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Original Scientific Paper

Smoking and myocardial infarction case-fatality: hospital and population approach

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Background **Smoking is a risk factor for coronary heart disease, but it has been associated with better short-term prognosis in hospitalized patients with acute myocardial infarction. The aims of this study were to determine the association between smoking and myocardial infarction 28-day case-fatality in hospitalized patients and at the population level; and, whether smokers presenting with fatal myocardial infarction are more likely to die before reaching a hospital.**

Design and methods **Population-based myocardial infarction registry, carried out in 1997–1998 in seven regions of Spain, used standardized methods to find and analyze suspected myocardial infarction patients (10 654 patients; 7796 hospitalized). Four categories of smoking status were defined: never-smokers, former smokers for more than 1 year, former smokers for less than 1 year, and current smokers.**

Results **The main end-point was 28-day case-fatality, found to be 20.1, 17.1, 15.6, and 8.9%, in the four smoking status categories, respectively, for hospitalized patients; and 37.4, 33.0, 24.5, and 23.2%, respectively, at population level. Hospitalized current smokers had lower age, sex, and comorbidity-adjusted 28-day case-fatality than never-smokers (odds ratio = 0.71; 95% confidence interval: 0.56–0.90). This association held at population level (odds ratio = 0.68; 95% confidence interval: 0.60–0.76), in which former smoking was also associated with lower case-fatality. In fatal cases, recent former smokers presented a lower risk of out-of-hospital death than never-smokers (odds ratio = 0.47; 95% confidence interval: 0.29–0.77), whereas current smoking was marginally associated with out-of-hospital death (odds ratio = 1.22; 95% confidence interval: 0.99–1.50).**

Conclusions **Current smoking is associated with lower 28-day case-fatality in hospitalized myocardial infarction patients. This association held at population level. Among fatal cases, smoking is associated with higher and recent former smoking with lower risk of dying out-of-hospital.** ***Eur J Cardiovasc Prev Rehabil*** **14:561–567 © 2007 The European Society of Cardiology**

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Introduction

Smoking is a major, independent, and modifiable risk factor for coronary heart disease (CHD) and other chronic diseases [1,2]. Smoking cessation also has been associated

with significant decrease in mortality after an acute myocardial infarction (MI) [3]. Some authors have, however, shown smoking to be related with lower case-fatality in patients hospitalized for MI [4–10].

Younger age and lower comorbidity [4,5,7,10], and better response to thrombolysis in smokers might account for part of this 'smoking paradox' [11]. The clinical view of case-fatality from MI in those reaching the hospital alive is, however, different from the population view, and there are consistent data showing that approximately two-thirds of 28-day case-fatality occur before reaching the hospital [12]. Therefore, another explanation for this paradox could be a higher out-of-hospital case-fatality in smokers than in nonsmokers.

This study sought to determine the association between smoking and MI 28-day case-fatality in hospitalized patients and at population level and to test the hypothesis that smokers presenting with fatal MI are more likely to die before reaching a hospital.

Methods

The IBERICA Study (Investigación, Búsqueda Específica y Registro de Isquemia Coronaria Aguda) is a population-based registry for 1997–1998 covering seven parts of Spain (Basque Country, Castilla-La Mancha, Girona, Majorca, Murcia, Navarra, and Valencia), with a population of 7 378 598 [13]. The study includes all patients with suspected MI aged 25–74 years.

Case-finding procedures were prospective for patients admitted to coronary care units and retrospective by screening discharge records for all hospitals of the participating regions. Primary and secondary ambulance records were screened to identify cases referred to hospitals out of the monitored area. Death certificates with International Classification of Diseases 9th codes 410–414 were investigated by reviewing medical records and interviewing the physician who signed the death certificate, family physician, and relatives or witnesses to identify fatal MI cases not otherwise detected.

Each event was classified according to a standardized algorithm [14] that takes into account symptoms, electrocardiograms, cardiac enzyme values, history of ischemic heart disease, and necropsy interpretation. The cases with the following diagnostic categories were included in this analysis: definite fatal or nonfatal MI, possible coronary death, and unclassifiable deaths.

Smoking

Information on smoking habits of hospitalized MI patients was collected through personal interview or medical record review. In out-of-hospital fatal cases, data were gathered from hospital records and a telephone questionnaire administered to family physicians, physicians who signed the death certificate, or relatives. Five groups were defined: never smoked, former smokers for less than 1 year, former smokers for more than 1 year, current smokers, and unknown, when insufficient data were available.

Other variables

The following data were also recorded: age, sex, hypertension, diabetes, and history of angina or previous MI. For hospitalized patients, electrocardiographic MI location, delay symptoms monitoring, the worst Killip classification during hospital stay, and the presence of severe ventricular arrhythmias were also recorded, as well as management variables including thrombolysis, primary percutaneous transluminal coronary angioplasty, antiplatelet drugs, β-blockers, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery.

End-points

The primary end-point was 28-day case-fatality. In fatal cases, a secondary end-point was defined: out-of-hospital vs. in-hospital mortality.

Quality control

All field investigators received 2 days of training in study protocols and had a high intraindividual and correct agreement in case classification (κ indexes > 0.90). All registered events were blindly reclassified in the coordinating center and all discrepancies were discussed with local investigators until consensus was reached.

To evaluate the quality of the out-of-hospital fatal-case finding procedure, the ratio between the number of fatal cases registered in the study and the number of CHD deaths in official mortality statistics was calculated. The result was 1.06 (> 1.0), which indicates that a proper out-of-hospital coverage was achieved in the study.

Sample size

Accepting an α risk of 0.05 and a β risk of 0.20 in a two-sided test, the sample size allows us to recognize as statistically significant an odds ratio (OR) lower than 0.85 when comparing smokers vs. never-smokers.

Statistical analysis

Differences between the defined categories of smoking and between death and survival in MI patients were assessed with χ^2 test for categorical variables and with analysis of variance for continuous variables.

Adjusted ORs of 28-day case-fatality for smoking categories were estimated using generalized additive models using the GAM procedure in SAS (SAS Institute Inc., Cary, North Carolina, USA). The models included all confounding variables (factors that, at $\alpha = 0.10$,

statistically differed in bivariate analysis between smokers and never-smokers and were further associated with mortality but could not be considered mechanisms of death) and allows penalized spline functions of the continuous confounders (age and delay symptoms monitoring).

A sensitivity analysis was performed for all patients with unknown smoking status. First, all these patients were included in the analysis as a further category. Then, these patients were considered never-smokers and, in turn, current smokers. In addition, we impute unknown smoking status using the multiple imputation (MI) procedure and then performed a multiple imputation analysis using the MIANALIZE procedure in SAS [15].

Results

Hospitalized patients

A total of 7796 hospitalized MI patients (79.7% men) were registered. Mean age was 61.3 years (standard deviation = 10.2 years), and smoking status was 36.4% never-smoker, 18.7% former smoker for more than 1 year, 3.5% former smoker for less than 1 year, 39.2% current smoker, and 2.2% unknown. The 28-day case-fatality was 16.0%.

Characteristics of the hospitalized MI patients by smoking status are shown in Table 1. More men than women were smokers and former smokers, with less sex difference among never-smokers. Current smokers were younger, with a lower proportion of comorbidity and complications than never-smokers. Never-smokers arrived later to the hospital. On the other hand, greater use of thrombolysis, aspirin, and β-blockers was observed in current smokers. No differences were detected in the proportion of severe arrhythmias across smoking groups. The 28-day case-fatality steeply decreased from 20.0% in never-smokers to 8.8% in current smokers. This association remained statistically significant even after multivariate adjustments (Table 2).

The interactions between smoking and thrombolysis, aspirin, age, and sex were also tested and none was statistically significant. The analyses were also performed for men and women, and similar results were obtained in both sexes.

Population approach

A total of 10 654 MI patients (78.9% men) were registered. Mean age was 61.9 years (standard deviation = 10.0 years), and smoking status was 34.0% never-smokers, 17.0% former smokers for more than 1 year, 2.8% former smokers for less than 1 year, 34.0% current smokers, and 12.2% unknown. The 28-day case-fatality was 38.5%.

Characteristics of the population by smoking status are shown in Table 3 and are similar to the profile of hospitalized MI patients. The 28-day case-fatality steeply decreased from 37.4% in never-smokers to 23.2% in current smokers. Characteristics of the 'unknown smoking status' group are also presented in Table 3. A high proportion of these patients also had missing data on comorbidity variables. Analysis of patients with unknown smoking status but valid data on comorbidity variables showed this group to be most similar to never-smokers (Table 3).

Table 1 Characteristics of hospitalized acute myocardial infarction patients by smoking status

	Never-smokers (n=2839)	Former smokers >1 year (n=1460)	Former smokers <1 year (n=270)	Smokers (n=3057)	P
Sex (female) (%)	47.1	2.2	3.7	6.1	<0.001
Age (years)[a]	65.2 (7.8)	64.6 (8.1)	60.6 (9.5)	56.0 (10.7)	<0.001
Delay symptoms monitoring <12 h (%)	81.4	86.6	87.0	85.6	<0.001
Hypertension (%)	56.8	47.3	38.8	34.6	<0.001
Diabetes (%)	40.2	28.2	28.5	18.5	<0.001
Previous MI (%)	18.0	29.8	29.7	11.1	<0.001
Previous angina (%)	44.2	50.9	45.3	35.0	<0.001
MI location					<0.001
Non-Q (%)	17.6	18.2	15.9	11.9	
Inferior (%)	40.3	44.6	51.9	52.7	
Anterior (%)	37.7	32.5	29.5	33.6	
Undetermined (%)	4.4	4.7	2.7	1.8	
Treatments and complications during hospitalization					
Thrombolysis (%)	34.4	38.5	37.7	50.5	<0.001
Primary PTCA (%)	4.9	3.5	4.1	5.5	0.033
AAS (%)	89.5	91.4	89.8	94.4	<0.001
Beta-blocker (%)	47.7	49.3	52.3	57.3	<0.001
Revascularization (%)	4.1	4.0	5.2	4.1	0.841
Killip III–IV (%)	23.6	20.3	19.2	12.4	<0.001
Arrhythmias[b] (%)	13.5	13.4	13.1	14.5	0.653
MI recurrence (%)	3.3	3.1	1.9	1.8	0.001
28-day case-fatality (%)	20.1	17.1	15.6	8.9	<0.001

AAS, aspirine; MI, myocardial infarction; Non-Q, absence of Q wave in the electrocardiogram; PTCA, percutaneous transluminal coronary angioplasty. [a]Mean (standard deviation). [b]Occurrence of ventricular fibrillation or sustained ventricular tachycardia requiring immediate medical treatment.

Table 2 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of 28-day case-fatality for smoking categories in hospitalized acute myocardial infarction patients

	Model 1 ($n=7626$)		Model 2 ($n=6670$)		Model 3 ($n=6575$)		Model 4 ($n=6522$)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Never-smokers	1		1		1		1	
Former smokers >1 year	0.89	0.74, 1.07	0.91	0.72, 1.16	0.84	0.64, 1.09	0.82	0.60, 1.12
Former smokers <1 year	0.96	0.67, 1.37	1.01	0.63, 1.61	0.94	0.58, 1.54	0.81	0.45, 1.44
Current smokers	0.61	0.51, 0.73	0.72	0.56, 0.91	0.65	0.50, 0.84	0.57	0.42, 0.78

Model 1: Adjusted for sex and spline function for age. Model 2: Adjusted for sex, spline function for age, hypertension, diabetes, previous myocardial infarction or angina, MI localization, and spline function for symptoms monitoring. Model 3: Adjusted for all variables in model 2 and thrombolysis, primary angioplasty, aspirin, and β-blocker treatment. Model 4: Adjusted for all variables in model 3 and occurrence of cardiogenic shock or acute pulmonary edema, and presence of severe arrhythmias (ventricular fibrillation or sustained ventricular tachycardia).

Table 3 Characteristics of population acute myocardial infarction patients across smoking categories

	Never-smokers ($n=3624$)	Former smokers >1 year ($n=1806$)	Former smokers <1 year ($n=302$)	Smokers ($n=3627$)	*P*	Smoking status unknown ($n=1295$)	
						Missing data for other variables (%)	Characteristics when valid data for other variables
Sex (female) (%)	46.8	2.0	3.6	5.7	<0.001	0	23.0
Age (years)[a]	65.3 (7.8)	64.9 (7.9)	60.9 (9.4)	56.6 (10.7)	<0.001	0	63.3 (10.1)
Hypertension (%)	57.8	49.3	41.1	36.4	<0.001	80.0	69.8
Diabetes (%)	39.9	29.7	28.3	19.3	<0.001	80.5	50.8
Previous MI (%)	20.0	33.3	32.6	13.6	<0.001	74.4	50.3
Previous angina (%)	43.6	50.7	44.6	35.1	<0.001	78.2	56.4
28-day case-fatality (%)	37.4	33.0	24.5	23.2	<0.001	0	95.7

MI, myocardial infarction. [a]Mean (standard deviation).

The adjusted association between smoking and 28-day case-fatality is shown in Table 4. Current and former smokers presented a significantly lower risk of death, even when the patients with unknown smoking status were included in the model as an independent category (Table 4a and b).

The results of the sensitivity analysis showed that when patients with unknown smoking status were categorized as current smokers, current smoking changed from a protective to a risk factor (Table 4c and d). In contrast, when only known first MI patients were analyzed ($n = 7741$), even when those with missing data on smoking, hypertension, and diabetes were considered as current smokers, hypertensive, and diabetic patients, respectively, current smoking was still associated with a lower case-fatality [OR = 0.84; 95% confidence interval (CI): 0.73, 0.97].

The multiple imputation analysis results showed an inverse association between current and former smoking and MI case-fatality (Table 4d).

The interactions between smoking and age and sex were also tested and were not statistically significant. The analyses were also performed for men and women, and similar results were obtained in both sexes.

Out-of-hospital 28-day case-fatality

When only fatal cases were considered ($n = 4105$), a total of 2858 registered patients died out-of-hospital (69.6%). Out-of-hospital fatal cases were younger than in-hospital fatal cases (63.6 vs. 65.4 years; $P < 0.001$), the proportion of women dying out-of-hospital was lower than that of men (66.3 vs. 70.7%; $P = 0.009$). The proportion of out-of-hospital fatal cases was 57.9% in never-smokers, 58.1% in former smokers for more than 1 year, 43.2% in former smokers for less than 1 year, 67.8% in current smokers, and 90.8% when smoking status was unknown.

In the multivariate analyses, recent former smokers (< 1 year) presented an age and sex-adjusted statistically significant lower risk of out-of-hospital death than never-smokers (OR = 0.48; 95% CI: 0.29, 0.77), whereas current smoking was marginally not associated with out-of-hospital death (OR = 1.22; 95% CI: 0.99, 1.51; $P = 0.057$). The results of the multiple imputation analysis support these findings: recent former smokers showed a lower risk (OR = 0.63; 95% CI = 0.41, 0.98; $P = 0.041$) and current smokers a higher risk of out-of-hospital death (OR = 1.28; 95% CI: 1.06, 1.56; $P = 0.012$) than never-smokers.

Discussion

The results of this study indicate that current smoking was associated with lower 28-day case-fatality in hospitalized MI patients, even after adjusting for confounding variables. The population approach should be interpreted with caution owing to the high proportion of out-of-hospital fatal cases with unknown data on smoking status. Nevertheless, our data show that current and former

Table 4 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of 28-day case-fatality for smoking in population acute myocardial infarction patients

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
(a) Excluding unknown smoking status				
Never-smokers	1		1	
Former smokers >1 year	0.82	0.72, 0.94	0.76	0.66, 0.88
Former smokers <1 year	0.62	0.47, 0.83	0.56	0.41, 0.76
Current smokers	0.68	0.60, 0.76	0.68	0.59, 0.78
	$n=9359$		$n=8701$	
(b) Including unknown smoking status as an independent category				
Never-smokers	1		1	
Former smokers >1 year	0.83	0.72, 0.94	0.76	0.66, 0.88
Former smokers <1 year	0.63	0.47, 0.83	0.56	0.41, 0.76
Current smokers	0.67	0.60, 0.76	0.68	0.59, 0.77
Unknown smoking status	42.48	32.09, 56.25	7.19	4.75, 10.97
	$n=10\,654$		$n=8846$	
(c) Patients with unknown smoking status defined as never-smokers				
Never-smokers	1		1	
Current smokers	0.28	0.25, 0.31	0.60	0.53, 0.69
	$n=10\,654$		$n=8846$	
(d) Patients with unknown smoking status defined as current smokers				
Never-smokers	1		1	
Current smokers	1.90	1.72, 2.11	0.80	0.70, 0.91
	$n=10\,654$		$n=8846$	
(e) Multiple imputation analyses				
Never-smokers	1		ND	
Former smokers >1 year	0.85	0.73, 0.98	ND	
Former smokers <1 year	0.70	0.53, 0.92	ND	
Current smokers	0.73	0.65, 0.82	ND	
	$n=10\,654$			

Model 1: Adjusted for sex and spline function for age. Model 2: Adjusted for sex, spline function for age, hypertension, diabetes, previous myocardial infarction, and angina. ND, not done.

smokers presented lower overall case-fatality, and that among fatal cases recent former smokers (< 1 year) presented lower risk of out-of-hospital death than never-smokers.

The better short-term prognosis of current smoking in hospitalized MI patients has been reported in several studies [4–10]. In most of them, this protective association disappears after adjusting for age and comorbidity [4,5,7,10]; in others [6,8,9], the association remains even after adjusting for these variables. Age is a particular relevant confounding variable because it is strongly associated with both smoking and case-fatality. Moreover, the association between age and case-fatality was not linear in some models and fitting a linear function for age could provide misleading results. We have used generalized additive models to fit semiparametric additive models that permit continuous variables, such as age and delay symptom monitoring, to present a nonlinear function and therefore reduce potential residual confounding. In our study, smoking was inversely associated with lower MI case-fatality even after adjusting for potential confounding variables.

The association between smoking and a better short-term prognosis after MI may be related to a different form of presentation of coronary atherothrombosis: less atherogenic multivessel disease [16], and more thrombosis of a less critical atherosclerotic plaque [17]. Smokers have a higher coagulability state than never-smokers [17,18], and a lower endogenous fibrinolytic capacity [18,19], probably related to endothelial dysfunction. For these reasons, smoker patients have a higher likelihood of ST elevation during the acute phase of MI [20]. In angiographic studies following thrombolysis, current smoking has been associated with better early infarct-related patency [16,21]. It has been suggested that thrombolytic therapy may be more effective in current smokers than in never-smokers [11]. In our study, however, the interaction between smoking and thrombolysis on 28-day case-fatality in hospitalized patients was not statistically significant, supporting the idea that thrombolysis is an effective treatment independent of smoking status [7,8].

Another possible explanation for this lower in-hospital case-fatality is that smoking is associated with a higher risk of out-of-hospital case-fatality. The predisposition to thrombosis also has been reported in male smokers with CHD who died suddenly [22]. Using a population register of 5106 MI patients, Sonke *et al.* [23] reported lower case-fatality among current smokers admitted to hospital, but no overall effect of current smoking on population MI case-fatality. Similar results were reported by McElduff and Dobson [24]. In the study by Sonke *et al.* [23], current smokers present a slightly (although

not statistically significant) higher risk of out-of-hospital death, counteracting the protective association between smoking and case-fatality in hospitalized patients. In our study, however, smokers presented lower 28-day case-fatality both in-hospital and at the population level, and when considering the whole sample, smoking was not associated with a higher risk of out-of-hospital fatality. Nevertheless, among fatal cases, smokers presented a higher risk to die out-of-hospital than never-smokers. All these results suggest that smoking is associated with lower population 28-day case-fatality, and that in fatal cases smoking is associated with higher risk of out-of-hospital death.

Nonetheless, the association between smoking and 28-day case-fatality at the population level remains controversial. The main concern in this approach is the high proportion of patients who die out-of-hospital and for whom smoking status is unknown (nearly 40% in our study). We used two strategies to deal with this potential bias: sensitivity and multiple imputation analyses. The results of the sensitivity analysis were not conclusive because the protective association reversed when patients with unknown smoking status were considered current smokers. When first MI patients alone were selected, however, current smoking was associated with lower case-fatality even in the worse scenario, in which patients with missing data on smoking, hypertension, and diabetes were considered to be current smoker, hypertensive, and diabetic patients, respectively. On the other hand, the characteristics of the group of patients with unknown smoking status were more similar to nonsmoker than to current smoker patients, suggesting that most of them were most probably nonsmokers. This suggestion was confirmed by the multiple imputation analysis that observed a protective association between smoking and former smoking and case-fatality.

A surprising result of our study is the inverse association between former smoking and MI case-fatality at the population level, also supported by Sonke *et al.* [23]. The low number of patients in the group of the recent former smokers (3.2%), the magnitude of the association, and the consistency with the results observed in former smokers for more than 1 year and current smokers also support the hypothesis of a protective association between smoking (former and current) and lower MI case-fatality.

The mechanisms involved in the protective association of former smoking should be different from those of current smoking. The prevalence of previous MI or angina among former smokers was higher than in never-smokers, which might have benefited them by an ischemic preconditioning effect [25]. Awareness of symptom characteristics may lead to faster recourse to healthcare and, among recent ex-smokers, to lower the risk of out-of-hospital death. Another plausible mechanism for this lower case-fatality among former smoker patients is the fact that those who quit smoking are not the highest risk group and have some characteristic that defines a better prognosis (e.g. more social support, higher social class) [26].

We must, however, reinforce the message that smoking is a major, independent, and modifiable risk factor for CHD [1,2] and that in the long term smoking cessation has been associated with a decrease in mortality after an acute MI [3].

Study characteristics and limitations

IBERICA is a population-based registry of MI patients that allows us to evaluate the association between smoking and short-term prognosis not only for hospitalized patients but also at the population level.

A limitation of the study is the high proportion of patients in the population with unknown smoking status. This is common to all the population-based studies [23,24], and we have used different statistical strategies to deal with this problem.

Although reported smoking is a valid method to assess smoking exposure [27], misclassification in smoking status could occur; nevertheless, we think that any misclassification would be expected to bias our results toward the null hypothesis.

This is an observational study and it is not aimed at determining the mechanisms of this 'smoking paradox'. Nevertheless, our results support the hypothesis that a different form of presentation of coronary atherothrombosis, less atherogenic multivessel disease, and more thrombotic disease, could be the mechanism to explain the lower MI 28-day case-fatality observed in current smokers.

Conclusion

Smoking is independently associated with better short-term prognosis after acute MI in patients who reach the hospital. This better prognosis is not explained by a higher risk of smokers for dying out-of-hospital. This study also suggests that both current and former smokers have lower 28-day MI case-fatality when out-of-hospital deaths are also considered. In fact, smokers who quit within the previous year presented lower risk of dying out-of-hospital than never-smokers.

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