Butyrylcholinesterase Activity Predicts Long-Term Survival in Patients with Coronary Artery Disease

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BACKGROUND: Low serum butyrylcholinesterase activity was associated with all-cause and cardiovascular mortality in a community-based study; however, there are no data from investigations of the long-term effects of butyrylcholinesterase on mortality in patients with diagnosed coronary artery disease (CAD). We therefore assessed the effect of butyrylcholinesterase activity on the outcomes of patients with CAD.

METHODS AND RESULTS: We prospectively included 720 patients in our study: 293 patients with stable CAD and 427 patients with acute coronary syndrome. During a median follow-up of 11.3 years corresponding to 6469 over-person-years, 278 deaths (38.6%) were recorded. We detected a significant and independent protective effect of butyrylcholinesterase on all-cause mortality (adjusted hazard ratio (HR) for a 1-SD increase, 0.62; 95% CI, 0.54 – 0.70; P < 0.001) and cardiovascular mortality (adjusted HR, 0.64; 95% CI, 0.54–0.76; P < 0.001) in a Cox proportional hazards regression analysis. The 10-year survival rates were 42%, 74%, and 87% in the first, second, and third tertiles of butyrylcholinesterase activity. The presentation of CAD affected the effect of butyrylcholinesterase on mortality (P for interaction = 0.012), with a stronger association found in patients with stable CAD (adjusted HR, 0.56; 95% CI, 0.45–0.70; P < 0.001).

CONCLUSIONS: Our study demonstrates a strong inverse association between butyrylcholinesterase activity and long-term outcome in patients with known CAD. Because butyrylcholinesterase added predictive information after adjustment for established cardiovascular risk factors, additional underlying pathophysiological mechanisms and the potential applicability of butyrylcholinesterase activity for secondary risk prediction needs to be addressed in future studies.

Atherosclerosis, the most prevalent manifestation of cardiovascular disease, is associated with high morbidity and long-term mortality (1). Recognition of the importance of these associations led to the first published recommendations for the prevention of coronary artery disease (CAD) in 1994 (2). Since that time, a large variety of cardiovascular risk factors have been identified and used to create risk charts that attempt to simplify the estimation of CAD risk (3). In countries with declining cardiovascular mortality rates, including most European countries, virtually all such risk scores currently overestimate CAD risk. Therefore, identification of additional risk factors and further recalibration will be crucial to improve cardiovascular risk prediction (3). Additionally, improved long-term risk prediction will be essential for the efficient application of measures of secondary prevention to patients who already have CAD. Such measures have proved effective in reducing readmission rates and overall mortality (4, 5).

Serum butyrylcholinesterase has been implicated in the development of CAD (6, 7). Calderon-Margalit et al. demonstrated that individuals in the lowest quintile of butyrylcholinesterase activity had significantly higher rates of all-cause and cardiovascular mortality (8). Nevertheless, information on the impact of butyrylcholinesterase in secondary prevention is scarce. Furthermore, there are no data from investigations of the long-term effects of butyrylcholinesterase on cardiovascular and all-cause mortality in patients with diagnosed CAD. We therefore assessed the influence of butyrylcholinesterase activity on the outcomes of CAD patients.

Between November 1999 and August 2000, we prospectively enrolled patients with acute coronary syndrome (ACS) or stable CAD in our study (9). The participants were recruited at the Cardiology Department of Vienna General Hospital, a university-affiliated tertiary center with a high-volume cardiac catheterization unit. The study protocol complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Vienna.

Diagnosis of ACS was consistent with the consensus document of the European Society of Cardiology and the American College of Cardiology (10). Stable CAD was confirmed angiographically and defined as a stenosis of an epicardial coronary artery of ≥60%. Conventional cardiovascular risk factors were recorded according to the respective guidelines. Fresh blood samples were analyzed according to the local lab-
oratory’s standard procedure. Butyrylcholinesterase was measured in serum at 25 °C with an enzyme kinetic assay using butyrylthiocholine iodide as substrate (11).

All-cause and cardiovascular mortality were defined as the study end points and obtained by screening the national register of death, including screening for specific causes of death [according to the International Classification of Diseases, Tenth Revision (ICD-10)]. The cause of mortality was verified by postmortem examination in 34% of the patients. A sample size of 720 patients with 35% of patients experiencing the primary end point allowed the detection of a risk ratio of 1.33 (α = 0.05; power = 80%).

Continuous data were presented as the median and interquartile range, and their association with butyrylcholinesterase activity was assessed with the Spearman ρ correlation coefficient. Discrete data were presented as count and percentage and analyzed with the χ² test. Cox regression analysis assessed the effect of butyrylcholinesterase activity on mortality, and the results are presented as the hazard ratio (HR) and the 95% CI for a 1-SD increase in continuous variables. To account for potential confounding effects, we calculated the risk for death for butyrylcholinesterase activity after adjusting for established cardiovascular risk factors, including age, sex, body mass index, hypertension, smoking, diabetes, family history of CAD, total cholesterol, HDL cholesterol, triglycerides, creatinine, albumin, multivessel disease, revascularization status (including percutaneous coronary intervention and coronary artery bypass surgery), and presentation of CAD (stable CAD or ACS). First-degree interactions were tested with interaction terms between the independent variables and all tested potential confounders. The effect of butyrylcholinesterase on survival was further analyzed with age-adjusted survival curves. Therefore, butyrylcholinesterase activity was categorized into tertiles. ROC curves were plotted to assess the predictive value of butyrylcholinesterase for long-term mortality. Two-sided P values <0.05 indicated statistical significance. The STATA 11 software package (StataCorp) and SPSS software (version 15.0; SPSS/IBM) were used for all analyses.

We prospectively included 720 patients in our study: 41% with stable CAD (n = 293) and 59% with ACS (n = 427). The mean (SD) butyrylcholinesterase activity in serum was 5.62 (1.47) kU/L for all patients, 5.58 (1.54) kU/L for patients with stable CAD, and 5.66 (1.36) kU/L for ACS patients. Butyrylcholinesterase activity showed significant associations with albumin, total cholesterol, LDL, body mass index, hypertension, and family history of CAD, and showed modest but significant inverse correlations with age and serum creatinine (Table 1). During a median follow-up of 11.3 years (corresponding to 6469 overall person-years), 39% of the patients (n = 278) died. A slightly higher percentage of ACS patients died (40% compared with 37% of the patients with stable CAD). Forty-four percent of the fatal events in patients with stable CAD and 68% of such events in ACS patients were due to cardiovascular causes.

We detected a significant protective effect of butyrylcholinesterase on all-cause mortality [crude HR, 0.58 (95% CI, 0.51–0.64; P < 0.001); adjusted HR, 0.62 (95% CI, 0.54–0.71; P < 0.001)] and cardiovascular mortality [crude HR, 0.56 (95% CI, 0.48–0.64; P < 0.001); adjusted HR, 0.64 (95% CI, 0.54–0.76; P < 0.001)] in the Cox proportional hazards models. Analogous results for all-cause mortality were detected for patients with stable CAD [crude HR, 0.44 (95% CI, 0.35–0.55; P < 0.001); adjusted HR, 0.56 (95% CI, 0.45–0.70; P < 0.001)] and ACS [crude HR, 0.63 (95% CI, 0.55–0.73; P < 0.001); adjusted HR, 0.68 (95% CI, 0.57–0.82; P < 0.001)]. The predictive value of butyrylcholinesterase activity was stronger in patients with stable CAD, with a significant modification of effect by the presentation of CAD (P = 0.012).

The area under the ROC curve (AUC) for butyrylcholinesterase activity was 0.34 for all patients (P < 0.001), 0.30 for patients with stable CAD (P < 0.001), and 0.37 for ACS patients (P < 0.01). These AUC values would be equivalent to AUCs of 0.66, 0.70, and 0.63 for risk factors positively associated with outcome. When butyrylcholinesterase activity was added to the multivariate model, the respective AUCs increased from 0.72 to 0.76 for all patients (P < 0.001, for comparison of AUCs), from 0.74 to 0.78 for patients with stable CAD (P = 0.01, for comparison of AUCs), and from 0.71 to 0.75 for ACS patients (P = 0.01, for comparison of AUCs). Survival curves for tertiles of butyrylcholinesterase activity demonstrated a significant decrease in all-cause mortality with increasing concentrations of butyrylcholinesterase for all patients (Fig. 1). The 10-year survival rates were 42%, 74%, and 87% in the first, second, and third tertiles, respectively. Similar trends were observed for patients with stable CAD and ACS (see Fig. 1 in the Data Supplement that accompanies the online version of this Brief Communication at http://www.clinchem.org/content/vol58/issue6).

Our results indicate a strong inverse association between butyrylcholinesterase activity and both overall mortality and cardiovascular mortality in CAD patients. These associations persisted after adjustment for potential confounders. Although the presentation of CAD was not associated with butyrylcholinesterase activity, the predictive value of butyrylcholinesterase was significantly stronger in patients with stable CAD, with an almost 50% risk reduction per 1-SD increase.
Our study extends the results of Calderon-Margalit et al., who demonstrated that low butyrylcholinesterase activities were associated with higher all-cause and cardiovascular mortality in individuals whose coronary artery status was unknown. In contrast to that cohort, the inverse association of butyrylcholinesterase activity with mortality in the present cohort with known CAD was independent of potential founders. In particular, adjustment for albumin did not affect the significant association of butyrylcholinesterase activity with mortality, despite a moderate correlation of butyrylcholinesterase with albumin ($r = 0.36$) in our cohort as well (8). The binding of butyrylcholinesterase to albumin is a potential explanation for this association (12). An alternative explanation may be that both values reflect the ability of the liver to synthesize proteins (8). Furthermore, in line with previous results for community-based study populations, we confirmed an association with the metabolic risk factors of body mass index, total cholesterol, LDL cholesterol, and triglycerides (8, 13). The inverse associa-

### Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>Correlation, $r$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butyrylcholinesterase, kU/L</td>
<td>4.20 (3.52–4.70)</td>
<td>5.53 (5.23–5.85)</td>
<td>7.02 (6.50–7.66)</td>
<td>-0.19</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>64 (56–73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>484 (72.7)</td>
<td>145 (67.1)</td>
<td>168 (77.1)</td>
<td>171 (73.7)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>26.8 (24.5–29.4)</td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>437 (66.1)</td>
<td>129 (60.8)</td>
<td>142 (65.1)</td>
<td>166 (71.9)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>193 (44.5)</td>
<td>89 (42.0)</td>
<td>92 (42.4)</td>
<td>112 (48.7)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>251 (43.1)</td>
<td>68 (35.8)</td>
<td>84 (45.2)</td>
<td>99 (47.8)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.20 (3.87–4.55)</td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.04 (0.94–1.20)</td>
<td>-0.09</td>
<td></td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>195 (29.6)</td>
<td>65 (30.7)</td>
<td>71 (32.9)</td>
<td>59 (25.5)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Hb A1c, %</td>
<td>6.2 (5.7–6.8)</td>
<td>-0.22</td>
<td></td>
<td></td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>197 (166–227)</td>
<td></td>
<td></td>
<td></td>
<td>0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>120 (94–150)</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>44 (36–53)</td>
<td>-0.12</td>
<td></td>
<td></td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>132 (96–193)</td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACS, n (%)</td>
<td>395 (59.3)</td>
<td>134 (62.0)</td>
<td>127 (58.3)</td>
<td>134 (57.8)</td>
<td>0.362</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>486 (81.1)</td>
<td>147 (79.9)</td>
<td>169 (84.1)</td>
<td>170 (79.4)</td>
<td>0.863</td>
<td></td>
</tr>
</tbody>
</table>

* Data for continuous variables are presented as the median (interquartile range), as indicated, and their association with serum butyrylcholinesterase activity was assessed with the Spearman correlation coefficient. Categorical data were analyzed with a test for linear association (Mantel–Haenszel $\chi^2$ test). $P$ values <0.05 are given in boldface.

* Factors for converting units in conventional units to SI units are as follows: albumin, 1 g/dL = 10 g/L; creatinine, 1 mg/dL = 88.4 μmol/L; Hb A1c, 1% of total hemoglobin = 0.01 (proportion); total cholesterol, HDL, and LDL, 1 mg/dL = 0.0259 mmol/L; triglycerides, 1 mg/dL = 0.0113 mmol/L.

* BMI, body mass index; Hb A1c, hemoglobin A1c (glycated hemoglobin).
tion of butyrylcholinesterase with mortality, however, remained unchanged after adjustment for these risk factors, indicating an independent association. Moreover, we confirmed an association of butyrylcholinesterase activity with hypertension (6). Yet, in accordance with the study by Calderon-Margalit et al., we found no association with HDL cholesterol (8); however, because butyrylcholinesterase added predictive information after adjustment for these metabolic risk factors, additional underlying pathophysiological mechanisms may be relevant. A significant association with a family history of CAD may indicate a genetic background for the association of butyrylcholinesterase activity with mortality in patients with CAD. Recent publications have emphasized the influence of genetics on variation in butyrylcholinesterase activity (14). One potential limitation of our study is that we were not able to provide more clinical data, including such important risk factors of secondary prevention as heart failure, left ventricular ejection fraction, and medications. Furthermore, the completeness of the follow-up might have been affected by migration of patients to another country. In our cohort, however, the frequency of migration was assumed to be low; it is therefore unlikely that loss due to migration has affected the presented results in a significant way.

In conclusion, the current study advances our knowledge about the predictive value of butyrylcholinesterase. Although a previous report demonstrated that butyrylcholinesterase might be a nonspecific risk factor for mortality (8), the current study demonstrates a strong and independent association between low butyrylcholinesterase activity and long-term outcome in patients with known CAD. These results are intriguing, because butyrylcholinesterase measurement, which was developed >70 years ago, is easily available in the laboratory (15). Nevertheless, the pathophysiological mechanisms underlying these associations and the potential applicability of butyrylcholinesterase in secondary risk prediction have to be further elucidated.

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References


