Reverse Epidemiology in Systolic and Nonsystolic Heart Failure
Cumulative Prognostic Benefit of Classical Cardiovascular Risk Factors

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Background—Observational studies indicate that classical cardiovascular risk factors as body mass index, total cholesterol, and systolic blood pressure are associated with improved rather than impaired survival in heart failure (“reverse epidemiology”). We estimated the prognostic role of these risk factors in unselected patients with heart failure.

Methods and Results—Consecutive subjects with heart failure of any cause and severity were enrolled (n = 1100), and survivors were followed for a median period of 594 days (25th to 75th percentile, 435 to 840). Mean age was 70 ± 13 years, 41% were female, New York Heart Association class distribution I through IV was 15%/29%/41%/15%, and 49% had preserved left ventricular ejection function. At follow-up, 34% of the patients had died. Low levels of any risk factor (ie, body mass index, total cholesterol, and systolic blood pressure in the low tertile) indicated the highest mortality risk. After adjustment for age, sex, New York Heart Association class, and ejection fraction, 1 or 2 risk factors in the high tertile indicated a relative reduction in mortality risk of 51% (hazard ratio, 0.49; 95% CI, 0.35 to 0.68; P = 0.001) compared with subjects with 3 risk factors in the low tertile. Further adjustment for cause of heart failure, relevant comorbidities, medication, and biomarkers attenuated this association only modestly (hazard ratio, 0.63; 95% CI, 0.45 to 0.89; P = 0.009).

Conclusion—In patients with heart failure, mortality risk counterintuitively increased on a cumulative scale with lower levels of body mass index, total cholesterol, and systolic blood pressure, irrespective of the type and severity of heart failure. Future studies need to identify whether risk factor control as presently recommended should be advocated in all patients with heart failure. (Circ Heart Fail. 2009;2:563-571.)

Key Words: heart failure ■ reverse epidemiology ■ prognosis ■ risk factor

Heart failure represents the common clinical manifestation of the advanced stage of many cardiovascular disorders.1 The onset of heart failure almost invariably indicates an unfavorable prognosis,2 eg, the mortality risk after myocardial infarction increases by a factor of 4.3 Classical risk factors such as diabetes, obesity, dyslipidemia, and hypertension contribute directly or indirectly to the development and likely also to the progression of heart failure.4,5 However, at some stage along the disease continuum, the prognostic significance of traditional risk factors as body mass index (BMI), total cholesterol, and systolic blood pressure seems to change: several larger–0 and a series of smaller observational studies (for review, see reference 10) found that in symptomatic heart failure these traditional risk factors were—counterintuitively—associated with improved rather than worse outcome. Whether and how much each of these factors contributes independently to the risk modification and whether the phenomenon of risk inversion occurs in both systolic and nonsystolic heart failure is unclear. Furthermore, the synergistic effect of multiple concurring risk factors (high BMI plus high total cholesterol plus high systolic blood pressure) on mortality is unknown.

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We therefore aimed to estimate the independent individual and cumulative prognostic role of BMI, total cholesterol, and blood pressure in a consecutively recruited unselected cohort with chronic heart failure of any cause. We hypothesized that lower levels of these risk factors might be associated with poorer outcome on a cumulative scale in both systolic and nonsystolic heart failure.

Methods
Study Design and Subjects
In total, 1054 consecutive patients were enrolled. They presented between June 2002 and July 2003 with either systolic heart failure...
defined as echocardiographic left ventricular ejection fraction (EF) \( \leq 40\% \) or nonsystolic heart failure defined as EF \( > 40\% \) and typical signs or symptoms of heart failure (at least one of the following: raised jugular venous pressure, peripheral edema, third heart sound, pulmonary congestion at clinical examination, or chest x-ray), which subsequently proved responsive to specific therapy. Patients were eligible regardless of heart failure severity and mode of admission, and all underwent a detailed standardized clinical examination (for details, see reference 11). EF was measured according to standard recommendations by an experienced sonographer during routine echocardiography as performed in the course of the patients’ clinical work up. All laboratory parameters such as C-reactive protein, albumin, hemoglobin, or total cholesterol were measured as part of the clinical examination of the patients in the central laboratory of the University Hospital. Because of incomplete laboratory values in 187 subjects, the present analysis was restricted to 867 patients with complete data. The study was approved by the Ethics Committee of the Medical Faculty of Würzburg University, and all patients provided written informed consent.

OutcomeAscertainment
Patient status (dead or alive) was ascertained between June and August 2005 by communication with the patient’s general practitioner or by review of hospital discharge letters. Follow-up was 100% complete.

Data Analysis

Risk Factor Categories
The 3 classical risk factors (BMI, total cholesterol, and systolic blood pressure) were categorized in tertiles for the whole cohort (for cut-off values refer Table 1). Levels in the high tertile were labeled as “risk factor present,” respectively. Then, patients were grouped according to the number of risk factors present (ie, 0 to 3 risk factors). Patients with none of the risk factors in the high tertile were chosen as referent. Because the number of patients with 3 risk factors in the high tertile was small (n = 33), patients with 2 and 3 risk factors were aggregated for prognostic analyses into 1 group.

Statistical Tests
Group comparisons between systolic (EF \( \leq 40\% \)) and nonsystolic (EF \( > 40\% \)) heart failure were made with the Fisher exact test and Mann–Whitney \( U \) test, as appropriate. Trend tests (\( x^2 \) test for trend, Kendall \( \tau \) for ordinal trends, or ANOVA) were computed to assess differences between risk factor categories. Correlations were described by Spearman correlation coefficient. To assess the assumption of linearity in the fitted multivariable models, we used restricted cubic spline transformations of the continuous predictors with a knot at the 25th, 50th, and 75th percentiles. We used the \texttt{rcs()} function implemented in the \texttt{Design} library of R to study the shape of the relationships of each continuous predictor (BMI, systolic blood pressure, and cholesterol) with the logarithm of the hazard of death.

For prognostic analyses, Cox proportional hazards regression was applied, and the proportional hazard assumption was checked using graphical methods (smoothed plots of scaled Schoenfeld residuals versus time). Age, sex, New York Heart Association (NYHA) class, and EF were forced into the multivariable models 1 to 4. All other variables entered a model on the basis of statistical significance and clinical relevance. The following 5 multivariable Cox models were constructed. Model 1, the basic model, included the risk factors and the variables age, sex, NYHA class, and EF. Model 2 extended the basic model by comorbidities (renal function, uncured malignancy, chronic obstructive pulmonary disease, atrial fibrillation, diabetes, anemia, coronary artery disease, and hypertension). Model 3 included the basic model and evidence-based heart failure pharmacotherapy (angiotensin converting enzyme inhibitor or angiotensin receptor blocker, \( \beta \)-blocker, spironolactone, and statin). Model 4 included the basic model and heart failure biomarkers as C-reactive protein, hemoglobin, and albumin (entered as continuous variables). The predictors of model 5 were sought using a stepwise backward modeling approach (\( P = 0.05 \) for inclusion; \( P = 0.10 \) for exclusion) including all variables from models 1 to 4 (except the risk factor variable). Interaction effects (specifically, the type of left ventricular dysfunction with numbers of risk factors) were sought by introducing product terms into the multivariable model. Statistical analysis was performed with SPSS 15.0.1 (SPSS, Inc, Chicago, Ill). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
The total cohort comprised 1054 patients. Subjects not in the analysis because of missing data (n = 187) were not different from the subjects in the analysis (n = 867) with regard to age, sex, NYHA class, type of heart failure, and EF (data not shown). The following results refer to patients with complete data.

Patient Characteristics
Table 1 summarizes the baseline characteristics of all subjects and subgroups according to reduced (51%) and preserved (49%) left ventricular EF. Women comprised 41% of the study population and suffered more often from nonsystolic heart failure. Patients with systolic heart failure were in higher NYHA classes and suffered more often from coronary artery disease than subjects with nonsystolic heart failure. Systolic blood pressure was considerably higher (\( P < 0.001 \)), and a trend for higher BMI (\( P = 0.088 \)) was found in patients with nonsystolic heart failure, whereas total cholesterol levels (\( P = 0.29 \)) were similar between groups. The prevalence of renal dysfunction, uncured malignancy, chronic obstructive pulmonary disease, and atrial fibrillation did not differ between groups, whereas a history of hypertension and anemia was more frequent in patients with nonsystolic heart failure. Patients with systolic heart failure received treatment with angiotensin converting enzyme inhibitor or angiotensin receptor blocker, \( \beta \)-blocker, spironolactone, and cardiac glycosides more often, whereas use of statins and diuretics was similar in both groups.

Table 2 shows the baseline characteristics according to the number of risk factors in the high tertile. Patients with no risk factor in the high tertile were older, had the highest prevalence of uncured malignancy, anemia, and renal dysfunction, the highest grade of inflammation as expressed by levels of C-reactive protein, and exhibited the lowest levels of EF, albumin, hemoglobin, and sodium. \( \beta \)-blocker use was lowest and use of cardiac glycosides was highest in these individuals. Of note, NYHA class, and other important comorbidities as, chronic obstructive pulmonary disease, diabetes, and atrial fibrillation were equally distributed across risk factor groups. The correlation between albumin and BMI was weak in the whole cohort (\( r = 0.09, P = 0.010 \)) and in EF subgroups. Figure 1 shows the association of BMI with albumin for patients with reduced and preserved ventricular fraction. Fourteen percent of total cohort exhibited normal (8%) or high (6%) values for BMI, despite low albumin levels.

Predictors of All-Cause Mortality Risk
During a median follow-up of 594 days for survivors (25th to 75th percentile, 435 to 840 days), 297 patients died (34%
mortality rate; 40% with reduced versus 28% with preserved EF). Crude mortality rates in patients with 0, 1, and 2 risk factors in the high tertile were 47%, 37%, and 16%, respectively (P for trend <0.001). The cause of death was cardiovascular (ie, cardiac, cerebrovascular, or sudden) in 48%, noncardiovascular in 27%, and undetermined in 25% of cases. In patients with 0 versus ≥2 risk factors in the high tertile, cardiovascular cause of death was similarly frequent: 48% versus 49%. The Kaplan–Meier survival plot (Figure 2) showed a gradually higher total mortality risk with lower cardiovascular risk burden (log rank <0.001). Consistently, higher levels of each of the 3 risk factors were associated with lower mortality risk in the total cohort and also in subgroups with systolic and nonsystolic heart failure (Figure 3). Table 3 lists further predictors of increased mortality risk after adjustment for age, NYHA class, sex, and EF. The size and direction of association of the other mortality predictors were consistent with reports from the literature.

### Table 1. Baseline Characteristics of Study Patients by Reduced and Preserved Left Ventricular Function

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (n=867)</th>
<th>EF ≤40% (n=438)</th>
<th>EF &gt;40% (n=429)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.4 (12.6)</td>
<td>69.3 (12.8)</td>
<td>71.5 (12.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class I/II/IIIIV, %</td>
<td>15.1/28.7/41.4/14.8</td>
<td>14.6/26.0/41.3/17.8</td>
<td>15.4/31.5/41.5/11.7</td>
<td>0.050</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>58.9</td>
<td>65.5</td>
<td>52.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9 (23.8 to 30.1)</td>
<td>26.5 (23.6 to 30.1)</td>
<td>27.3 (24.2 to 30.3)</td>
<td>0.088</td>
</tr>
<tr>
<td>Body mass index tertile, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;25.1</td>
<td>&lt;24.5</td>
<td>&lt;25.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25.1 to 28.9</td>
<td>24.5 to 28.6</td>
<td>25.5 to 29.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;28.9</td>
<td>&gt;28.6</td>
<td>&gt;29.1</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>182 (149 to 215)</td>
<td>178 (149 to 211)</td>
<td>184 (148 to 218)</td>
<td>0.29</td>
</tr>
<tr>
<td>Total cholesterol, tertile, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;162</td>
<td>&lt;160</td>
<td>&lt;164</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>163 to 203</td>
<td>164 to 201</td>
<td>164 to 204</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;203</td>
<td>&gt;201</td>
<td>&gt;204</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130 (110 to 145)</td>
<td>120 (105 to 140)</td>
<td>131 (115 to 149)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, tertile, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;115</td>
<td>&lt;110</td>
<td>&lt;120</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>116 to 140</td>
<td>110 to 134</td>
<td>120 to 140</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;141</td>
<td>&gt;134</td>
<td>&gt;140</td>
<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>43.0 (15.0)</td>
<td>30.9 (7.4)</td>
<td>55.4 (9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal dysfunction, %</td>
<td>48.8</td>
<td>48.3</td>
<td>49.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Uncured malignancy, %</td>
<td>14.0</td>
<td>13.5</td>
<td>14.4</td>
<td>0.70</td>
</tr>
<tr>
<td>COPD, %</td>
<td>26.0</td>
<td>25.1</td>
<td>26.8</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>33.3</td>
<td>32.4</td>
<td>34.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>45.9</td>
<td>50.7</td>
<td>41.0</td>
<td>0.005</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>66.9</td>
<td>58.5</td>
<td>75.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia, %</td>
<td>35.3</td>
<td>30.8</td>
<td>40.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>32.9</td>
<td>31.1</td>
<td>34.7</td>
<td>0.30</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>141 (139 to 143)</td>
<td>141 (138 to 143)</td>
<td>141 (139 to 143)</td>
<td>0.066</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9 (3.5 to 4.3)</td>
<td>3.9 (3.6 to 4.3)</td>
<td>4.0 (3.5 to 4.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.3 (11.7 to 14.6)</td>
<td>13.4 (12.1 to 14.8)</td>
<td>13.0 (11.3 to 14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>1.04 (0.38 to 3.15)</td>
<td>0.98 (0.40 to 2.96)</td>
<td>1.13 (0.36 to 3.29)</td>
<td>0.42</td>
</tr>
<tr>
<td>ACE inhibitor/ARB, %</td>
<td>75.0</td>
<td>78.1</td>
<td>71.8</td>
<td>0.034</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td>63.7</td>
<td>66.9</td>
<td>60.4</td>
<td>0.048</td>
</tr>
<tr>
<td>Statin, %</td>
<td>34.8</td>
<td>37.4</td>
<td>32.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Diuretic, %</td>
<td>81.3</td>
<td>83.1</td>
<td>79.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Spironolactone, %</td>
<td>23.3</td>
<td>31.5</td>
<td>14.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac glycoside, %</td>
<td>42.0</td>
<td>47.9</td>
<td>35.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD) or median (25th to 75th percentile), unless indicated otherwise. P values refer to χ²-test, Fisher exact test, or Mann–Whitney U test, as appropriate.

Renal dysfunction indicates estimated glomerular filtration rate <60 ml/min per 1.73 m²; COPD, chronic obstructive pulmonary disease; hypertension, systolic blood pressure >140/90 mm Hg or treatment for hypertension; anemia according to WHO definition, hemoglobin <12 g/dL in women and <13 g/dL in men; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor-1 blocker.
Multivariable Analyses

Five models were constructed to examine the effect of comorbidity, medication, and laboratory values on the association between cardiovascular risk burden and mortality risk (Table 4). The prognostic power of cardiovascular risk burden was slightly reduced after adjustment for age, sex, NYHA class, and EF (basic model; Table 4, model 1). In models 2 to 4, the level of adjustment was expanded to include alternatively the comorbidities listed in Table 1 (model 2), the prognostically relevant heart failure medication (model 3), or prognostically important laboratory markers as C-reactive protein, hemoglobin, and albumin (model 4). Again, the strength and direction of the associations did not change materially. Among laboratory markers, albumin had the largest effect on the association of cardiovascular risk burden and mortality risk. When selecting from variables contained in models 1 to 4 by backward stepwise regression, the following variables remained independently predictive: age, NYHA class, EF, renal function, uncured malignancy, intake of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, C-reactive protein, and albumin. If included into model 5, the associations between cardiovascular risk burden and outcome remained consistent and stable. Qualitatively similar results were obtained in subgroups with systolic and nonsystolic heart failure.

We also assessed the linearity of the association of BMI, cholesterol, or systolic blood pressure (as continuous variables) with mortality risk in separate Cox models adjusting for age and NYHA class. BMI showed a negative linear association with mortality risk from very low values up to 29 kg/m². There was no indication that very high BMI levels were protective. Similar observations were made for total cholesterol (nadir at ~110 mg/dL) and systolic blood pressure (nadir ~145 mm Hg). Interestingly, values of total cholesterol and systolic blood pressure beyond the nadir seemed to indicate another increase in the risk of death, although the graph did not cross the line of indecision a second time (log relative hazard=0; Figure 4).

### Table 2. Baseline Characteristics of Study Patients According to Number of Risk Factors in the High Tertile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0 Risk Factors (n=306)</th>
<th>1 Risk Factors (n=347)</th>
<th>2 Risk Factors (n=181)</th>
<th>3 Risk Factors (n=33)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.8 (13.2)</td>
<td>69.6 (12.4)</td>
<td>69.9 (12.1)</td>
<td>67.9 (10.6)</td>
<td>0.022</td>
</tr>
<tr>
<td>NYHA functional class III/IV</td>
<td>12.7/27.5/42.2/17.6</td>
<td>16.7/28.5/41.5/13.3</td>
<td>14.9/28.7/42.0/14.4</td>
<td>21.2/42.4/30.3/6.1</td>
<td>0.36</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>62.7</td>
<td>59.7</td>
<td>52.5</td>
<td>51.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6 (22.1 to 26.8)</td>
<td>27.0 (24.3 to 30.4)</td>
<td>30.5 (29.0 to 33.0)</td>
<td>33.0 (30.4 to 34.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>160 (129 to 180)</td>
<td>186 (153 to 221)</td>
<td>216 (186 to 246)</td>
<td>225 (212 to 250)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>115 (100 to 130)</td>
<td>130 (110 to 144)</td>
<td>147 (125 to 160)</td>
<td>160 (153 to 170)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF, %</td>
<td>40.8 (15.3)</td>
<td>43.4 (15.0)</td>
<td>45.9 (14.3)</td>
<td>44.3 (15.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>EF ≤40%, %</td>
<td>56.5</td>
<td>50.4</td>
<td>41.4</td>
<td>45.5</td>
<td>0.013</td>
</tr>
<tr>
<td>Renal dysfunction, %</td>
<td>56.3</td>
<td>48.0</td>
<td>39.3</td>
<td>36.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Uncured malignancy, %</td>
<td>19.6</td>
<td>10.7</td>
<td>9.9</td>
<td>18.2</td>
<td>0.003</td>
</tr>
<tr>
<td>COPD, %</td>
<td>26.1</td>
<td>25.1</td>
<td>28.2</td>
<td>21.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>33.3</td>
<td>32.6</td>
<td>37.0</td>
<td>21.2</td>
<td>0.34</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>52.0</td>
<td>42.9</td>
<td>40.3</td>
<td>51.5</td>
<td>0.038</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>60.9</td>
<td>67.2</td>
<td>73.5</td>
<td>84.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Anemia, %</td>
<td>42.1</td>
<td>35.1</td>
<td>26.3</td>
<td>24.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>33.6</td>
<td>33.4</td>
<td>32.2</td>
<td>24.1</td>
<td>0.77</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140 (138 to 143)</td>
<td>141 (139 to 144)</td>
<td>141 (139 to 143)</td>
<td>141 (139 to 144)</td>
<td>0.032</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.8 (3.4 to 4.2)</td>
<td>4.0 (3.5 to 4.4)</td>
<td>4.1 (3.7 to 4.4)</td>
<td>4.2 (4.0 to 4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.0 (11.3 to 14.3)</td>
<td>13.3 (11.7 to 14.5)</td>
<td>13.7 (12.2 to 15.1)</td>
<td>13.3 (12.0 to 15.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>1.26 (0.48 to 4.83)</td>
<td>0.95 (0.33 to 2.85)</td>
<td>0.90 (0.38 to 2.17)</td>
<td>0.66 (0.29 to 1.59)</td>
<td>0.001</td>
</tr>
<tr>
<td>ACE inhibitor/ARB, %</td>
<td>70.6</td>
<td>77.2</td>
<td>77.9</td>
<td>75.8</td>
<td>0.18</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td>55.6</td>
<td>68.6</td>
<td>65.7</td>
<td>75.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Statin, %</td>
<td>35.3</td>
<td>36.9</td>
<td>29.3</td>
<td>39.4</td>
<td>0.33</td>
</tr>
<tr>
<td>Diuretic, %</td>
<td>81.4</td>
<td>81.0</td>
<td>82.9</td>
<td>75.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Spironolactone, %</td>
<td>26.8</td>
<td>23.6</td>
<td>17.7</td>
<td>18.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiac glycoside, %</td>
<td>50.0</td>
<td>39.5</td>
<td>37.0</td>
<td>21.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD), median (25th to 75th percentile), or n (%).

Definition of risk factors (body mass index, systolic blood pressure, total cholesterol) and respective tertiles as detailed in Table 1.

Renal dysfunction indicates estimated glomerular filtration rate <60 mL/min per 1.73 m²; COPD, chronic obstructive pulmonary disease; history of hypertension, systolic blood pressure >140/90 mm Hg or treatment for hypertension; anemia according to WHO definition, hemoglobin <12 g/dL in women and <13 g/dL in men; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor-1 blocker.
This prospective cohort study showed that higher levels of the 3 classical risk factors BMI, total cholesterol, and systolic blood pressure were independent and cumulative predictors of improved survival in unselected patients with chronic heart failure. The associations were strong and consistent in both types of heart failure, and only weakened to a minor degree by factors describing disease severity or comorbid conditions. Associations compatible with the concept of “reverse epidemiology” have been described in several other chronic conditions such as end-stage renal disease, malignancies, chronic obstructive lung disease, or the acquired immunodeficiency syndrome. In heart failure, however, earlier reports on the inverse association of BMI, total cholesterol, and systolic blood pressure with outcome focused on subjects with systolic heart failure and investigated only 1 single component. We here report for the first time that higher levels of these risk factors were associated with better prognosis on a cumulative scale in both systolic and nonsystolic heart failure.

It seems that an inverse relationship with outcome exists for only a few of the classical risk factors. However, some authors attributed these associations to systematic bias inherent to nonrandomized data. For example, the existence of the “obesity paradox” (ie, greater survival in overweight compared with normal weight patients) has been ascribed to diagnosis bias (ie, misdiagnosis of obesity-related symptoms mimicking heart failure) or lead-time bias (ie, obese patients are identified and, hence, treated at an earlier stage of the disease). Nevertheless, stringent proof of such bias affecting the outcome data available is also lacking and, in support of the obesity paradox, inverse relations between body weight and outcome have been described in patients with both early and end-stage systolic heart failure.

As already mentioned, reverse associations have also been described in other chronic diseases as end-stage renal disease, which shares many clinical and pathophysiological aspects with heart failure. Both conditions comprise patient groups suffering from a severe and similar burden of comorbidities, as anemia, diabetes, and other cardiovascular risk factors that mutually contribute to disease progression. The survival benefit of obese patients in both conditions may be explained by a better nutritional status and may be perceived as the mirror image of catabolism, muscle wasting, and cachexia. These conditions are clinical manifestations of the malnutrition-inflammation complex syndrome addressing the close interrelation between mal- or undernourishment and the inflammatory disease state found in chronic heart failure and end stage renal disease. Clinical assessment of the malnutrition-inflammation complex syndrome involves nutritional parameters and changes in body weight. In this analysis, lower BMI showed a surprisingly consistent graded relationship with worse outcome, also after multivariable adjustment. However, BMI may only partially capture information on the nutritional status because its correlation with serum albumin, a sensitive marker of malnutrition, was poor (r = 0.09; P = 0.010). Low serum albumin, by contrast, is an acknowledged strong indicator of poor outcome and, consistently, had the most pronounced impact on mortality.

Figure 1. Relation of BMI and serum albumin in patients with heart failure with impaired (EF ≤40%) and preserved (EF >40%) left ventricular function. The 2 horizontal lines indicate the range for BMI values considered normal in subjects older than 65 years (ie, 24 to 29 kg/m²). The vertical line indicates the cut-off for hypoalbuminemia (ie, <3.5 g/dL). The shaded area indicates the proportion of the total cohort (ie, 14%) that had normal (8%) or high (6%) values for BMI, despite low albumin levels.

Figure 2. Accumulation of classical cardiovascular risk factors (RF) indicates prognostic benefit in patients with chronic heart failure. Kaplan–Meier plot of the association between all-cause mortality risk and the number of 3 cardiovascular risk factors (BMI, total cholesterol, systolic blood pressure) in the high tertile. HRs with 95% CIs and probability values derived from univariable Cox regression analysis comparing each group with the referent (ie, 0 risk factors in the high tertile) were as follows: 1 risk factor in high tertile, 0.64 (95% CI, 0.49 to 0.82; P = 0.001); 2 risk factors in high tertile, 0.42 (95% CI, 0.31 to 0.59; P = 0.001).
risk in multivariable analyses. Importantly, 21% of the total cohort had hypoalbuminemia (ie, serum albumin level <3.5 g/dL), but 67% of these subjects had normal to high BMI values (Figure 1). Of note, this was observed both in subjects with impaired and preserved EF. Hence, a compromised nutritional state is common in both types of heart failure but is only insufficiently reflected by BMI. It has been proposed that adipose tissue may produce soluble tumor necrosis factor-α receptors that bind and deactivate potentially harmful tumor necrosis factor-α, suggesting an anti-inflammatory response.

**Table 3. Predictors of All-Cause Mortality Risk***

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per decade</td>
<td>1.31</td>
<td>1.16 to 1.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class, per class</td>
<td>2.26</td>
<td>2.93 to 2.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, yes vs no</td>
<td>1.13</td>
<td>1.16 to 1.47</td>
<td>0.33</td>
</tr>
<tr>
<td>Ejection fraction, per 5% increase</td>
<td>0.93</td>
<td>0.89 to 0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, per 5 kg/m² increase</td>
<td>0.81</td>
<td>0.71 to 0.95</td>
<td>0.004</td>
</tr>
<tr>
<td>Total cholesterol, per 10-mg/dL increase</td>
<td>0.96</td>
<td>0.93 to 0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, per 10-mm Hg increase</td>
<td>0.89</td>
<td>0.84 to 0.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal function, per stage 1 through 5</td>
<td>1.32</td>
<td>1.18 to 1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uncured malignancy, yes vs no</td>
<td>1.46</td>
<td>1.09 to 1.95</td>
<td>0.011</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, yes vs no</td>
<td>1.10</td>
<td>0.85 to 1.41</td>
<td>0.48</td>
</tr>
<tr>
<td>Diabetes, yes vs no</td>
<td>1.24</td>
<td>0.98 to 1.57</td>
<td>0.07</td>
</tr>
<tr>
<td>Coronary artery disease, yes vs no</td>
<td>1.01</td>
<td>0.80 to 1.28</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension, yes vs no</td>
<td>0.76</td>
<td>0.60 to 0.97</td>
<td>0.025</td>
</tr>
<tr>
<td>Anemia, yes vs no</td>
<td>1.67</td>
<td>1.32 to 2.11</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, yes vs no</td>
<td>1.16</td>
<td>0.91 to 1.48</td>
<td>0.22</td>
</tr>
<tr>
<td>Log sodium, per SD</td>
<td>0.96</td>
<td>0.86 to 1.07</td>
<td>0.46</td>
</tr>
<tr>
<td>Albumin, per g/dL</td>
<td>0.52</td>
<td>0.43 to 0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, per g/dL</td>
<td>0.86</td>
<td>0.81 to 0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein, per mg/dL</td>
<td>1.06</td>
<td>1.04 to 1.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor/ARB, yes vs no</td>
<td>0.54</td>
<td>0.42 to 0.69</td>
<td>0.001</td>
</tr>
<tr>
<td>β-blocker, yes vs no</td>
<td>0.55</td>
<td>0.43 to 0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin, yes vs no</td>
<td>0.62</td>
<td>0.47 to 0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretic, yes vs no</td>
<td>1.44</td>
<td>0.99 to 2.10</td>
<td>0.058</td>
</tr>
<tr>
<td>Spironolactone, yes vs no</td>
<td>1.00</td>
<td>0.76 to 1.31</td>
<td>0.99</td>
</tr>
<tr>
<td>Cardiac glycoside, yes vs no</td>
<td>1.37</td>
<td>1.08 to 1.73</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Renal function according to K/DOQI guidelines, stage 1, estimated glomerular filtration rate (GFR) >90; stage 2, GFR 60 to 89, stage 3, GFR 30 to 59, stage 4, GFR 15 to 29, stage 5, <15 mL/min per 1.73 m²; hypertension, systolic blood pressure >140/90 mm Hg or treatment for hypertension; standard deviation for log normalized sodium was 0.031, anemia according to WHO definition, hemoglobin <12 g/dL in women and <13 g/dL in men; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor-1 blocker.

*Adjusted for age, sex, NYHA functional class and ejection fraction except for the first 4 variables that were only triple adjusted, as appropriate.
effect of higher BMI. In this study, however, no correlation between BMI and C-reactive protein levels as a more general marker for systemic inflammation could be observed ($r=0.01$; $P=0.96$).

Total cholesterol and its derivatives may affect disease progression in heart failure beyond the conventional risk factor hypothesis, too. Higher levels of total and low-density lipid cholesterol may indicate a better defense system detoxifying bacterial lipopolysaccharides that are increased in heart failure. In our data, levels of total cholesterol and C-reactive protein correlated inversely ($r=-0.23$; $P<0.001$), emphasizing its role as a negative acute phase protein that is down-regulated by several cytokines. From our data, it seemed that high levels of total cholesterol were a strong predictor of decreased mortality risk (hazard ratio [HR] per 10 mg/dL increase, 0.93; 95% CI, 0.91 to 0.95; $P<0.001$). Importantly, this effect concurred with an independent protective effect of statin treatment (HR, 0.57; 95% CI, 0.44 to 0.75; detailed data not shown). Confounding by indication is certainly a possibility because those with higher lipid levels are more likely to receive statin therapy. Alternatively, pleiotropic and anti-inflammatory effects of statins have been discussed. Of note, despite substantial lipid-lowering effects and favorable anti-inflammatory effects, recent large randomized trials failed to show a prognostic benefit of statin therapy both in diabetics with end stage renal disease and patients with heart failure.

Systolic blood pressure is also a marker susceptible to various sources of bias. Lower values may indicate worse left ventricular pump function and inadequate organ perfusion (consistent with the concept of “reverse causation”) or (supra-)optimal heart failure pharmacotherapy. However, earlier studies in patients with systolic heart failure found that the survival advantage with higher systolic blood pressure was independent of pump function. Furthermore, from studies in patients with end stage renal disease, it was concluded that it is still unclear, which blood pressure level is sufficient to maintain adequate organ perfusion. In our cohort with patients with systolic and nonsystolic heart failure, gradually lower systolic blood pressure levels were associated with worse outcome regardless of the type of heart failure. Low systolic blood pressure may therefore predispose to compromised organ perfusion pressure. Hence, our findings highlight the fact that the definition of an optimal blood pressure and its control along the disease continuum in heart failure remains a challenge for future research.

Table 4. Inverse Association of Multiple Classical Cardiovascular Risk Factors With All-Cause Mortality Risk (HR with 95% CI and P value)

<table>
<thead>
<tr>
<th>No. of Risk Factors* in the High Tertile</th>
<th>0 Risk Factors (n=306)</th>
<th>1 Risk Factor (n=347)</th>
<th>≥2 Risk Factors (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 Referent</td>
<td>0.71 (0.55 to 0.91), $P=0.007$</td>
<td>0.49 (0.35 to 0.68), $P&lt;0.001$</td>
<td>0.095 (0.41 to 0.82), $P=0.002$</td>
</tr>
<tr>
<td>Model 2 Referent</td>
<td>0.80 (0.61 to 1.04), $P=0.009$</td>
<td>0.55 (0.39 to 0.78), $P=0.001$</td>
<td>0.047 (0.41 to 0.82), $P=0.002$</td>
</tr>
<tr>
<td>Model 3 Referent</td>
<td>0.82 (0.63 to 1.07), $P=0.14$</td>
<td>0.69 (0.52 to 0.93), $P=0.016$</td>
<td>0.14 (0.40 to 0.78), $P&lt;0.001$</td>
</tr>
<tr>
<td>Model 4 Referent</td>
<td>0.77 (0.60 to 1.00), $P=0.054$</td>
<td>0.62 (0.44 to 0.88), $P=0.007$</td>
<td>0.042 (0.32 to 0.80), $P=0.009$</td>
</tr>
<tr>
<td>Model 5 Referent</td>
<td>0.89 (0.68 to 1.16), $P=0.39$</td>
<td>0.63 (0.45 to 0.89), $P=0.009$</td>
<td>0.14 (0.40 to 0.78), $P&lt;0.001$</td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age, sex, NYHA class, ejection fraction (basic model); Model 2, adjusted for basic model plus renal function, uncured malignancy, chronic obstructive pulmonary disease, atrial fibrillation, diabetes, anemia, coronary artery disease, and hypertension; Model 3, adjusted for basic model plus intake of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, spironolactone, statin; Model 4, adjusted for basic model plus C-reactive protein, hemoglobin, albumin; and Model 5, adjusted for age, NYHA class, ejection fraction, renal function, uncured malignancy, intake of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, C-reactive protein, albumin.

*Risk factor, BMI or systolic blood pressure or total cholesterol. Cut-off values of tertiles as specified in Table 1.

Figure 4. Spline-transformed associations of BMI, total cholesterol, and systolic blood pressure with time to all-cause death. Cox regression with adjustment was made for age, sex, NYHA functional class, and EF. The solid line indicates the estimated risk of death, and the dark dotted lines represent pointwise 95% CI. The horizontal dotted line indicates the line of indecision (log relative hazard of 0, consistent with a hazard ratio of 1).
Our data question the traditional view that the classical cardiovascular risk factors should be treated in patients with heart failure across all stages with similar vigor and persistence as in subjects with coronary heart disease without signs and symptoms of heart failure. It is presently unclear whether and in which groups of patients with heart failure weight loss and lowering of total cholesterol and blood pressure may translate into prognostic benefit. Few studies so far tested the efficacy of nutritional supplementation in heart failure, but they were underpowered and of limited duration. These questions remain therefore open for dedicated randomized studies investigating the effect of targeted risk factor modification.

Certain limitations need to be considered in our study. We investigated a heterogeneous sample of consecutively recruited patients with chronic heart failure of any cause and severity and, hence, some of the observed effects may be aggravated or diminished in certain subgroups. Nevertheless, because the cohort resembles clinical practice our findings may be generalizable to the “real world” of heart failure. Patients with preserved EF are more likely to be obese and to suffer from hypertension. However, all survival analyses were adjusted for EF. BNP as a major prognosticator in heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. Am Heart J. 2003;145:73–79.

In conclusion, this study in patients with systolic and nonsystolic heart failure showed that higher levels of 3 classical cardiovascular risk factors (BMI, total cholesterol, and systolic blood pressure) independently predicted better survival on a cumulative scale. Further studies need to clarify whether the control of classical cardiovascular risk factors approved for patients with coronary heart disease should be advocated in more advanced heart failure.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

To prevent the development of heart failure, identification and treatment of well-recognized illnesses and risk factors, such as obesity, hyperlipidemia, and hypertension, are considered of paramount importance. However, in more advanced heart failure, higher values of classical risk factors such as body mass index, systolic blood pressure, and total serum cholesterol have been associated with significant decreases in mortality and morbidity risk. This counterintuitive observation has been termed “reverse epidemiology.” This prospective cohort study analyzed the individual and cumulative predictive value of these 3 risk factors in consecutively recruited patients with preserved (ejection fraction ≥40%) and reduced left ventricular function (ejection fraction ≤40%). Consistent with the concept of reverse epidemiology, we found an inverse graded mortality risk with increasing levels of each risk factor. The absence of all 3 risk factors identified patients with the highest mortality risk. This association was robust after adjustment for clinically relevant information including comorbidities, medication, and laboratory measurements. Our findings demonstrate a cumulative deleterious impact of these 3 inverse associations on prognosis, thus, challenging the traditional approach to treat these risk factors in all patients with heart failure with the same vigor and persistence as recommended in the general population.
Reverse Epidemiology in Systolic and Nonsystolic Heart Failure: Cumulative Prognostic Benefit of Classical Cardiovascular Risk Factors

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