Relationship between adiponectin and copeptin levels with long-term cardiovascular mortality in ST-segment elevation myocardial infarction after percutaneous coronary intervention

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Abstract

Objective: The aim of this study was to determine adiponectin and copeptin levels that might be prognostic for cardiovascular mortality (CvsM) in ST-segment elevation myocardial infarction (STEMI) patients who had percutaneous coronary intervention (PCI).

Methods: Patients who underwent PCI between November 2010 and April 2011 were enrolled and followed for more than eight years. The baseline, demographic and angiographic findings, in-hospital follow up, laboratory results including adiponectin and copeptin levels, and echocardiographic data of the patients were evaluated.

Results: There were 78 males and 20 females. The CvsM rate was 26.66% at 112 months of follow up. Some factors were significantly related to CvsM and adiponectin level was an independent predictor of mortality. A cut-off value of ≥ 8 950 ng/ml for adiponectin and ≥ 7.41 ng/ml for copeptin was related to a 3.01- and 2.83-times higher CvsM risk, respectively.

Conclusion: Adiponectin level was a predictor for CvsM. Higher levels of adiponectin and copeptin could predict a higher risk of CvsM in STEMI patients.

Keywords: ST-segment elevation myocardial infarction, mortality, adiponectin, copeptin

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ST-segment elevation myocardial infarction (STEMI) is regarded as a type of acute coronary syndrome, and it occurs by rupture or erosion of the atherosclerotic plaque, causing a thrombotic occlusion in the related artery.¹ The prognosis of STEMI patients was related to high risk for developing adverse events in the short or long term due to multiple factors.²,³

Although the mortality rates were higher in the study by Kristenson et al.,⁴ the SAFARI trial, with a large population, reported lower mortality rates at 1.3 and 1.5% at a 30-day follow up.¹ For longer follow ups, the HORIZON-AMI trial reported mortality rates between 1.3 and 10.5% at three years of follow up in different countries.⁶

In the recent literature, copeptin is reported to be used as a novel biomarker to predict poor outcomes and all-cause mortality in MI patients, as an alternative to arginine vasopressin levels, due to its long-term stability and simplicity in measurement.⁷ Furthermore, Zhang et al. reported that although copeptin could be used to predict clinical outcomes, the underlying mechanism of the relationship between this biomarker and mortality should be investigated further.⁸ Moreover, the follow-up period of many studies was no longer than 12 months.

Adiponectin is a protein derived from adipocytes, and via its anti-atherogenic and anti-inflammatory abilities, it has cardioprotective effects.⁹ The association between high adiponectin levels and low cardiovascular risk has been shown in healthy subjects.¹⁰,¹¹ However, just the opposite association was also reported for patients with cardiovascular disease.¹² In patients presenting with STEMI, adiponectin is shown to be a predictor for cardiovascular mortality (CvsM) in the long term.¹³ Due to contradictory and paradoxical reports, further evaluation of the predictive role of copeptin and adiponectin on mortality in STEMI patients in the long term might be beneficial.

Therefore, this study aimed to determine serum adiponectin and copeptin levels predictive of CvsM in the long term, and...
any possible cut-off values for adiponectin and copeptin that might be definitive for CvsM in patients who were all treated with primary percutaneous coronary intervention (PCI) within the first 12 hours of symptom development.

Methods

This retrospective study was designed according to the principles of the Helsinki Declaration and approved by the Yeditepe University ethics committee (no: 1129). All patients signed an informed consent.

Patients with STEMI, who were referred to the emergency department of the hospital and had emergency PCI between November 2010 and April 2011, were enrolled in the study. The inclusion criteria were: patients presenting within 12 hours from the beginning of symptoms (typical chest pain lasting at least 30 minutes), ST-segment elevation 1 mm or more in at least two contiguous ECG leads, or new onset of complete left bundle branch block. Once the STEMI diagnosis was verified, the patients were directly transferred to the primary PCI unit of the same centre. Since primary PCI is possible throughout 24 hours, no thrombolytic therapy was preferred. Patients who did not attend follow ups or could not be reached, who were pregnant, who had chronic renal disease stage 3, 4 or 5, or who died from non-cardiac reasons were excluded.

All patients underwent an initial clinical examination, including physical examination, family and medical history, 12-lead ECG, continuous bedside ECG monitoring, screening blood tests and saturation monitoring with pulse oximetry. The baseline demographics, clinical history, as well as the cause of admission, vital parameters and laboratory results were recorded.

The following baseline and demographic findings were included in the study. Diabetes mellitus was defined as a history of diabetes according to the diagnostic criteria of the World Health Organisation. The patients were regarded as hypertensive if they were already on anti-hypertensive therapy. Hyperlipidaemia was defined as low-density lipoprotein cholesterol levels > 150 mg/dl (3.89 mmol/l), total cholesterol levels > 200 mg/dl (5.18 mmol/l), or triglyceride levels > 200 mg/dl (1.7 mmol/l).

Smoking was defined as the inhaled use of cigars, pipes or cigarettes at any quantity. Body mass index was calculated as the weight (kg) divided by the square of the height (m). Waist circumference was measured on the level of the umbilicus. Cardiogenic shock was defined according to the SHOCK trial. The Killip classification was evaluated as described elsewhere. The CADILLAC score was calculated from the patients' clinical, ECG and angiographic characteristics.

Angiographic findings and in-hospital follow up included hospitalisation period, contrast-induced nephropathy (CIN), inotropic period, in-hospital shock, intra-aortic balloon pump (IABP), in-hospital atrial fibrillation (AF), pre-PCI ST-elevation, post-PCI ST-elevation, DELTA ST-elevation, absence of reflow (no-reflow), intervened artery, pre-PCI thrombolysis in myocardial infarction (TIMI) flow grade, post-PCI TIMI flow grade and number of intervened arteries.

CIN was defined as impairment of renal function measured as either a 25% increase in the serum creatinine level from baseline or a 0.5 mg/dl increase in the absolute serum creatinine value within 48–72 hours after intravenous contrast administration.

Coronary flow was graded according to the TIMI criteria between 0 and 3. Lack of ST resolution by 50% was considered as an established marker of no-reflow, between the initial ECG and post-PCI first-hour follow-up ECG.

Regarding laboratory results and echocardiographic data, the glomerular filtration rate (GFR) was estimated using the MDRD-4 formula, as described elsewhere. Routine laboratory methods were used for other blood tests. Blood samples were collected at the admission after STEMI diagnosed on ECG, before the patients were sent to the catheterisation laboratory. The results of those blood tests were collected from the archives for this study.

Previous studies described the release pattern and structure of copeptin. Copeptin plasma levels were evaluated from EDTA blood samples. Samples were centrifuged at 2 000 rpm for 20 minutes at 4°C. Platelet-poor plasma was separated and stored at −80°C until analysis. A commercial automated immunofluorescent assay (Copeptin, Hennings, BRAHMS, GmbH, Germany) was performed on a Kryptor analyser.

For adiponectin measurements, venous blood was collected in EDTA tubes and centrifuged for 10 minutes at 2 000 rpm, so that the plasma was isolated and stored at −80°C. Total plasma adiponectin levels were measured by an enzyme-linked immunosorbent assay (Assaypro, MO, USA). The lower limit of detection of the assay was 0.246 ng/ml.

Two-dimensional transthoracic echocardiography was performed using a GE Vivid-3 ultrasound machine. The left ventricular ejection fraction (LVEF) was calculated from the modified Simpson method.

All-cause mortality was obtained from the national death records. CvsM was assessed by telephone interviews with the patients, relatives or physicians between January and February 2020. Cardiovascular long-term mortality was identified as death associated with MI, arrhythmia, heart failure (HF), cardiac arrest (due to other unknown cause), or cerebrovascular accident.

Statistical Analyses

Statistical analyses were performed with the Number Cruncher Statistical System 2007 statistical software (Utah, USA) for Windows. Besides standard descriptive statistical calculations (mean and standard deviation, median, interquartile range), when the variables showed a normal distribution, the independent-samples t-test was used in the comparison of the groups, whereas, when the variables did not show a normal distribution, the Mann–Whitney U-test was used in the comparison of the groups, and the chi-squared test was performed during evaluation of the qualitative data.

Risk factors for mortality were examined in multivariate logistic regression analyses. The Hosmer–Lemeshow test was used for evaluating goodness of fit for logistic regression models. To calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio (LR) (+) for the adiponectin and copeptin measurements at varying cut-off values, a conventional receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to test adiponectin and copeptin as biomarkers. From the AUC, the best adiponectin and copeptin cut-off values for the mortality groups were determined.
The Kaplan–Meier life-table method, estimating cardiac-related death, was used to summarise the follow-up experience in the patient population. The differences in the survival curves were tested using the log-rank test, adjusting for the adiponectin and copeptin prognostic risk factors. The results were evaluated within a 95% confidence interval (CI). The statistical significance level was established at \( p < 0.05 \).

**Results**

We selected 147 patients, of whom 42 could not be reached, resulting in 105 patients in the study. The results showed a total mortality rate of 33.33\% (35 out of 105 patients). The CvsM rate was 26.66\% (28 out of 105 patients). Among the mortalities, seven died because of non-cardiac reasons, and therefore, they were excluded from the study, resulting in a population of 98 patients (78 male, 20 female) (Fig. 1).

The mean ages of the survivors and the non-survivors were 54.69 ± 11.49 and 65.88 ± 12.29 years, respectively. The total follow-up period was 112 months (mean follow-up 97.06 ± 28.83). The mean survival time for CvsM was 52.15 ± 6.57 months. Furthermore, 21.4\% of the mortality was observed in the first month, and 30.8\% was in the first six months. The baseline demographics and findings in relation to mortality status are shown in Table 1.

At the initial admission age, female gender, diabetes mellitus (DM), peripheral arterial disease, cerebrovascular accident, previous PCI, previous MI, cardiogenic shock and Killip classification score of 4, symptom-to-ballooning time, heart rate and CADILLAC score were significantly higher among the non-survivors than the survivors (\( p < 0.05 \)). No significant difference was observed between other baseline data (\( p > 0.05 \)).

The angiographic findings are shown in Table 2. There was no significant relationship between the angiographic findings and mortality rate for most of the data. However, post-PCI TIMI flow grade 0 and 1 and no-reflow after performing intervention to the vein were significantly higher in the non-survivor group (\( p < 0.05 \)). At the in-hospital follow-up, the requirement of the inotropic period, in-hospital shock and IABP were significantly higher among the non-survivors (\( p < 0.05 \)).

The laboratory results and echocardiographic data are shown in Table 3. The peak creatine kinase MB level, triglyceride and initial glucose levels, platelet count, adiponectin levels (survivors: 5996.69 ± 3746.46, non-survivors: 15764.85 ± 19609.06, \( p = 0.0001 \)) and copeptin levels (survivors: 0.6 ± 0.47, non-survivors: 1.25 ± 0.72, \( p = 0.0001 \)) were significantly higher in the non-survivor group (\( p < 0.05 \)). Only the LVEF was significantly lower in the non-survivor group (\( p = 0.005 \)). There were no significant differences observed for the other data.

When the multivariate logistic regression analyses were performed for the factors that were found to be statistically significant in the univariate analyses, the final results are shown in Table 4. Among all the factors included, only the baseline BMI (OR: 3.34, 95\% CI: 1.05–10.41, \( p = 0.039 \)) and the post-PCI TIMI flow grade (OR: 3.15, 95\% CI: 1.00–9.65, \( p = 0.047 \)) were independently associated with mortality.
of the goodness-of-fit test showed a good fit for the model of factors affecting long-term mortality (Table 4). The results significant in the univariate tests, DM, higher CADILLAC scores, higher adiponectin levels and lower LVEF were found to be factors affecting long-term mortality (Table 4). The results of the goodness-of-fit test showed a good fit for the model of variables (chi-square: 2.97, \( p = 0.887 \)).

According to CvsM, the subjects were divided into two groups. The AUC of adiponectin (0.785, 95% CI: 0.686–0.864), with the optimal cut-off level of 8.950 ng/ml, revealed 73.08% sensitivity and 75.71% specificity in the prediction of patients with increased mortality rates. The AUC of copeptin (0.789, 95% CI: 0.691–0.868), with the optimal cut-off level of 7.41 ng/ml, revealed 80.95% sensitivity and 71.43% specificity.
in the prediction of patients with increased mortality rates. The PPV, NPV and LR are shown in Table 5.

The risk of mortality of a patient with an adiponectin level of \( \geq 8950 \) ng/ml was 3.01 times higher than for a patient with an adiponectin level of \(< 8950 \) ng/ml. Additionally, the mortality risk of a patient with a copeptin level of \( \geq 7.41 \) ng/ml was 2.83 times higher than a patient with a copeptin level of \(< 7.41 \) ng/ml (Table 5, Fig. 2).

Fig. 3 demonstrates the Kaplan–Meier survival curve for the adiponectin and copeptin cut-off values. As shown in Fig. 3 and Table 6, an adiponectin level of \( \geq 8950 \) ng/ml and a copeptin level of \( \geq 7.41 \) ng/ml were associated with a decreased survival time (log-rank statistic = 18.02 and 18.94, \( p = 0.0001 \) and \( p = 0.0001 \), respectively). The mortality rate was significantly higher in patients who had an adiponectin level of \( \geq 8950 \) ng/ml than in patients who had an adiponectin level of \(< 8950 \) ng/ml (\( p = 0.0001 \)). Similarly, patients who had a copeptin level of \( \geq 7.41 \) ng/ml showed a significantly higher mortality rate than patients who had a level of \(< 7.41 \) ng/ml (\( p = 0.0001 \)).

### Discussion

A CvsM rate of 26.66% was observed in this cohort of unselected patients, who were all diagnosed with STEMI and had had PCI. Second, the multivariate tests showed adiponectin level to be a significant predictor for CvsM. Third, adiponectin and copeptin showed significant cut-off levels regarding CvsM in the long term. To the best of our knowledge this is the first study showing such relationships for adiponectin and copeptin in STEMI patients at a long-term follow up of 112 months.

The pattern of long-term mortality after STEMI in the presence of PCI has been described in previous studies. All-cause mortality rates were reported between 8.05 and 28.9% in those

![Fig. 2. ROC curve of adiponectin and copeptin levels and mortality rate.](image)

Table 5. Receiver operating characteristics analyses for adiponectin and copeptin

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>SE</th>
<th>95% CI</th>
<th>Criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LR (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>0.785</td>
<td>0.063</td>
<td>0.686-0.864</td>
<td>( \geq 8950 )</td>
<td>73.08</td>
<td>75.71</td>
<td>52.8</td>
<td>88.3</td>
<td>3.01</td>
</tr>
<tr>
<td>Copeptin</td>
<td>0.789</td>
<td>0.062</td>
<td>0.691-0.868</td>
<td>( \geq 7.41 )</td>
<td>80.95</td>
<td>71.43</td>
<td>45.9</td>
<td>92.6</td>
<td>2.83</td>
</tr>
</tbody>
</table>

AUC: area under the curve, SE: standard error, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio.

![Fig. 3. Kaplan–Meier cumulative survival curve according to adiponectin (A) and copeptin (B) cut-off levels.](image)

Table 6. Kaplan–Meier survival analyses for adiponectin and copeptin

<table>
<thead>
<tr>
<th>Follow up</th>
<th>Adiponectin &lt; 8950 ng/ml</th>
<th>Adiponectin ( \geq 8950 ) ng/ml</th>
<th>Copeptin &lt; 7.41 ng/ml</th>
<th>Copeptin ( \geq 7.41 ) ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>0.983</td>
<td>0.811</td>
<td>0.983</td>
<td>0.811</td>
</tr>
<tr>
<td>2 years</td>
<td>0.983</td>
<td>0.811</td>
<td>0.983</td>
<td>0.811</td>
</tr>
<tr>
<td>3 years</td>
<td>0.966</td>
<td>0.784</td>
<td>0.981</td>
<td>0.811</td>
</tr>
<tr>
<td>5 years</td>
<td>0.949</td>
<td>0.757</td>
<td>0.962</td>
<td>0.744</td>
</tr>
<tr>
<td>10 years</td>
<td>0.881</td>
<td>0.541</td>
<td>0.905</td>
<td>6.15</td>
</tr>
</tbody>
</table>

Survival, median ± SD: 104.69 ± 2.57, 97.76 ± 7.35, 108.43 ± 1.40, 82.51 ± 6.86. 95% CI: 99.66–109.72, 65.35–94.17, 105.67–111.17, 69.06–95.96. Log rank: 18.02, \( p = 0.0001 \) log rank: 18.94, \( p = 0.0001 \).
studies, at different follow-up periods, from one to eight years. 23–26 Our study focused on the CvsM in a cohort of unselected STEMI patients after PCI.

A literature search revealed the CvsM rate between 2.3 and 25.4% at different follow ups between 18.6 months and 4.7 years. 23–26 The CvsM rate observed in this study was 26.66%, which was found to be higher than previous reports. The greater prevalence of co-morbidities among patients might have caused those different CvsM rates. However, this study was the longest to date for the long-term CvsM outcome of PCI in STEMI patients, which might support the findings that longer follow-up periods might be associated with higher CvsM rates.

Furthermore, studies showed that CvsM was relatively high in the first month, and it fell considerably after the first month to < 1.5% per year. 26 This supports that, once unselected patients had survived from the acute phase of STEMI with PCI, they had a better late cardiac prognosis, even similar to that of selected patients of other trials. 28 This finding was similar in our study, where 21.4% of the mortality was observed within the first month, and 30.8% was within six months. These results suggest that, for prevention and treatment of cardiac death, resources should be directed to the early phase of STEMI.

The prognostic value of adiponectin has been investigated intensely in the last decade. Although early reports indicated a protective association with the outcome, 30,31 recent reports associated higher adiponectin levels with a worse prognosis in healthy subjects and patients with MI or HF. 21

Rathmann and Herder proposed that adiponectin may be upregulated in a counter-regulatory pattern to prevent the progression of cardiovascular dysfunction and atherosclerosis. 32 Conversely, Wannamethee et al. showed that a high adiponectin level was independently associated with CvsM. However, with the inclusion of NT-proBNP, the association disappeared. 33 Similarly, Lindberg et al. extended these findings to STEMI patients, reporting the importance of considering the levels of natriuretic peptide while evaluating the adiponectin levels for risk stratification. 34

On the contrary, Reinstadler et al. showed that increased aortic stiffness was associated with high plasma adiponectin concentrations, which is a potential promoter of ischaemic heart disease in patients after acute STEMI, independent of gender, age, total cholesterol level, smoking status or NT-proBNP level. 35 Adiponectin was not related to LVEF or NT-proBNP in other reports on coronary artery disease and STEMI patients. 30,34

It was reported that, even in younger adults without any prevalent cardiometabolic disease, adiponectin level had an independent positive association with CvsM at a follow up of 10.4 years. 37 However, there are only a few studies that investigated the long-term prognostic value of adiponectin level in STEMI patients undergoing PCI. 38

Although Delhaye et al. observed preprocedural adiponectin as an independent predictor of mortality in patients with symptomatic stable coronary artery disease and non-ST elevation acute coronary syndrome in patients undergoing PCI at 3.7 years of follow up, 39 Lindberg et al. showed adiponectin to be an independent predictor of CvsM in STEMI patients treated with primary PCI. 39 In this study, the multivariate tests showed that higher levels of adiponectin were an independent predictor of CvsM. Moreover, we calculated a cut-off value using ROC curve analysis and found that a preprocedural adiponectin level of 8,950 ng/ml could predict increased CvsM rates with 73.08% sensitivity and 75.71% specificity. The mortality risk was 3.01 times higher for a patient with an adiponectin level higher than 8,950 ng/ml than a patient with a level below this cut-off value.

Early studies showed that higher copeptin levels were an independent prognostic factor for both poor functional outcome and mortality in cardio-cerebrovascular disease. 40,41 Several studies confirmed strong associations of all-cause mortality with copeptin in patients presenting to emergency departments due to stable angina pectoris or MI, in patients with acute HF and in haemodialysis patients with DM. 42–43

Tasevska et al. reported that fasting copeptin levels predicted both CvsM and total mortality in a cohort of unselected healthy patients with or without DM at a follow-up period of 6.5 years. Additionally, it was reported as a predictor of coronary artery disease. 8 The authors suggested that subjects belonging to the top quartile of copeptin had a > 70% increased risk of dying from cardiovascular disease than those in the lowest quartile. 44 Engelbertz et al. suggested that patients who had elevated copeptin levels had an increased rate of mortality within 180 days, and copeptin level was a sole independent predictor of mortality. 41

In a recent meta-analysis conducted by Zhang et al., the authors showed that the risk of death increased by 3% per unit increase in baseline level and by more than 200% for a 10-fold copeptin level increase. 45 Furthermore, in comparison to the group with a lower level, the patients with HF who had higher levels were at 1.69 times higher risk from all-cause mortality. 44 These multiple reports stated that circulating copeptin levels were necessary for risk stratification, 44,45 and defining uniform values will be helpful to use copeptin as a valuable predictor in everyday practice. 46

Doğanay et al. reported that a higher copeptin level of 6.8 ng/ml was a predictor of occluded infarct-related arteries. Further copeptin levels were significantly related to TIMI flow grade in infarct-related arteries in STEMI patients who presented to the emergency departments within the first three hours of chest pain. 41 Although the results of this study showed a significant relationship between copeptin values and CvsM, it was not an independent predictor according to logistic regression analysis. Nevertheless, it was found that a cut-off preprocedural copeptin value of 7.41 ng/ml was strongly and significantly predictive for CvsM, and a value higher than this cut-off value was related to a 2.83-times higher CvsM risk in STEMI patients who underwent PCI procedure.

Limitations

One limitation was that this study specifically focused on CvsM. However, analyses of causes of cardiac death might be limited, because they might have been influenced by other diseases, particularly in patients with multiple organ dysfunction and patients who were found dead, especially for studies with these long follow-up periods. What is more, this was a single-centre study with a limited number of patients. Additionally, the data were observational data, therefore we cannot prove causality.

Adiponectin and copeptin levels were only determined at baseline and not at follow up. It would have been interesting to know whether adiponectin and copeptin levels had changed after successful PCI. Nevertheless, the blood samples were collected within the first 12 hours. Therefore, the detected values
of copeptin and adiponectin were not strongly corresponding with the real raised values within the window of the first hour. Additionally, the population of the study in terms of admission causes was strongly heterogeneous. Therefore, we believe that the population reflected a typical, critically ill population that physicians face on an everyday basis, which represents the major strength of these data.

Conclusions

The result of this study showed that, although some factors were significantly related to CvsM, adiponectin levels were an independent predictor of CvsM. Besides, the results showed that an adiponectin level of ≥ 8 950 ng/ml and a copeptin level of ≥ 7.41 ng/ml could predict CvsM with a high sensitivity and specificity in STEMI patients who had had PCI. Therefore, these markers might be helpful to provide information, not only in decision making for treatment, but also in the prediction of clinical outcomes. However, these findings should be further investigated in future studies.

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