	0.9	1.8	0.5	0.9	1.6	3.4
No	Multivessel	0.8	1.5	2.7	5.4	1.6	2.7	4.9	9.2
	1 vessel	0.3	0.5	1.0	2.1	0.6	1.0	1.9	3.8
	<50% stenosis	0.3	0.5	0.9	2.0	0.5	0.9	1.8	3.7
	none	0.1	0.2	0.5	1.0	0.3	0.5	0.9	1.8
	CERT2	0-3	4-6	7-8	9-12	0-3	4-6	7-8	9-12

Relative risk of 1 year CVD death (%)									
Prior MI	Disease extent	No diabetes				Diabetes			
Yes	Multivessel	12	20	36	67	22	36	61	102
	1 vessel	4	7	14	28	8	14	25	49
	<50% stenosis	4	7	13	27	8	13	24	47
	none	2	3	6	13	4	6	12	25
No	Multivessel	6	11	20	40	12	20	36	68
	1 vessel	2	4	7	15	4	7	14	28
	<50% stenosis	2	4	7	15	4	7	13	27
	none	1	2	3	7	2	3	6	14
	CERT2	0-3	4-6	7-8	9-12	0-3	4-6	7-8	9-12

RISK	LOW	MODERATE	HIGH

The relative risk has been normalized to subjects without prior MI, no stenosis, no DM2, and CERT2 0–3. The risk categories have been defined according to the European guidelines for CCS (low 0–1%; moderate 1–3%; high over 3% risk of CVD death in 1 year).
CCS, chronic coronary syndrome; CVD, cardiovascular disease; DM2, diabetes mellitus type 2; MI, myocardial infarction.

possible by using only a small number of risk factors jointly. The present results show the non-benign prognosis of the non-obstructive CAD (<50% stenosis) and, therefore, support risk assessment also in patients with non-obstructive atherosclerotic coronary disease. In fact, there seem to be no risk difference between <50% stenosis and one-vessel disease. Thus, these two categories could have been grouped together for the risk chart. However, the presence of a 50% diameter stenosis of the coronary artery has often been used as the threshold value for therapy. Thus, in that case the treating physicians could use the 'percent stenosis' as an additional criteria and neglect the non-benign prognosis of the non-obstructive CAD (<50% stenosis). Therefore, it appears useful to demonstrate that MIs are equally likely to originate from a non-significant lesions compared to >50% stenosis lesions. In other words, coronary lesions <50% are not normal and by default of low risk.

Medical treatment and lifestyle coaching are the cornerstones of successful CAD prevention. A reliable and practical risk stratification tool can be used to direct patients to different intensity paths of care. In principle, all CHD patients need to be treated appropriately, however, the same intensity may not be needed for everyone and health care systems are not able to sustain costs caused by a widespread intensive treatment with the most recent medical innovations and multiple outpatient clinic visits due to lifestyle coaching. To this end, the recent ESC guideline for stable CCS has recognized very high-risk patients (>3% annual cardiac mortality) and provided targeted medical treatment suggestions for those patients.[1] In the guideline, assessment of event risk is recommended in every patient being evaluated for suspected CAD or with a newly diagnosed CAD, as it has major impacts on therapy decisions. As some of the guideline suggested imaging modalities may not always be available and the routinely used ICA is still a rather rough risk estimation tool, as demonstrated in the present study, we developed an alternative risk estimation system. The ceramide/phospholipid (CERT2) assay can be executed in routine clinical laboratory facilities on a high-throughput, automated 96-well plate format and mass spectrometry with affordable and readily available reagents, and the cost of production is at a typical lower end of the industrial norms.

In conclusion, these data demonstrate that identification of very high-risk patients is possible by combining information on CAD extent, prior MI, prevalence of DM2, and CERT2 score. This newly

developed risk chart is designed to aid in selecting high-risk stable CHD patients for guideline-recommended special medical care.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Data availability statement

For sharing of de-identified data used in this study, the COROGENE and LURICstudies will consider any reasonable application for scientific collaboration. For COROGENE, the contact person is prof. Juha Sinisalo (juha.sinisalo@hus.fi) and for LURIC study prof. Winfried März (Winfried.Maerz@synlab.com).

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Conflict of interest: Zora Biosciences Oy holds patent disclosures related for the diagnostic and prognostic use of ceramides and phospholipids in CVD. M.H., A.J., M.L., and R.L. are employees and R.L. and R.H are shareholders of Zora Biosciences Oy.

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