Elevated serum neopterin levels and adverse cardiac events at 6 months follow-up in Mediterranean patients with non-ST-segment elevation acute coronary syndrome

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Abstract

Background: Little information exists regarding the prognostic role of biomarkers of inflammation in Mediterranean patients. High C-reactive protein and neopterin levels – a marker of macrophage activation – predict cardiovascular events in stable angina patients and patients with acute coronary syndromes (ACS). We sought to assess whether plasma neopterin levels predict adverse clinical outcomes in Mediterranean patients with non-ST elevation (NSTE) ACS, i.e. unstable angina (UA) and NSTE myocardial infarction (MI).

Methods: We prospectively assessed 397 patients (74% men) admitted with NSTEACS, 147 (37%) had unstable angina and 250 (63%) NSTEMI. Blood samples for neopterin and CRP assessment were obtained at admission. The study endpoint was the composite of cardiac death, acute myocardial infarction and unstable angina at 180 days.

Results: Baseline neopterin concentrations (nmol/L) were similar in unstable angina and NSTEMI patients (8.3 [6.6–10.7] vs. 7.9 [6.2–10.9]; p = 0.4). Fifty-nine patients (14.9%) had events during follow-up. Twenty-nine (21.5%) patients with neopterin levels in the highest third experienced the combined endpoint, compared to 30 (11.5%) patients with neopterin levels in the second and the lowest thirds

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; UA, unstable angina; CD, cardiac death; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CRP, C-reactive protein; TIMI, thrombolysis in myocardial infarction; NSTEACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction.

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Inflammation and macrophage activation play a central role in atherogenesis and plaque vulnerability [1]. In patients with acute coronary syndrome (ACS) plaque disruption is more likely to occur at sites where the fibrous cap is heavily infiltrated by activated macrophages [2]. Little information exists regarding the predictive role of markers of inflammation in Mediterranean patients admitted to hospital with ACS. Circulating neopterin, a marker of macrophage/monocyte activation, is increased in patients with ACS compared with stable ischemic heart disease patients [3,4], and high neopterin levels correlate with the presence of vulnerable coronary atheromatous plaques [5,6]. In man, neopterin is secreted by activated macrophages in response to stimulation with interferon-γ, mainly derived from activated T-helper type-1 lymphocytes [7]. Previous studies showed that increased serum neopterin levels predict rapid angiographic coronary artery disease (CAD) progression [8] and acute coronary events in chronic stable angina (CSA) patients [9,10] and also in hypertensive patients without obstructive CAD [11]. Recently, high neopterin levels were shown to predict further events in the PRavastatin Or atorVastatin Evaluation Infection Therapy–Thrombolysis In Myocardial Infarction (PROVE IT–TIMI 22) trial [12].

In the present study we assessed whether neopterin levels correlate with further adverse cardiac events in a patient population that differs from that in PROVE IT–TIMI 22, namely “real-life” (as opposed to trial patients) Mediterranean patients admitted with non-ST-segment elevation acute coronary syndromes (NSTEACS).

1. Methods

1.1. Patients

The present prospective study involved 397 consecutive patients who participated in the multicenter Systemic Inflammation Evaluation in patients with non-ST-segment elevation Acute coronary syndromes (SIESTA) study. The SIESTA study protocol has been reported in detail previously [13]. Briefly, from June 2002 to December 2003 we enrolled patients who presented with chest pain suggestive of ACS and at least one of the following: (1) electrocardiographic (ECG) signs of myocardial ischemia (ST-segment depression, T wave inversion, or both), (2) elevated markers of myocardial necrosis (i.e. cardiac troponin), and (3) documented coronary, cerebrovascular, or peripheral vascular disease. We did not include patients with ST-segment elevation, left bundle branch block, aortic stenosis, hypertrophic or dilated cardiomyopathy, acute myocardial infarction (AMI) <12 weeks, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during the preceding 12 weeks, a previous history of heart failure, acute cerebrovascular or peripheral vascular events <12 weeks, anemia, acute or chronic infections, thyrotoxicosis, systemic inflammatory diseases, end stage renal disease, malignancies, or any other disease that could compromise patient survival within 2 years. Patients were treated in accordance to the ACS guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) [14], blinded to CRP and neopterin results. All patients gave written informed consent before study entry, and the study protocol was approved by the Research Ethics Committee.

1.2. Definitions

Unstable angina (UA) and AMI definitions were based on ACC/AHA ACS guidelines [14]. Briefly, UA was defined as pain at rest lasting >5 min, with typical ST-segment depression and/or T wave inversion in two contiguous ECG leads, with the exception of lead aVR. AMI was diagnosed in the presence of typical chest pain (>20 min) or ST-segment deviation and increased cardiac troponin levels exceeding the decision limit (percentile 99th). Non-ST elevation myocardial infarction (NSTEMI) was diagnosed in the presence of typical chest pain and increased troponin levels exceeding the decision limit (percentile 99th), in the absence of ST-segment elevation or left bundle branch block. Cardiac death (CD) was defined as death occurring during the course of an ACS, or sudden CD. Multivessel CAD was defined as ≥2 large epicardial coronary arteries showing lumen diameter narrowings >50%.

1.3. Biochemical measurements

In every patient venous blood samples were obtained at the time of hospital admission, within 12 h of symptom onset (average 8.5 h). Samples were centrifuged immediately, and both serum and plasma stored at −80°C until assessment at the end of the study. Routine hematological and biochemical profiles were obtained for each patient.

Serum neopterin concentration was measured using a commercially available immunoassay (ELISA Kit, IBL, Hamburg, Germany). The within-coefficient of variability

(\log\text{-}\text{rank \ 7.435, } p = 0.024). On multivariable hazard Cox regression, neopterin (highest vs. 1st and 2nd thirds, HR 1.762, 95% CI [1.023–3.036]) was independently associated with the combined endpoint.

Conclusion: Increased neopterin levels are an independent predictor of 180-day adverse cardiac events in Mediterranean patients with NSTEACS.

Keywords: Prognosis; Unstable angina; Myocardial infarction; Neopterin
was <3% in the 7.7 nmol/L range and <4% in the 20 nmol/L range. CRP measurements were performed with COBAS Integra (Roche Diagnostics Limited, Lewes, East Sussex, UK) using the CRP-latex assay in both the high-sensitivity application (analytical range 0.2–12 mg/L) and the normal application (analytical range 2–160 mg/L). The estimated creatinine clearance was assessed by the “Modification of Diet in Renal Disease” method (MDRD) [15]. As we did not specifically sought to evaluate the prognostic role of troponin, participating centers were allowed to use cardiac troponin T or I assays as per standard practice in each center. Patients were therefore classified as those with and without elevated troponin levels. In all cases the cut point used was that corresponding to the 99 percentile, and the coefficient of variation was <10%.

1.4. Clinical characterization, follow-up and study endpoints

Demographic, clinical, angiographic and biochemical data collected at study entry are summarized in Table 1. Left ventricular ejection fraction was assessed in 296 patients (74.6%) by echocardiography and/or contrast ventriculography. Patient status at follow-up was assessed, as per study protocol, with outpatient visits scheduled at 1 and 6 months. We have painstakingly ensured accurate recording and classification of endpoints, which were adjudicated by a central events committee. The composite study endpoint was UA, AMI and CD at 180-day follow-up. Of importance, complete follow-up data were available in all 397 patients (100%).

1.5. Statistical analysis

This study had a statistical power of 84% to detect a difference of 12 percent units assuming an expected event rate of 12% in subjects in the 1st and 2nd thirds (information obtained in previous pilot work from our group) and a type I error of 0.05. As the relationship between neopterin levels and patient outcome is known to be non-linear we compared the highest neopterin tertile versus tertiles 1 and 2 considered together, as previously carried out by Avanzas et al. [9] and Ray et al. [12]. Differences between the patient group with adverse events and the group without events, and between subjects in the upper neopterin third versus those belonging to the remaining two thirds were assessed using the Pearson $\chi^2$-test or Fisher’s exact test for categorical variables, and the Student’s $t$-test or the Mann–Whitney test for continuous variables, as appropriate. The occurrence of the combined endpoint over time was analyzed by the Kaplan–Meier method, and differences were compared using the log-rank (Cox–Mantel) test. To determine variables independently associated with the occurrence of the composite study endpoint, enter-method multivariable hazard Cox regression analysis was used. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. Variables included in the multivariable analysis (covariates) were (1) variables that showed a significant association with both the study endpoint and the highest third of neopterin on univariate analysis ($p < 0.05$), (2) variables showing a trend ($p < 0.20$) towards an association, and (3) variables considered to be of clinical relevance (i.e. TIMI risk score, left ventricular ejection fraction, estimated creatinine clearance, heart failure at presentation, ST-segment deviation, elevated cardiac troponin, type 2 diabetes mellitus). We tested the proportional hazard assumption with the Schoenfeld residuals test and visual plots, and appeared valid for all analyses. We used a multivariate fractional polynomial approach to test the probability of a threshold effect. In patients in whom ejection fraction was not measured, the value was imputed with the sample median to include all subjects in the model. Logarithmic transformation was performed to normalize the distribution of CRP. Also, receiver-operating-characteristic (ROC) curves were plotted for models with and without neopterin. Because standard methods do not exist for deriving ROC curves for time-to-event data, we used occurrence as compared to non-occurrence of events within 6 months as the outcome for these analysis. The statistical significance level was defined as a two-tailed $p < 0.05$. Statistical analyses were performed using the SPSS 13.0 (SPSS Inc., Chicago, IL) and STATA 9.1 (Statacorp., TX, USA).

2. Results

2.1. Patients’ baseline characteristics

Of the 397 patients enrolled in the study 74% were male. Diagnoses at hospital admission were UA in 147 (37%) patients and NSTEMI in 250 patients (63%). Baseline neopterin levels (nmol/L, median [P25–P75]) did not differ in UA patients compared to AMI patients (8.3 [6.6–10.7] vs. 7.9 [6.2–10.9]; $p = 0.4$). Conversely, CRP concentrations (mg/L, median [P25–P75]) were significantly higher in NSTEMI compared to UA (8.2 [3.8–20.7] vs. 5.1 [2.2–11.1], respectively; $p = 0.07$). Patients with elevated troponin levels experienced more adverse events compared to those with negative troponin (38 [15.2%] vs. 21 [14.3%]; $p = 0.8$). Baseline clinical and biochemical characteristics of the study patients are summarized in Table 1.

2.2. Neopterin concentrations and adverse cardiac events during follow-up

During the 6 months follow-up 59 patients (14.9%) had cardiovascular events, which were considered to represent the study endpoint (i.e. UA, AMI and CD), and 338 had no adverse events. The distribution of the individual components of the combined endpoint is shown in Table 2. Fig. 1 shows Kaplan–Meier curves for the combined endpoint in patients in the top third of neopterin versus those in the remaining thirds. Twenty-nine (21.5%) patients with neopterin levels in the highest third experienced the combined
Table 1
Baseline characteristics of 397 consecutive patients with NSTEACS: comparison between patients with and without cardiovascular events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort n = 397</th>
<th>No events 338 (85.1%)</th>
<th>Events 59 (14.9%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 11</td>
<td>64 ± 11</td>
<td>67 ± 11</td>
<td>0.03</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>295 (74)</td>
<td>254 (75)</td>
<td>41 (69)</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140 ± 22</td>
<td>140 ± 22</td>
<td>139 ± 23</td>
<td>0.46</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78 ± 13</td>
<td>78 ± 12</td>
<td>76 ± 15</td>
<td>0.85</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
<td>27 ± 4</td>
<td>28 ± 5</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous history of CAD, n (%)</td>
<td>166 (42)</td>
<td>134 (40)</td>
<td>32 (54)</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>42 (11)</td>
<td>32 (9)</td>
<td>10 (17)</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>19 (5)</td>
<td>14 (4)</td>
<td>5 (8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>40 (10)</td>
<td>31 (9)</td>
<td>9 (15)</td>
<td>0.16</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>110 (28)</td>
<td>86 (26)</td>
<td>24 (41)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>216 (55)</td>
<td>182 (54)</td>
<td>34 (57)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>235 (60)</td>
<td>193 (58)</td>
<td>42 (71)</td>
<td>0.05</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>109 (28)</td>
<td>97 (29)</td>
<td>12 (20)</td>
<td>0.17</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>94 (24)</td>
<td>76 (23)</td>
<td>18 (30)</td>
<td>0.21</td>
</tr>
<tr>
<td>Cardiac catheterization, n (%)</td>
<td>260 (65)</td>
<td>222 (66)</td>
<td>38 (64)</td>
<td>-</td>
</tr>
<tr>
<td>Number of diseased vessels ≥ 50% stenosis, median (Q1, Q3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.43</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>132 (51)</td>
<td>110 (32)</td>
<td>22 (37)</td>
<td>0.39</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>168 (42)</td>
<td>138 (41)</td>
<td>30 (51)</td>
<td>0.15</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>61 ± 12</td>
<td>61 ± 12</td>
<td>60 ± 11</td>
<td>0.72</td>
</tr>
<tr>
<td>TIMI risk score, median (Q1–Q3)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>4 (2–4)</td>
<td>0.05</td>
</tr>
<tr>
<td>ST-deviation, n (%)</td>
<td>161 (41)</td>
<td>133 (40)</td>
<td>28 (48)</td>
<td>0.24</td>
</tr>
<tr>
<td>Heart failure during hospitalization, n (%)</td>
<td>19 (5)</td>
<td>15 (4)</td>
<td>4 (7)</td>
<td>0.51</td>
</tr>
<tr>
<td>In-hospital CABG, n (%)</td>
<td>25 (6)</td>
<td>23 (7)</td>
<td>2 (3)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean values ± standard deviation or median (interquartile range Q1–Q3); categorical variables are presented as percentage.

ACE: angiotensin converting enzyme; AMI: acute myocardial infarction; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; CABG: coronary artery by-pass graft; CAD: coronary artery disease; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LV: left ventricle; MDRD: estimated creatinine clearance by modification of diet in renal disease method; NSTEACS: non-ST-segment elevation acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction; WBCC: white blood cell count.

endpoint, compared to 30 (11.5%) patients with neopterin levels in the second and the lowest thirds (log-rank 7.435, p = 0.024). No difference was found with regard to the incidence of the study endpoint when patients in the 1st and 2nd tertiles were compared. This finding suggested the presence of a threshold effect, which we specifically tested using a multivariate fractional polynomial model that identified a neopterin threshold at 9.5 nmol/L. No significant differences were found between the proportion of men and women who suffered an event (13.9% vs. 17.6%, respectively; p = 0.36). On the univariable comparison of patients who experienced the study endpoint versus those who did not, and patients in the top third of neopterin versus those in the remaining tertiles, we observed that age, previous PCI, previous stroke,
systemic hypertension and current smoking were all associated \((p<0.20)\) both with the occurrence of the combined endpoint and the highest third of neopterin, and were therefore considered to represent potential confounding variables. Neopterin (highest third) was significantly associated with the combined study endpoint on univariate analysis (unadjusted \(HR = 1.99, 95\% \text{ CI } 1.19–3.32, p<0.01\)). CRP levels, however, were not significantly different in patients with events compared to those without events (adjusted \(HR = 0.98, p = 0.89, 95\% \text{ CI } 0.80–1.21\)). On multivariable hazard Cox regression, neopterin levels in the highest third \((HR 1.762, 95\% \text{ CI } 1.023–3.036, p = 0.04)\) were independently associated with the combined study endpoint in a model adjusted by age, previous PCI, previous stroke, current smoking, systemic hypertension, TIMI risk score, left ventricular ejection fraction, glomerular filtration rate (estimated by modification of diet in renal disease, MDRD method), heart failure during hospitalization, ST-deviation, elevated troponin, and type 2 diabetes mellitus. Of importance, raised neopterin levels (highest third, >9.56 nmol/L) in these patients yielded a 76% adjusted increase of risk in the 180-day combined outcome.

The area under the ROC curve was 0.617 for TIMI risk score \((95\% \text{ CI } 0.538–0.695)\), which increased 0.9% after including CRP \((AUC = 0.626 [95\% \text{ CI } 0.546–0.706])\). Interestingly, the AUC for TIMI risk score plus neopterin \((AUC = 0.651 [95\% \text{ CI } 0.574–0.727])\) was 3.4% \((95\% \text{ CI } 3.2–3.6\%)\) higher compared with TIMI risk score alone and 2.5% \((95\% \text{ CI } 2.1–2.8\%)\) higher compared with TIMI risk score plus CRP.

Fig. 2 shows the magnitude of the point estimate of neopterin in different risk categories for the combined endpoint. No significant interaction was found for gender or MDRD regarding the association of circulating neopterin levels and the study endpoint \((p \text{ for the interaction } = 0.12 \text{ and } 0.07\) respectively). Conversely the magnitude of the HR appeared to be somewhat higher in patients with <65 years \((p = 0.03)\), unstable angina \((p = 0.04)\), those with type 2 diabetes mellitus \((p < 0.01)\), TIMI risk score below the median \((p < 0.01)\) and low LVEF \((p = 0.03)\).

### 3. Discussion

Our study showed that neopterin is an independent predictor for cardiac adverse events in patients of Mediterranean origin admitted with NSTEACS. The risk of adverse cardiovascular events in patients in the highest third of neopterin was 76% higher compared with patients in the second and the lowest thirds. Moreover, we show here for the first time that the addition of neopterin to TIMI risk score increases its prognostic ability, albeit modestly. Of importance, high neopterin levels were consistently associated with the study endpoint across different risk subgroups.

The present findings are in agreement with data by van Haelst et al. [16], and more importantly, with recent findings by Ray et al. [12] in the large PROVE-IT–TIMI 22 study. There are differences between the Ray study [12] and ours, however, in that whilst our study focused exclusively on Mediterranean patients presenting with NSTE ACS, the Ray study did not include Mediterranean patients, and 33% of patients had UA, 33% NSTEMI and 33% STEMI.
As pointed out by Ray et al. [12] the quantitative – as opposed to the qualitative relationship – between neopterin levels and events during follow-up might have been influenced by the fact that the PROVE-IT–TIMI 22 study included patients who were highly selected for participation in a clinical trial. In this regard our study included unselected patients who were older than those in the Ray study (mean age, 64 years vs. 58 years), more patients with type 2 diabetes (28% vs. 17.5%), and less current smokers (28% vs. 37%). Moreover in-hospital PCI was performed less frequently in our study compared to that of Ray et al. (42% vs. 69%). These differences might have accounted for the small discordances observed between the two studies regarding hazard ratios for the individual components of the total endpoint. Of note, in the Ray study [12] the hazard ratio for all-cause death (HR = 1.86) was higher than that for softer endpoints (i.e. UA (HR = 1.12) and AMI (HR = 1.35)). In the present study the higher hazard ratio was for UA (HR = 2.19) followed by that of cardiac death (HR = 1.94) and AMI (HR = 1.45).

3.1. Neopterin as a predictor of risk in acute coronary syndromes

There are several possible reasons why neopterin may be a marker of cardiovascular risk in ACS patients, as found in the present study. Oxidative stress is known to play a major role in both early phases of atherogenesis and the progression of atherosclerotic cardiovascular disease. Neopterin can activate both constitutive and inducible nitric oxide synthase, and in consequence increase the production of cytotoxic NO-free radicals [17]. Enhanced oxidative stress induced by neopterin has also been suggested, in animal models, to induce left ventricular dysfunction [18]. Neopterin has previously been shown in several studies to be a useful marker of macrophage/monocyte activity [19], and a biomarker of immune activation in various inflammatory conditions such as infections, cancer and autoimmune disorders [20]. In vitro, neopterin stimulates nuclear factor κ-B translocation to the nucleus thus promoting the activation of inflammatory genes and the production of adhesion molecules, inflammatory cytokines, immune mediators, and tissue factor [21], all of which participate actively in the inflammatory processes that lead to atherothrombosis.

ROC curve analysis showed that a neopterin cut-point of 9.5 nmol/L has moderate sensitivity (0.51) and specificity (0.68) regarding the prediction of the study endpoint. We used tertiles for assessment in our study – and not quartiles as in the Ray’s study [12] – as the multivariate fractional polynomial analysis that we carried out identified an optimal threshold that corresponds to the third tertile. Our approach using tertiles shows clearly, in the Kaplan–Meier survival curves, the differences that exist between patients in the top third (higher risk) and the rest. Of interest, dividing our cohort into quartiles yielded a similar pattern (more patients in the 4th quartile experienced events [23%] vs. 12% than patients in the remaining quartiles; log-rank = 8.899, p = 0.03).

We also compared two multivariate models, with and without the inclusion of neopterin; the AUC for the 180-day combined endpoint before incorporation of neopterin was 0.696 (95% CI 0.623–0.770), which increased to 0.712 (95% CI 0.637–0.786) after including neopterin in the model. Covariates assessed in the model were age, previous PCI, previous stroke, current smoking, systemic hypertension, TIMI risk score, left ventricular ejection fraction, glomerular filtration rate, heart failure during hospitalization, ST-segment deviation, elevated cardiac troponin, and type 2 diabetes mellitus.

CRP levels in our study correlated weak but significantly with neopterin levels (r = 0.147, two-tailed p = 0.003). Although on univariate analysis CRP levels correlated with patient outcome at 6 months, this association was not main-
tained after adjusting for several variables on multivariable analysis.

3.2. Study limitations

The lack of predictive power of CRP in our study contrasts with data on previous reports in the literature [22,23]. Although this is a puzzling finding, other authors have reported results regarding CRP that contrast with the literature [24,25], suggesting that the predictive value of CRP suggested by several studies might not be universal. The reason for this puzzling observation in this specific patient population involving Mediterranean patients is not known and may deserve further investigation.

The HR for the combined endpoint in this study was mainly driven by the component “unstable angina”. This contrasts – as discussed above – with previous data from Ray et al. [12]. In our study we observed a relatively low prescription rate of clopidogrel (55%). Prescription of statins was confirmed in 78% of patients. These rates contrast with current recommendations and findings in large trials. This apparent limitation of our study endorses our claim that patients in our study were unselected, real-life subjects. Several reasons account for the discrepancy between recommendations based on evidence from large trials and both registries and real-life practice, and a discussion of this issue is beyond the scope of our study.

4. Conclusions

Of importance, cumulative evidence in recent years [4–6,8–11] – in particular the findings reported here – and the recent study by Ray et al. [12] indicate that neopterin, a molecule that is frequently ignored in articles dealing with biomarkers of cardiovascular risk [26,27], may be a useful tool in the assessment of further cardiovascular risk in patients with ACS. Indeed, these two studies, assessing patients of different ethnic origins, have reached a similar conclusion namely that neopterin may have a clinical role that deserves further investigation.

Conflict of interest

None.

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Appendix A. SIESTA study collaborators


References


