Routinely available biomarkers improve prediction of long-term mortality in stable coronary artery disease: the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score

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Received 7 April 2012; revised 3 May 2012; accepted 15 May 2012; online publish-ahead-of-print 28 June 2012

Aims

Previous risk assessment scores for patients with coronary artery disease (CAD) have focused on primary prevention and patients with acute coronary syndrome. However, especially in stable CAD patients improved long-term risk prediction is crucial to efficiently apply measures of secondary prevention. We aimed to create a clinically applicable mortality prediction score for stable CAD patients based on routinely determined laboratory biomarkers and clinical determinants of secondary prevention.

Methods and results

We prospectively included 547 patients with stable CAD and a median follow-up of 11.3 years. Independent risk factors were selected using bootstrapping based on Cox regression analysis. Age, left ventricular function, serum cholinesterase, creatinine, heart rate, and HbA1c were selected as significant mortality predictors for the final multivariable model. The Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score based on the aforementioned variables demonstrated an excellent discriminatory power for 10-year survival with a C-statistic of 0.77 (P < 0.001), which was significantly better than an established risk score based on conventional cardiovascular risk factors (C-statistic = 0.61, P < 0.001). Net reclassification confirmed a significant improvement in individual risk prediction by 34.8% (95% confidence interval: 21.7–48.0%) compared with the conventional risk score (P < 0.001).

External validation of the risk score in 1275 participants of the Ludwigshafen Risk and Cardiovascular Health study (median follow-up of 9.8 years) achieved similar results (C-statistic = 0.73, P < 0.001).

Conclusion

The VILCAD score based on a routinely available set of risk factors, measures of cardiac function, and comorbidities outperforms established risk prediction algorithms and might improve the identification of high-risk patients for a more intensive treatment.

Keywords

Stable coronary artery disease • Risk prediction • Risk score • Survival

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Introduction

Atherosclerosis is a chronic immuno-inflammatory disease with stable and unstable clinical presentation. In patients with stable coronary artery disease (CAD), atherosclerosis is characterized by fibrous proliferation in medium- and large-sized arteries mainly driven by lipid accumulation and eventually resulting in calcification of the vessel wall. Consequently, atherosclerosis leads to a gradual luminal narrowing over decades. In contrast, acute coronary syndromes (ACS) are driven by a dynamic component, mostly atherosclerotic plaque rupture followed by thrombosis and coronary occlusion. Although, stable CAD and ACS represent two entities of the same disease, they differ distinctly in their long-term prognosis. In ACS patients major cardiovascular events occur frequently during the following months. Therefore, various risk assessment scores including the Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (PURSUIT) risk score, the Thrombolysis in Myocardial Infarction (TIMI) risk score or the Global Registry of Acute Coronary Events (GRACE) risk score have been developed. In stable CAD patients the rate of major cardiovascular events is much lower with an estimated annual rate of 1–2%, and thus the prediction of the short-term and the intermediate-term risk is less relevant. In this patient population it is more important to have sufficient diagnostic tools for the estimation of the accumulating long-term risk to guarantee an efficient application of measures of secondary prevention including the lifelong administration of drugs, associated with reduced readmission rates and overall mortality. However, there is currently no established mortality prediction score for patients with stable CAD. So far, only a score published by Marschner et al. has been developed for patients with ACS but has been proposed for risk prediction in stable CAD patients. This risk score encompasses cardiovascular risk factors such as age, gender, smoking habits, hypertension, diabetes, and history of previous cardiovascular events, but does not include laboratory markers except for lipoprotein levels. While these established cardiovascular risk factors are crucial for risk estimation of the development of CAD, different clinical or laboratory variables may become important for the long-term outcome in patients with manifest CAD. Notably, renal and liver function may be relevant, particularly if these patients receive a set of drugs over decades.

The aim of our study was to assess the independent predictive power of known clinical risk factors and routinely tested laboratory biomarkers for long-term mortality in stable CAD patients. We further aimed to create a clinically applicable mortality prediction score for this specific patient population based on a stringent statistical selection procedure.

Methods

Derivation cohort

We prospectively included 1152 consecutive CAD patients referred to the Department of Cardiology of the Vienna General Hospital between November 1999 and August 2000. Of these, 547 patients with stable CAD were selected for this study. The study protocol complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Vienna.

Validation cohort

We used the Ludwigshafen Risk and Cardiovascular Health (LURIC) study for external validation of risk prediction. The detailed study protocol has been previously described. In brief, 3500 patients referred to the Heart Center of Ludwigshafen for coronary angiography were enrolled between July 1997 and January 2000. For the purpose of this study we selected 1275 patients with proven CAD who presented in a stable condition.

Clinical definitions

Stable CAD was defined as angiographical evidence of stenosis of an epicardial coronary artery of ≥ 60% in the derivation cohort and of ≥ 50% in the validation cohort. Cardiovascular risk factors such as hypertension, diabetes mellitus, current smoking, and lipid disorders were recorded according to the respective guidelines. Left ventricular ejection fraction (LVEF) was estimated using the Simpson method and categorized into normal (≥ 55%), mildly reduced (45–54%), moderately reduced (30–44%), and severely reduced (< 30%). Blood samples were analysed without freezingaccording to local laboratory standard procedure.

Study endpoints and follow-up

The primary study endpoint was all-cause mortality and obtained by screening the national register of death, including screening for the cause of death (according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision). In the derivation cohort, post-mortem examination was performed in 34% of patients to verify the cause of death. In the validation cohort (LURIC), information was obtained from local registries and death certificates were used to classify who died of cardiovascular and non-cardiovascular cause as previously described.

Statistical analysis

Continuous data were presented as median and interquartile range, discrete data as counts and percentages. The Mann–Whitney U test and χ² test were used for comparisons between groups, as appropriate. Cox proportional hazard regression analysis was applied to assess the effect of variables on survival. Continuous variables underwent log transformation before analysis. A bootstrap resampling procedure was used to identify best-fitting variables for the multivariable Cox regression model. Before inclusion of variables into the bootstrapping procedure collinearity between biomarkers was assessed using Pearson correlation coefficients (data not shown). In case of close correlation only the strongest univariate predictor of a cluster (defined by the highest univariate hazard ratio (HR) for an increase of 1 standard deviation (SD)) entered the selection procedure. Samples with a size of 80% of the original cohort were chosen for repeats. Hundred repeats with forward selection and 100 repeats with backward selection (with a P < 0.1 for selection) were performed. Variables selected in > 80% of all repeats were included in the final multivariable model. The discriminatory power of the designed risk scores was assessed using Harrell’s C-statistic. For further analysis we stratified the cohort by tertiles of the multimarker risk scores. An improvement in individual risk prediction was examined by the net reclassification improvement (NRI) as described by Pencina et al. Kaplan–Meier analysis (log-rank test) was applied to verify the time-dependent discriminative power of risk scores. Cut-off values for a simplified score using categorized variables were estimated using χ² values derived from Martingale residuals of the Cox model for all possible cut-off values. For optimized clinical
Results

Baseline characteristics and univariate survival analysis

We prospectively enrolled 547 stable CAD patients into our derivation cohort (Vienna). Thirty-nine per cent of all patients (n = 211) died during a median follow-up of 11.3 years (IQR: 6.9–11.5) corresponding to 4974 overall person-years of follow-up. Fifty-seven per cent of deaths in patients were due to cardiovascular causes. The validation cohort (LURIC) includes 1275 prospectively enrolled stable CAD patients with a median follow-up of 9.8 years (IQR 7.0–10.5). Of these patients 35% (n = 499) died during the observation period (primary endpoint), 51% died from cardiovascular causes. Baseline characteristics of both study cohorts are displayed in Supplementary material online, Table S1.

In the univariate analysis, the strongest adverse risk factors for long-term outcome in stable CAD patients were age with an HR of 1.94 per 1 – SD increase in the derivation cohort and an HR of 1.84 in the validation cohort, and LVEF with an HR of 1.67 for a reduction in one semi-quantitative category in the derivation cohort and an HR of 1.75 in the validation cohort, respectively. Cholinesterase had a strong inverse effect on mortality with an HR of 0.57 per 1 – SD increase in the derivation cohort and of 0.72 in the validation cohort (Table 1).

Bootstrapping results and multivariable survival analysis

After variable selection by a bootstrap technique age, LVEF, serum cholinesterase, creatinine, heart rate and HbA1c were selected as significant mortality predictors for the final multivariable model (Figure 1). In this multivariable model age and LVEF remained the strongest adverse risk factors and cholinesterase the strongest inverse risk factor (Table 1).

Risk score design and internal validation

In a second step, we computed a weighted risk score, the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score, for 10-year survival using the aforementioned variables obtained by the bootstrapping procedure (see Supplementary material online, Method 1 for the formula). The C-statistic demonstrated an excellent discriminatory power of the VILCAD risk score for 10-year survival with a value of 0.77 (P < 0.001). The discriminatory ability of our score to predict 10-year mortality was significantly better than that of a conventional risk score published by Marschner et al.7 (C-statistic 0.61; P < 0.001 for comparison of the two scores). The predictive value of the new multimarker score was also superior to that of the GRACE score (C-statistic = 0.67; P < 0.001 for the comparison between the two scores).14

Kaplan–Meier analysis confirmed a high discriminative power when plotting tertiles of the VILCAD risk score (P < 0.001 between all tertiles, Figure 2A) with 10-year survival rates of 90,
75, and 33% in the first, second, and third tertile of the score. The NRI showed an improvement in individual risk classification of 34.8% [95% confidence interval (CI): 21.7–48.0%] compared with the conventional risk score published by Marschner et al.\(^7\) (Table 2, \(P < 0.001\)). With regard to cardiovascular mortality, a comparable trend for the 10-year survival was observed, with survival rates of 94, 86, and 52% in the first, second, and third tertile of the new risk score (\(P \leq 0.001\) between all tertiles).

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**Figure 1** Variable selection by a bootstrap resampling procedure based on Cox regression analysis. Variables selected in > 80% of all repeats (black bars) were included in the final multivariable model. Hba1c values of the complete study population were used for the bootstrap resampling procedure. Fasting glucose, non-high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, hypertriglyceridaemia and triglycerides, iron, protein, aspartate aminotransferase and alanine aminotransferase, C-reactive protein, thrombin time, mean platelet volume, leukocyte count, and relative neutrophil count were excluded before bootstrap selection due to close correlation with other variables entering the bootstrap selection. A post hoc analysis showed that pharmacological treatment including aspirin, thienopyridines, renin–angiotensin–aldosterone system inhibitors, beta-blockers, and statins would not qualify for the final model.

**Figure 2** Kaplan–Meier estimates of all-cause mortality according to tertiles of the Vienna and Ludwigshafen Coronary Artery Disease risk score for stable coronary artery disease for the derivation (A) and validation cohorts (B, both \(P < 0.001\) between all tertiles, log-rank test).
Table 2  Reclassification table

<table>
<thead>
<tr>
<th>Risk class</th>
<th>Conventional risk score</th>
<th>VILCAD risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>n = 210</td>
<td>n = 210</td>
</tr>
<tr>
<td>No event</td>
<td>Low 62 (76)</td>
<td>Moderate 41 (48)</td>
</tr>
<tr>
<td>Event</td>
<td>Low 11 (4)</td>
<td>Moderate 13 (10)</td>
</tr>
<tr>
<td>Event</td>
<td>Low 58 (227)</td>
<td>Moderate 34 (85)</td>
</tr>
<tr>
<td></td>
<td>Low 32 (124)</td>
<td>Moderate 47 (118)</td>
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<tr>
<td>Validation</td>
<td>Low 826</td>
<td>Moderate 19 (26)</td>
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<tr>
<td></td>
<td>Low 58 (227)</td>
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<td>Moderate 25 (28)</td>
</tr>
<tr>
<td></td>
<td>Low 33 (37)</td>
<td>Moderate 25 (28)</td>
</tr>
</tbody>
</table>

Reclassification table comparing the weighted VILCAD risk score with the conventional risk score by Marschner et al. Data are given as % row (n).

External validation

We validated our multimarker risk score in the LURIC study population. A C-statistic of 0.73 confirmed the strong and superior discriminatory power of our risk score to predict long-term mortality (P < 0.001 for comparisons with the C-statistics of 0.64 for the Marschner risk score and of 0.61 for the GRACE risk score). Kaplan–Meier analysis confirmed a high discriminative value when plotting tertiles of the new risk score (P < 0.001 between all tertiles, Figure 2B) with 10-year survival rates of 85, 73, and 37% in the first, second, and third tertile of the score. With regard to cardiovascular mortality, a comparable trend for the 10-year survival was observed, with survival rates of 93, 83, and 52% in the first, second, and third tertile of the VILCAD risk score (P < 0.001 between all tertiles). An NRI of 14.8% (95% CI: 6.5–23.2%) confirmed a significant improvement in individual risk classification in the validation cohort compared with the conventional risk score by Marschner et al. (P < 0.001, Table 2).

Simplified score

Finally, we designed a simplified risk score for optimal clinical use. This score was based on the same variables as the VILCAD risk score. Continuous variables were dichotomized according to optimal cut-off levels, as described in Figure 3. Two points were assigned to the variables age and LVEF with the strongest predictive value. This simplified risk score still had a strong predictive value for 10-year mortality with a C-statistic of 0.74 in the derivation cohort and of 0.70 in the validation cohort (both P < 0.001 for comparison with the conventional risk score). The simplified score showed a highly discriminative value with 10-year mortality of 11% in patients with 0 points and of 89% in patients with at least 5 points in the derivation cohort and a similar spread in the validation cohort (Figure 3A and C). As cholinesterase may not be available in all centres we also calculated a simplified risk score without cholinesterase, which showed a similar predictive value in the derivation and validation cohorts and a comparable discrimination of mortality risk (Figure 3B and D).

Discussion

We developed a multimarker score for patients with stable CAD providing an excellent discriminatory power for the prediction of 10-year survival. The final set of six variables was selected by a stringent bootstrap resampling procedure from 48 clinical variables and routinely available biomarkers which reflect a broad range of relevant pathophysiological pathways, determinants of heart disease and comorbidities. The clinical relevance of the VILCAD score was further emphasized by a significant improvement in net reclassification by 34.8%, which reflects the proportion of individuals, who may benefit from an improved risk prediction compared with a conventional risk score. Most importantly, we additionally performed an external validation of our risk score in the LURIC study population, a large prospective European cohort study, and obtained comparable results confirming the accuracy of our risk score. Despite the large number of published risk scores, model transportability has rarely been evaluated in external study populations but is crucial for the objective and critical evaluation of evolving risk scores.

Previous risk assessment scores for CAD patients have predominantly focused on the high-risk patients presenting with ACS ranging from the PURSUIT risk score over the TIMI risk score to the GRACE risk score. In comparison, the area under the receiver operating curve (AUC) of the TIMI, PURSUIT and GRACE risk scores ranged from 0.69 to 0.79 for mortality prediction in ACS populations. In contrast to the present study, these risk scores were based on relatively short follow-up times of 1 year and used the less stringent receiver operating characteristic curves instead of the recommended C-statistic. In our study population
The GRACE score only reached a C-statistic of 0.67 in the derivation cohort and of 0.61 in the validation cohort and was distinctly weaker than the presented VILCAD score. There is increasing evidence that stable CAD patients differ significantly from patients with ACS in terms of plaque morphology and extent of affection of coronary arteries. Therefore, it is likely that different risk factors might be relevant with regard to long-term mortality prediction. Thus, ACS risk scores may not be applicable to patients with stable CAD. However, information on long-term prediction of patients with established stable CAD is scarce and, to the best of our knowledge, there is no established mortality prediction score for stable CAD patients. One previous risk score published by Marschner et al. included CAD patients with an acute cardiac event 3–36 months before inclusion and has recently been proposed as risk assessment score for stable CAD patients. The application of the Marschner score in our cohort resulted in a C-statistic of 0.61 in the derivation cohort and of 0.64 in the validation cohort, which was strikingly lower than the C-statistic achieved with the new VILCAD score (P < 0.001 for both cohorts). Recently, another multimarker score for stable CAD integrating the novel biomarkers N-terminal pro-B-type natriuretic peptide, growth differentiation factor 15, mid-regional-pro-atrial natriuretic peptide, cystatin C, and mid-regional-pro-adrenomedullin has been published. While integration of a comprehensive set of potentially relevant pathomechanisms is supposed to improve risk prediction, the aforementioned score yielded an AUC of only 0.69 with respect to a median follow-up of 3.6 years. Additional costs for the determination of novel biomarkers may limit the use of the aforementioned score in clinical practice.

The relative importance of established cardiovascular risk factors differs in patients with manifest CAD compared with primary prevention strategies. In addition to established cardiovascular risk factors, determinants of heart disease such as left ventricular function, heart rate, normal ECG, multi-vessel disease, and coronary revascularization status gain importance in secondary risk prediction. Moreover, liver and renal function may affect the treatment with established cardiac medication and the outcome of stable CAD patients. Accordingly, a wide range of easily available clinical and laboratory markers may be important and were included in the bootstrapping procedure. The final model selected

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**Figure 3** Risk prediction of simplified risk score. The bars show 10-year mortality stratified by the simplified score in the derivation (A and B) and validation (C and D) cohorts with (A and C) or without the inclusion of cholinesterase (B and D). The following cut-off values were applied for the generation of the simplified score: \[ \text{age} \geq 75 \text{ years (82nd percentile)} = 2 \] + [ left ventricular ejection fraction moderate = 1, severe = 2 ] + [ HbA1c \geq 6.5\% in patients with known diabetes (66th percentile) = 1 ] + [ creatinine \geq 1.3 \text{ mg/dL (86th percentile)} = 1 ] + [ heart rate \geq 75 \text{ b.p.m. (70th percentile)} = 1 ] + [ cholinesterase \leq 4.4 \text{ kU/L (10th percentile)} = 1 \text{ for A and C} ]. Percentiles derived from the derivation cohort.
by a stringent statistical method encompassed age, cardiac parameters (LVEF and heart rate), renal function (creatinine), liver function (CHE), and HbA1c, a metabolic measurement of poor glycaemic control in diabetic patients. While we confirmed the already known importance of age, LVEF, heart rate, creatinine, and HbA1c in cardiovascular disease the role of cholinesterase is less well established. Serum cholinesterase is a non-specific cholinesterase enzyme that hydrolyses different choline esters and has previously been implicated in the development of CAD. A previous study by Calderon-Margalit et al. demonstrated that cholinesterase might be a non-specific risk factor for mortality. Moreover, an analysis from our group demonstrated a strong association between decreased cholinesterase and long-term outcome in patients with known CAD, which was stronger in stable CAD patients than in those with ACS.

Despite their repeatedly proven accuracy, risk scores are underused in clinical practice mainly due to time constraints. Therefore, we also developed a simplified multimarker score optimized for clinical use based on the variables selected by the bootstrapping procedure. The simplified multimarker score divides markers only in two to three categories based on optimized cut-off values as recently propagated by Kooter et al. In contrast to more complex risk scores this simplified multimarker risk score can conveniently be computed by hand without the use of a calculator. This simplified risk score is cost-effective as it comprises routinely determined laboratory measurements and conventional clinical data. The simplified score still had a competitive predictive performance resulting in a C-statistic of 0.74 in the derivation cohort and of 0.70 in the validation cohort which is illustrated by the following comparison: a 74-year-old patient with stable CAD, a creatinine of 1.5 mg/dL but none of the other included risk predictors would reach 1 point in our score and would have a 37% risk of death during the following 10 years (Figure 3). On the contrary, a 77-year-old patient with a severely reduced LVEF, and an HbA1c of 6.8% (5 points) would expect an 89% risk of death within the next 10 years. The use of easily applicable scores is important as a previous report has shown that multimarker scores improve the accuracy of risk prediction compared with the sole clinical judgement of the treating physician. Awareness of the risk of a patient may have important consequences on the choice of treatment options. Aggressive treatment options might be underused as high-risk patients might not be recognized due to an inaccurate risk assessment.

Limitations

We are aware of the following limitations of our study: the patient cohort was recruited at a university-affiliated tertiary care centre with a high-volume cardiac catheterization unit and may therefore not be representative for stable CAD patients in general. Furthermore, patients were included into the study between 1999 and 2000. Since then secondary prevention strategies have been modified (e.g. drug eluting stents, automated implantable cardioverter defibrillator implantation guidelines, cardiac resynchronization therapy, and heart rate modification). These new prevention strategies might affect the accuracy of our risk score. Moreover, different laboratory markers may be available in different health-care systems. Yet, the performance of the score was robust when variables such as cholinesterase were excluded which may not be routinely available in other centres. Third generation troponin T assays were not available at the time of study enrollment. However, the variable ECG abnormalities suggesting (clinically silent) ischaemia were not selected for the final model. Also, brain natriuretic peptide was not routinely measured in stable CAD patients. However, myocardial function measured by echocardiography was selected most frequently and was one of the strongest risk factors in the final model. While these evolving biomarkers may improve the prediction of long-term mortality, a C-statistic of >0.77 has been rarely achieved for long-term mortality. Therefore, it is improbable that the predictive value of the new VILCAD score will be significantly improved by a single biomarker. Finally, the analysis of net reclassification is limited by the lack of generally accepted risk categories for long-term mortality in this patient cohort.

Conclusion

A distinct set of clinical and laboratory variables seem to be relevant to determine the long-term survival of patients presenting with stable CAD. The presented VILCAD score fills a gap in risk prediction of these patients. The selected variables encompass age, cardiac, renal and liver function, and HbA1c, a measurement of poorly controlled diabetes. The presented risk score may improve the precision of the prediction of survival as evidenced by its high discriminatory power and its confirmation in an external validation cohort. One may speculate that improved risk prediction may help to more specifically tailor possible treatment options in secondary prevention of CAD and to specifically select high-risk patients who may benefit from an intensified treatment.

Supplementary material

Supplementary material is available at European Heart Journal online.

Funding

LURIC has received funding from the 6th Framework Program (integrated project Bloodomics, grant LSHM-CT-2004-503485) and 7th of Framework Program (integrated project AtheroRemo, Grant Agreement number 201668) of the European Union.

Conflict of interest: none declared.

References

Routinely available biomarkers improve prediction of CAD


