In-hospital mortality of habitual cigarette smokers after acute myocardial infarction

The ‘smoker’s paradox’ in a countrywide study

G. K. Andrikopoulos¹, D. J. Richter¹, P. E. Dilaveris¹, A. Pipilis², A. Zaharoulis³, J. E. Gialafos¹, P. K. Toutouzas⁴ and E. T. Chimonas⁵

¹State Cardiac Department of Hippokration Hospital, Athens, Greece; ²Cardiac Department, Ygeia Hospital, Athens, Greece; ³Cardiac Department, Georgios Gennimatas Hospital, Athens, Greece; ⁴Department of Cardiology, University of Athens Medical School, Athens, Greece; ⁵Hellenic Society of Cardiology, 251 Airforce General Hospital, Athens, Greece

Aims Habitual cigarette smokers, paradoxically, present improved short-term prognosis after acute myocardial infarction, a phenomenon often termed ‘smoker’s paradox’. We sought to examine cigarette smokers’ post-infarction survival advantage in a countrywide survey of unselected, consecutive patients presenting with acute myocardial infarction.

Methods and Results The study population was derived from the registry of the Hellenic study of acute myocardial infarction, which recruited 7433 consecutive patients with acute myocardial infarction from 76, out of a total of 86, hospitals countrywide. Cigarette smokers presented with lower unadjusted mortality rates (7.4% vs 14.5%, P < 0.001), were younger, predominantly of male gender and were less likely to suffer from diabetes mellitus and arterial hypertension. When all univariate predictors of poor outcome were included as covariates in multivariate analysis, smoking status was not significantly associated with in-hospital mortality (relative risk = 1.12, 95% CI = 0.86–1.44, P = 0.399). The beneficial effect of thrombolytic therapy was independent of the smoking status in both univariate and multivariate analysis.

Conclusion Unadjusted mortality rates are significantly lower in smokers, but age accounted for much of their seemingly improved outcome. When a number of additional clinical variables were taken into consideration, no significant influence of habitual smoking on early outcome following acute myocardial infarction was observed.


Key Words: Acute myocardial infarction, prognosis, cigarette smoking.

See page 724 for the Editorial comment on this article

Introduction

A large number of population studies have provided convincing evidence of the hazardous effects of cigarette smoking on public health[1]. Cigarette smoking is considered to be responsible for 50% of all avoidable deaths in the industrialised world[2]. One half of these deaths are due to cardiovascular disease[1] and habitual smoking is recognized as a major modifiable risk factor for coronary artery disease[3,4]. However, considerable evidence in the literature suggests that habitual cigarette smokers present lower unadjusted mortality rates following acute myocardial infarction[5–16], a phenomenon often termed ‘smoker’s paradox’[10]. Despite the plethora of data supporting smokers’ post-infarction survival advantage, the role of cigarette smoking in the short-term prognosis after acute myocardial infarction remains to be clarified. Some investigators have shown that cigarette smokers, suffering an acute myocardial infarction, tend to be younger with less diffuse coronary artery disease and fewer co-morbidities compared to non-smokers[6,7,13] and these differences have been invoked to explain many of the differences in early mortality. Furthermore, angiographic studies have demonstrated that coronary artery occlusion in smokers is predominantly caused by thrombosis and thus may have a better response to spontaneous or therapeutic thrombolysis[9,12].
We examined the prognosis of habitual cigarette smokers following an acute myocardial infarction in the countrywide survey of the Hellenic Multicenter Study of Acute Myocardial Infarction. This study was primarily designed to evaluate the incidence and in-hospital mortality of acute myocardial infarction in the Greek population. The present study is a secondary analysis, assessing the possible independent association of habitual cigarette smoking with in-hospital mortality of acute myocardial infarction. We also evaluated the gender-related differences and the influence of thrombolytic therapy on survival, in relation to smoking status.

Methods

Patient population

The study population was derived from the registry of the Hellenic study of acute myocardial infarction, which included 7433 patients — 5755 men and 1678 women — who were admitted to hospital with an acute myocardial infarction during a 12-month period (1 May 1993 to 30 April 1994). Seventy-six out of a total of 86 hospitals countrywide participated in this study. The study investigators and the participating hospitals are presented in the Appendix.

Patients were enrolled if they were admitted to hospital within 24 h of the onset of symptoms. The diagnosis was established on the basis of the presence of typical pain lasting at least 30 min, a temporal rise and fall of serially obtained values of serum levels of cardiac enzymes (creatine kinase, MB isoenzyme of creatinine kinase, aspartate aminotransferase and lactate dehydrogenase) and dynamic electrocardiographic abnormalities of the ST segment. The dynamic changes of Q/QS and/or T waves were also taken into consideration. Possible infarctions were not included in the study.

Acute myocardial infarction was considered definite in cases with definite electrocardiographic evidence, or in cases with symptoms typical or atypical or inadequately described, together with probable electrocardiographic evidence and abnormal enzymes, or in cases with typical symptoms and abnormal enzymes, with ischaemic or a non-diagnostic electrocardiogram. An electrocardiogram was considered definite if a diagnostic Q wave was recorded, or where evolution of an injury current lasted more then one day. An ST-segment elevation lasting more than one day and T wave progression on three or more records were considered indicative of evolution of a myocardial injury current.

Patients, who died from myocardial infarction before admission to hospital, even if the diagnosis of acute myocardial infarction as the primary cause of death was validated by post-mortem examination, were excluded from the study. Due to the design of the study, patients admitted for unstable or variant angina who developed a myocardial infarction during their hospitalization were also not included in the study population. Finally, only the first recorded admission was included in case a patient suffered from a second myocardial infarction, within the period of the patient’s enrolment.

The acquisition of demographic and historical data took place immediately following admission. The time from the onset of symptoms to arrival at hospital, as well as the time to fibrinolytic therapy, where indicated, were also recorded. The study investigators were asked to comply with the current indications for thrombolytic therapy in patients with acute myocardial infarction. The study form was completed by the end of the hospitalization period, when data concerning therapy procedures and outcome were available. The primary scope of this study was to record the basic epidemiological variables of myocardial infarction in the Greek population. Thus, the study protocol did not affect either diagnostic procedures, or therapeutic interventions of the studied patients. The study was conducted under the auspices of the Hellenic Cardiology Society. The scientific committee of the study and the local ethics committees of the participating hospitals approved the study protocol.

Definition of smoking status

Information about smoking status was obtained from the patient or a representative at the time of admission. Current smokers were considered to be those who reported smoking cigarettes at entry to the study. Only those who had never smoked were considered non-smokers. Patients who failed to answer the yes/no question but gave evidence of tobacco use, ex-smokers, those with a smoking history of less than a month, and those who smoked only pipes or cigars were excluded from the analysis. In total, 5507 patients (3853 smokers and 1654 non-smokers, 4479 men and 1028 women) met the inclusion criteria.

Statistical analysis

Values are expressed as mean ± SD. Pearson’s chi-square test, t-test and analysis of variance, where appropriate, were employed to compare the baseline characteristics of the groups. Logistic regression analysis was employed to detect possible significant associations between a dichotomous dependent variable (in-hospital mortality) and a number of independent ones. We used a series of logistic–regression models to assess the effect of groups of variables on the associations of interest. Contrary to other variables, age was modelled as a continuous variable. The forward stepwise method was selected to perform the analysis. Variable selection was terminated when no candidate variables for entry were significant at P<0.05, and all those selected for entry remained significant at P<0.10. All tests of statistical significance were two-tailed and were considered to be
significant at a 0.05 level of statistical significance. Statistical analyses were performed with SPSS statistical software (version 8.0, SPSS, Chicago, IL, U.S.A.).

Results

Characteristics of smokers and non-smokers

The baseline characteristics of the studied patients are presented in Table 1. As expected, the groups of smokers and non-smokers differed significantly. Non-smokers, on average, were approximately 11 years older and were more often females. Males were also significantly younger than females in this study population. The proportion of patients in relation to gender included in each of the selected four age categories is presented in Fig. 1.

Non-smokers were more likely to suffer from diabetes mellitus and arterial hypertension while they were less likely to receive thrombolysis. When thrombolysed, non-smokers were mostly treated with streptokinase, in contrast to smokers who were more likely to be treated with tissue plasminogen activator. Cigarette smokers more often had a positive family history of coronary artery disease compared to non-smokers (Table 1).

All characteristics were significantly different in the univariate analysis, and were included as covariates in multivariate logistic regression analysis, which aimed to detect the clinical variables independently related to smoking status. According to multivariate analysis, older age (odds ratio 0.94, 95% CI 0.94–0.95, P<0.001), diabetes mellitus (odds ratio 0.78, 95% CI 0.66–0.92, P=0.003) and arterial hypertension (odds ratio 0.80, 95% CI 0.69–0.93, P=0.003) were independently and negatively related to baseline habitual cigarette smoking, while male gender (odds ratio 9.6, 95% CI 8.0–11.6, P<0.001) and a positive family history for coronary artery disease (odds ratio 1.2, 95% CI 1.0–1.4, P=0.047) were independently and positively associated with habitual cigarette smoking.

In-hospital mortality rates

Current cigarette smokers showed significantly lower unadjusted mortality rates compared to non-smokers (7.4% vs 14.5%, P<0.001). In addition, when the studied patients were divided into four age groups it was apparent that, with the exception of patients younger than 60 years, cigarette smokers still presented lower unadjusted in-hospital mortality rates (Fig. 2).

Univariate analysis demonstrated that age was strongly related to early prognosis. The mean age of the patients with unfavourable short-term prognosis was significantly higher compared to the patients who survived (61 ± 12 vs 72 ± 11 years, P<0.001). The results of univariate analysis of in-hospital mortality rates,

Table 1 Baseline characteristics of the study population according to smoking status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Smokers (n=3853)</th>
<th>Non-smokers (n=1654)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 12</td>
<td>70 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>7.4%</td>
<td>14.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>93.8%</td>
<td>52.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18.6%</td>
<td>33.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>34.8%</td>
<td>36.5%</td>
<td>0.128</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.4%</td>
<td>55.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heredity for CAD</td>
<td>30.1%</td>
<td>22.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>17.1%</td>
<td>18.1%</td>
<td>0.194</td>
</tr>
<tr>
<td>Thrombolyzed patients</td>
<td>52.4%</td>
<td>36.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>33.9%</td>
<td>42.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APSAC</td>
<td>12.0%</td>
<td>11.7%</td>
<td>0.876</td>
</tr>
<tr>
<td>t-PA</td>
<td>54.1%</td>
<td>45.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CAD=coronary artery disease; MI=myocardial infarction; APSAC=anisoylated streptokinase plasminogen activator complex; t-PA=tissue plasminogen activator.

Figure 1 The proportion of patients in relation to gender in each of the selected age-categories. Values represent the percentage of males and the percentage of females in each age category. □=women; ■=men.

Figure 2 Unadjusted in-hospital mortality rates in relation to smoking status. □=smokers; ■=non-smokers.
Table 2  Significant predictors of in-hospital mortality in univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>In-hospital mortality rates (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Males</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>Cigarette smokers</td>
<td>7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Non-smokers</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diabetics</td>
<td>16.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Non-diabetics</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>Thrombolysed patients</td>
<td>6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Non-thrombolysed patients</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertensives</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Normotensives</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>Patients with prior MI</td>
<td>14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Patients without prior MI</td>
<td>8.5</td>
<td></td>
</tr>
</tbody>
</table>

MI=myocardial infarction.

according to the baseline characteristics, are shown in Table 2. All significant univariate predictors of in-hospital mortality, apart from smoking status (age, sex, diabetes mellitus, fibrinolytic therapy, hypertension and history of a prior myocardial infarction) were included in a logistic regression model in order to examine their independent association with in-hospital mortality. Older age (relative risk 1.08, 95% CI 1.07 to 1.09, \( P = 0.001 \)), female sex (relative risk 1.18, 95% CI 1.01 to 1.26, \( P = 0.001 \)), diabetes mellitus (relative risk 1.61, 95% CI 1.30 to 2.01, \( P < 0.001 \)) and the existence of a prior myocardial infarction (relative risk 1.62, 95% CI 1.28 to 2.05, \( P < 0.001 \)) remained significant predictors of poor short-term prognosis in multivariable analysis. In the same multivariate logistic regression model with all the aforementioned variables included as covariates, arterial hypertension (relative risk 0.91, 95% CI 0.74 to 1.28, \( P = 0.397 \)) and fibrinolytic therapy (relative risk 0.88, 95% CI 0.69 to 1.11, \( P = 0.269 \)) were negatively, but not significantly associated with in-hospital mortality. The results of the logistic regression analysis are shown in Fig. 3. When considered without regard to other covariates, smoking status was associated with significantly lower in-hospital mortality rates (relative risk 0.47, 95% CI 0.39 to 0.56, \( P < 0.001 \)). However, adjustment for age reduced a smoker’s survival advantage (relative risk 0.94, 95% CI 0.76 to 1.16, \( P = 0.5586 \)). After age-adjustment, survival differences between smokers and non-smokers did not reach the 0.05 level of statistical significance. Adjustment for gender and diabetes mellitus also resulted in no significant associations with mortality. Finally, when the entire mortality model was used with all the aforementioned variables included as covariates, cigarette smoking was not significantly related to in-hospital mortality (Fig. 3, model 6).

**Thrombolysis**

Out of the 5507 patients included in this study, 2614 received thrombolysis. Two thousand and nineteen of them (77%) were classified as cigarette smokers, while the remaining 595 (23%) were classified as non-smokers. As shown in Table 1, cigarette smokers were more likely to receive fibrinolytic therapy compared to non-smokers (52% vs 34%, \( P < 0.001 \)). The patients who received thrombolysis were younger (58 ± 11 vs 66 ± 13 years, \( P = 0.001 \)), and were more likely to be males (87% vs 76%, \( P < 0.001 \)) while they were less likely to be diabetics (19% vs 26%, \( P < 0.001 \)) and hypertensives (38% vs 48%, \( P < 0.001 \)). Finally, thrombolysed patients were less likely to have a history of a prior myocardial infarction (15% vs 19%, \( P < 0.001 \)).

Cigarette smokers’ unadjusted in-hospital mortality was significantly lower in both thrombolysed (5.4% vs 8.6%, \( P = 0.005 \)) and non-thrombolysed patients (9.4% vs 17.8%, \( P < 0.001 \)), when compared to non-smokers.

![Figure 3](https://example.com/figure3.png)

**Figure 3** The relative risks and the 95% confidence intervals of cigarette smokers for in-hospital mortality in a series of logistic regression models. The variables included as covariates in these models are as follows: in model 1 smoking status only, in model 2 smoking status and age, in model 3 smoking status, age and gender, in model 4 smoking status, age, gender and diabetes mellitus, in model 5 smoking status, age, gender, diabetes mellitus and history of a previous myocardial infarction, and in the 6th model smoking status, age, gender, diabetes mellitus, history of a previous myocardial infarction, hypertension and thrombolytic therapy.
(Fig. 4). Furthermore, in multivariate analysis with only thrombolysis and smoking status included as covariates, thrombolysis was significantly and independently related to lower in-hospital mortality (relative risk 0.50, 95% CI 0.41 to 0.61, \(P<0.001\)). In this model, the interaction of smoking status with thrombolytic therapy was not significantly related to prognosis (relative risk 1.25, 95% CI 0.82 to 1.91, \(P=0.304\)). Thrombolysis was also significantly and independently associated with prognosis when gender (relative risk 0.52, 95% CI 0.42 to 0.64, \(P<0.001\)) was entered in the multivariate model. In contrast, the interaction of smoking status with thrombolytic therapy was not significantly related to prognosis (relative risk 1.15, 95% CI 0.75 to 1.77, \(P=0.5102\)) when also included in this model. The relative risks of thrombolyzed and non-thrombolyzed cigarette smokers in a series of logistic regression models are presented in Fig. 5 (Parts A and B, respectively).

Discussion

This study, based on a countrywide survey of consecutive unselected patients admitted to hospital with acute myocardial infarction, clearly demonstrates that habitual cigarette smoking is not related to improved short-term prognosis after acute myocardial infarction. Furthermore, thrombolytic therapy was associated with lower in-hospital mortality in both smokers and non-smokers, and multivariate analysis showed no interaction of thrombolytic therapy with the smoking status in relation to short-term prognosis.

Pathogenesis of acute myocardial infarction in relation to smoking status

The main demographic characteristics of cigarette smokers in this study population are lower age and the predominance of males. Along with the lower prevalence of diabetes mellitus, these baseline differences were also observed in the vast majority of previous large-scale studies.[7,10,14,15]

Figure 4 Unadjusted in-hospital mortality rates in both smokers and non-smokers in relation to thrombolytic therapy.

Figure 5 The relative risks for in-hospital mortality and the 95% confidence intervals of thrombolyzed and of non-thrombolyzed cigarette smokers are shown in the upper (a) and in the lower (b) part of the figure, respectively. The variables included as covariates in these series of logistic regression models are as follows: in model 1 smoking status only, in model 2 smoking status and age, in model 3 smoking status, age and gender, in model 4 smoking status, age, gender and diabetes mellitus, and in model 5 smoking status, age, gender, diabetes mellitus and history of a previous myocardial infarction.

Cigarette smoking has been associated by Vlietstra and co-workers[18] with less extensive and less severe coronary artery disease in a cohort of 15 298 patients with established coronary artery disease, who were enrolled in the Coronary Artery Surgery Study.Hasdai et al.[19], demonstrated that cigarette smokers who underwent transluminal percutaneous coronary revascularization had fewer lesions in the target coronary artery, even after adjustment for baseline characteristics including age and diabetes mellitus. Similarly, in patients with acute myocardial infarction, multivessel disease has been also documented to be less frequent in current smokers than in non-smokers[9,12,13]. Barbash et al.[10] studied the 2400 patients recruited in the angiographic substudy of the GUSTO-I trial. In agreement with previous reports they showed that cigarette smokers were less likely to have multivessel disease while they had more right coronary artery infarctions compared to non-smokers.

Accordingly, data derived from both epidemiological and angiographic studies suggest that acute myocardial infarction in cigarette smokers occurs in a relatively premature stage of coronary artery atherosclerosis. Nonetheless, the exact pathophysiological mechanisms underlying the aforementioned clinical observations and their prognostic implications have not been fully clarified, possibly due to the multifactorial pathogenesis of...
acute coronary syndromes and the multiple biological actions of cigarette smoking.

The hypercoagulable state of current smokers due to increased haematocrit[9], fibrinogen and thrombin generation[8,20] and enhanced platelet activation[4,22] has been invoked to explain many of the differences regarding the occurrence and prognosis of acute myocardial infarction in cigarette smokers. In addition to previous reports, Newby et al.[23], recently demonstrated that the endothelium of active smokers has impaired capacity to release tissue plasminogen activator acutely, despite higher basal plasma levels. The authors suggest that the impaired endogenous fibrinolytic capacity of cigarette smokers could result in a more efficient response to thrombolytic therapy.

Conclusively, accumulating evidence supports the theory that myocardial infarction in smokers occurs in a less severe lesion than in non-smokers and may be generated by a different, predominantly thrombogenic, mechanism.

Mechanisms possibly associated with cigarette smokers’ survival advantage

In previous studies, older age has been consistently regarded as the most important factor influencing early prognosis after acute myocardial infarction[11,24,25]. In accordance with previous studies[6-14] we also noticed that cigarette smokers were significantly younger. The average age difference between smokers and non-smokers in the large-scale previous studies[7,8,10,11,14] was 8 to 11 years. Similarly, in our study, cigarette smokers were 11 years younger compared to non-smokers, and age-related differences contributed markedly to the unadjusted survival differences. Notably, when age was entered in multivariate analysis, the differences between smokers and non-smokers regarding in-hospital mortality rates were no longer significant.

Cigarette smokers were most likely to be males. The independent influence of gender on early mortality after acute myocardial infarction has been well documented by Vaccarino et al.[25] in a cohort of 384 878 patients. We have also previously shown that female gender is a significant independent predictor of increased in-hospital mortality[26] in this study population. Adjustment for age and gender eliminated cigarette smokers’ post-infarction survival advantage in this study, but not in all previous studies. Molstad[27] has shown that adjustment for baseline characteristics, including age and gender, did not eliminate smokers’ survival advantage 3 months after admission to hospital. The conclusions of this study could be amenable to criticism, mainly due to the small number of the studied patients (155 cigarette smokers out of a total population of 484 patients). In the study by Kelly et al.[6], which was conducted in the pre-thrombolytic era and recruited 2955 patients with acute myocardial infarction, age-adjustment alone did not entirely abolish smokers’ survival advantage. However, the authors concluded that age difference alone is sufficient to explain most or all of the increased mortality rate among non-smokers and finally emphasized that smoking at the time of acute myocardial infarction does not appear to be an independent predictor of death. The independent prognostic role of habitual cigarette smoking after acute myocardial infarction after adjustment for age and other clinical variables was also supported by Barbash et al.[28] who addressed the issue in the registry of the International Tissue plasminogen Activator/Streptokinase Mortality trial and by Lee and co-workers[21] who examined the 30-day mortality after acute myocardial infarction in relation to smoking status in a population of 41 021 patients enrolled in the GUSTO-I study. In contrast, Gottlieb et al.[14], in a nationwide survey of 999 consecutive unselected patients, demonstrated that the seemingly better prognosis of cigarette smokers early after acute myocardial infarction could be ascribed to their younger age and more favourable risk profile.

Although the results of the previous studies appear to be discrepant, the explanations related to the aforementioned differences in short-term mortality after acute myocardial infarction could be plausible. All large-scale studies that have already addressed the issue are randomized thrombolytic trials. These trials, although powered to detect significant differences due to the large number of the study participants, are susceptible to the systematic bias of excluding the patients who were not eligible for fibrinolytic therapy. Similarly, small angiographic studies and angiographic substudies of large trials, although capable of including angiographic data such as the number of diseased vessels and TIMI grade flow in the multivariate analysis, are still susceptible to the same restrictions. Generally, angiographic substudies recruit only a small, selected, proportion of patients eligible for thrombolytic therapy. Angiographic data could not possibly be retrieved from a large sample of consecutive unselected patients with acute myocardial infarction and hence the available information derived from angiographic substudies, although valuable in order to clarify the pathophysiological mechanisms underlying the pathogenesis and prognosis of acute myocardial infarction, should not be over-extrapolated to the whole population of patients with acute myocardial infarction.

Therefore, it would be logical to hypothesize that the discrepancy in the results of our study with some previous studies, may, at least partly, reflect differences in patient selection criteria. According to this hypothesis it is noteworthy that our results, derived from a country-wide survey of consecutive unselected patients admitted to hospital with acute myocardial infarction, are consistent with those retrieved from the Israeli nationwide survey[14].

Possible unfavourable effects of cigarette smoking on early prognosis after acute myocardial infarction

Age adjustment seems to entirely abolish smokers’ post-infarction in-hospital survival advantage. We could
hypothesize that the expected age-adjusted improved prognosis of cigarette smokers, due to a more favourable anatomy, may be counterbalanced by uncontrolled mechanisms. Although specifically designed prospective studies are needed to clarify the pathophysiological relevance of these mechanisms, the hypercoagulable state of cigarette smokers may be, at least partly, responsible for the seemingly discrepant observations. However, the hypercoagulability of cigarette smokers may not only predispose them to the early occurrence of myocardial infarction, but also could predispose them to reinfarction and to more frequent episodes of intravenous or intracardiac thrombosis. In addition, Celermayer et al. and Migliacci and Gresele have demonstrated that cigarette smokers present with impaired endothelium dependent dilatation, an observation with profound prognostic significance in the post-infarction period.

As shown in previous studies, cigarette smoking causes an unfavourable modulation of autonomic cardiac control. A shift towards sympathetic predominance could be accompanied by increased levels of catecholamines, lower arrhythmogenic threshold, increased vasoconstriction and thus with increased myocardial oxygen consumption. Early studies by Lewis and Boudoulas suggested that the excessive catecholamine secretion observed in cigarette smokers after an acute myocardial infarction could induce life-threatening arrhythmias. Twenty years later, Peters et al. reported that, in a cohort of 2752 post-infarction patients enrolled in the Cardiac Arrhythmia Suppression Trial, smoking cessation was accompanied by a significant reduction in arrhythmic death and overall mortality.

In conclusion our data, derived from a countrywide survey of consecutive unselected patients with acute myocardial infarction, emphasize that habitual cigarette smoking is not associated with improved short-term prognosis after myocardial infarction and that the beneficial effects of thrombolytic therapy are independent of the smoking status of the treated patients. Based on previous studies, which confirmed that cigarette smokers suffering an acute myocardial infarction do have less severe coronary artery disease than non-smokers, we could hypothesize that the well known detrimental effects of habitual smoking on the cardiovascular system possibly counterbalance any potential favourable effect that could be attributed to cigarette smokers’ more favourable coronary anatomy.

The use of terms such as ‘smoker’s paradox’ and ‘paradoxically beneficial’ effects of cigarette smoking on early outcome after acute myocardial infarction does not seem to be fully justified and most importantly may lead to misunderstandings by the public. Cardiologists should continue to emphasize the pivotal role of smoking cessation in risk reduction especially in patients with established coronary artery disease, as the task force of the European Society of Cardiology recently suggested.

The Hellenic Study of Acute Myocardial Infarction was supported and supervised by the Hellenic Cardiological Society and was also supported by Servier Hellas S.A. The authors are indebted to all the cardiologists and to all the directors of the Cardiac departments that participated in the study. The authors would also like to thank Dr Dimitri Grammatopoulos and Mr Edward W. A. Needham, for their valuable assistance in the preparation of this manuscript.

**Limitations**

This was not a randomized prospective study specifically designed to address this issue and hence all data should be interpreted in the light of this major methodological limitation. In addition, we excluded from this analysis a considerable proportion of patients originally enrolled in the Hellenic Study of Acute Myocardial Infarction in order to avoid dilution of the study groups (smokers and non-smokers) with ex-smokers. Ex-smokers, cigar or pipe smokers and those who smoked only a few cigarettes per day have been reported to present variable prognosis after acute myocardial infarction. In order to avoid misclassification we compared only the patients whose smoking status could be clearly and reliably characterized. We did not control for the association of the number of cigarettes with prognosis because in 30% of the studied patients the relative data were inadequate. Prospective data on 30-day and 12-month mortality, which could validate and possibly expand our hypothesis, are not available because the studied patients were not prospectively followed. Finally, our conclusions, until validated by specifically designed studies, should not be applied to patients who died before hospitalization, those with recurrent myocardial infarction or to patients with unstable angina.

**References**

In-hospital mortality of smokers after AMI

Appendix

Coordinating centre: 251 Airforce General Hospital, Athens, Greece.
Principal investigator: Elias T. Chimonas, Chairman of the Group of Epidemiology and Prevention of the Hellenic Cardiological Society.
Participating centres, Directors of the participating cardia