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Smoking and Prognosis After Acute Myocardial Infarction in the Thrombolytic Era (Israeli Thrombolytic National Survey)

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Objectives. **This study sought to compare the relation between smoking and the 30-day and 6-month outcome after acute myocardial infarction in an Israeli nationwide survey.**

Background. **Studies before and during the thrombolytic era reported similar or lower early mortality after acute myocardial infarction in smokers than in nonsmokers. This finding is intriguing and may be misleading because numerous epidemiologic studies have clearly shown that smoking is an independent risk factor for atherosclerosis, myocardial infarction and death.**

Methods. **The study cohort comprised 999 consecutive patients with an acute myocardial infarction from a prospective nationwide survey conducted during January and February 1994 in all coronary care units operating in Israel. The prognosis of 367 patients (37%) who were smokers (current smokers and those who smoked up to 1 month before admission) was compared with that of 632 nonsmokers (past smokers or those who never smoked).**

Results. **Smokers were on average 10 years younger and were more frequently men and patients with a family history of coronary heart disease and inferior infarction and less frequently patients with a previous infarction or a history of angina, hypertension and diabetes than nonsmokers. Smokers also had a lower incidence of congestive heart failure on admission or during the hospital period. Thrombolytic therapy (49% vs. 40%, $p < 0.01$) and aspirin (89% vs. 80%, $p < 0.001$) were administered more frequently in smokers than nonsmokers. The crude 30-day (6.0% vs. 15.7%) and cumulative 6-month (7.9% vs. 21.5%) mortality rates were significantly lower ($p < 0.0001$ for both) in smokers than nonsmokers, respectively. However, after adjustment for age, baseline characteristics, thrombolytic therapy and invasive coronary procedures, the lower 30-day (odds ratio [OR] 0.75, 95% confidence interval [CI] 0.43 to 1.29, $p = 0.30$) and 6-month (hazard ratio 0.84, 95% CI 0.54 to 1.30, $p = 0.42$) mortality rates in smokers and nonsmokers were not significantly different. The model had a power of 0.80 for OR 0.50, with alpha 0.1.**

Conclusions. **In our nationwide survey, the seemingly better prognosis of smokers early after acute myocardial infarction was no longer evident after adjustment for baseline and clinical variables and may be explained by their younger age and a more favorable risk profile. Smokers develop acute myocardial infarction a decade earlier than nonsmokers. Efforts to lower the prevalence of smoking should continue.**

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Despite the fact that literally all epidemiologic studies have shown that smoking is an independent risk factor for atherosclerosis, acute myocardial infarction and death (1–3), some investigators (4–6) have reported a lower in-hospital mortality rate after myocardial infarction in smokers than nonsmokers. Surprisingly, smoking emerged as an independent predictor of better prognosis after acute myocardial infarction in the prethrombolytic (4,5) and thrombolytic eras (6,7). A possible explanation for this apparent paradox was forwarded by Ockene and Ockene (8) who hypothesized that smokers developing acute myocardial infarction are younger, have a more benign risk factor profile on admission and consequently have lower morbidity and mortality rates than nonsmokers. Recent studies from the thrombolytic era (9–11) have shown that a better Thrombolysis in Myocardial Infarction (TIMI) flow grade is achieved after thrombolysis in smokers, suggesting that among smokers, thrombogenicity plays a greater role than in nonsmokers in the pathophysiology of acute myocardial infarction.

Stimulated by these publications, we compared the early and 6-month prognosis of smokers and nonsmokers among 1,012 consecutive patients with acute myocardial infarction from a prospective nationwide survey conducted during a 2-month period in early 1994 in all 25 coronary care units in Israel. Our survey also enabled us to compare the baseline characteristics, management and outcome of smokers with and

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Abbreviations and Acronyms

AIMS = APSAC Intervention Mortality Study
CI = confidence interval
CK = creatine kinase
ECG = electrocardiogram, electrocardiographic
GUSTO-1 = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HR = hazard ratio
OR = odds ratio
TIMI = Thrombolysis in Myocardial Infarction

without thrombolysis and thereby to assess the mechanisms underlying the better prognosis among smokers.

Methods

Patients. A nationwide prospective survey was performed during a 2-month period (January and February 1994) in all 25 coronary care units operating in Israel. Demographic, historical and clinical data were collected on special forms for all 1,012 participants. Thirteen patients with incomplete data were excluded from the analysis. The diagnosis of acute myocardial infarction was based on the presence of two of the following: pain suggestive of myocardial infarction lasting for at least 30 min; unequivocal new electrocardiographic (ECG) alterations (Q/QS or ST-T segment or both, and T wave changes); or increase of at least two of the three serum cardiac enzymes (creatine kinase, aspartate aminotransferase and lactate dehydrogenase) to more than 1.5 times the upper normal limit, or concomitant increase in creatine kinase (CK) and MB isoenzyme. *Current smokers* were defined as patients who were smoking or had quit smoking within 1 month before admission. *Nonsmokers* were defined as patients who had either never smoked or had stopped smoking >1 month before admission. Thirty-day and 6-month mortality was assessed from the medical charts and by matching the identification number of patients with the Israeli National Population Registry.

Statistical analysis. All analyses were performed using SAS statistical software (12). Chi-square and *t* tests were used to determine the significance of the differences between proportions and mean values, respectively, where appropriate. Results of continuous variables are reported as mean value ± SD. Two-sided p values are reported.

A direct age adjustment (95% confidence interval [CI]) was performed to compare mortality rates between smokers and nonsmokers. To compare 30-day mortality in smokers and nonsmokers in terms of odds ratio ([OR] with 95% CI; where nonsmokers were the reference group, OR = 1), a stepwise logistic regression analysis (SAS Logistic Procedure) was performed, adjusting for age, gender, diabetes, hypertension, family history of coronary artery disease, history of angina, previous infarction, anterior Q wave during the index infarction, systolic blood pressure <100 mm Hg, heart rate >100 beats/min and Killip class ≥II on admission, thrombolytic therapy and invasive coronary procedures (coronary angiography, coronary angioplasty and coronary artery bypass grafting) during the hospital period. A stepwise Cox proportional hazards regression model (SAS PHREG Procedure) adjusting for the same variables and for in-hospital complications, such as congestive heart failure and paroxysmal atrial fibrillation, was used to compare cumulative 6-month mortality in smokers versus nonsmokers in terms of hazard ratio ([HR] and 95% CI; where nonsmokers were the reference group, HR = 1). A variable was allowed to enter into the model if it made a significant contribution at the 0.10 level of significance and was removed if after subsequent addition of other variables to the model, it no longer made a contribution at the 0.15 level of significance. The sample size was large enough to produce a power of 0.8, if the OR for smokers to nonsmokers is 0.50, under a type 1 error of alpha = 0.1.

Unadjusted survival curves were constructed using the method of Kaplan-Meier. The significance of the difference between the survival curves was assessed by the log-rank test (SAS Lifetest Procedure). Adjusted survival curves were produced using variables entered into the best selected Cox model (SAS PHREG Procedure).

Table 1. Baseline Characteristics of Smokers and Nonsmokers After Acute Myocardial Infarction

	Smokers (n = 367)	Nonsmokers (n = 632)	p Value
Men	334 (91)	387 (61)	< 0.0001
Age (yr)	57 ± 12	67 ± 11	0.0001
Prior MI	86 (23)	204 (33)	0.002
Prior angina	72 (20)	183 (29)	0.001
Hypertension	107 (29)	311 (49)	< 0.0001
Diabetes	68 (19)	213 (34)	< 0.0001
Hypercholesterolemia	99 (27)	144 (23)	0.14
Family history of CAD	79 (22)	52 (8)	0.0001
Prior CABG	10 (3)	24 (4)	0.37
Prior PTCA			0.40
Prior stroke	14 (4)	42 (7)	0.06
MI type/location*			0.05
Anterior Q wave	109 (30)	198 (31)	
Inferior Q wave	130 (36)	180 (29)	
Lateral Q wave	10 (3)	10 (2)	
Non-Q wave	115 (32)	236 (38)	

*Determined in 365 smokers and in 629 nonsmokers. Data presented are mean value ± SD or number (%) of patients. CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Results

Baseline characteristics. The baseline characteristics of 999 patients with acute myocardial infarction participating in the survey, including 367 (37%) smokers and 632 nonsmokers, are presented in Table 1. Smokers were on average 10 years younger (57 ± 12 vs. 67 ± 11 years, p < 0.0001); and were more frequently men, patients with a family history of coronary artery disease and inferior infarction and less frequently pa-

Table 2. Hospital Course of Smokers and Nonsmokers After Acute Myocardial Infarction

	Smokers (n = 367)	Nonsmokers (n = 632)	p Value
On admission			
Systolic BP <100 mm Hg	21 (6)	33 (5)	0.74
Heart rate >100 beats/min	52 (14)	144 (23)	0.001
Killip class ≥II	83 (23)	242 (38)	0.00001
Peak CK (IU)	1,246 ± 1,284	1,250 ± 1,812	0.97
Complications			
PAF	17 (5)	72 (11)	0.0003
Advanced AVB	29 (8)	52 (8)	0.86
VT/VF	44 (12)	85 (13)	0.51
New BBB	8 (2)	27 (4)	0.08
CHF/PE	38 (10)	141 (22)	0.0001
Cardiogenic shock	11 (3)	56 (9)	0.0001
Severe MR	1 (0.3)	13 (2)	0.02
Recurrent MI	11 (3)	18 (3)	0.89
Recurrent ischemia	36 (10)	62 (10)	1.00
Stroke	2 (0.5)	6 (1)	0.49

Data presented are mean value ± SD or number (%) of patients. AVB = atrioventricular block; BBB = bundle branch block; BP = blood pressure; CHF/PE = congestive heart failure/pulmonary edema; CK = creatine kinase; MI = myocardial infarction; MR = mitral regurgitation; PAF = paroxysmal atrial fibrillation; PE = pulmonary edema; VT/VF = ventricular tachycardia/ventricular fibrillation.

tients with a previous infarction, a history of angina, stroke, hypertension and diabetes.

In-hospital complications and management. On admission, smokers had a better Killip class and lower heart rate than nonsmokers (Table 2). Congestive heart failure, shock, severe mitral regurgitation, paroxysmal atrial fibrillation and new bundle branch block were significantly less frequent among smokers than nonsmokers, although peak CK-estimated infarct size was similar in both groups (Table 2). Nonsmokers were more frequently treated with digitalis, angiotensin-converting enzyme inhibitors and diuretic drugs and less frequently with calcium antagonists, thrombolytic therapy, heparin and aspirin than were smokers (Table 3). Coronary angiography and coronary artery bypass graft surgery were performed in similar proportions in both groups, whereas smokers more often underwent coronary angioplasty (Table 3).

Mortality. The crude 30-day mortality rate was significantly lower in smokers than nonsmokers (6.0% vs. 15.7%, respectively, $p < 0.0001$). However, after direct age adjustment, the 30-day mortality rates were not significantly different between smokers (8.8%, 95% CI 5.0% to 12.5%) and nonsmokers (13.5%, 95% CI 11.0% to 16.0%) (Table 4). Similarly, after adjusting for age and other baseline characteristics, thrombolytic therapy and invasive coronary procedures (see Methods), the lower 30-day mortality rate in smokers was not of statistical significance (OR 0.75, 95% CI 0.43 to 1.29, $p = 0.30$) (Table 4). Other variables entered (in decreasing order) into the final stepwise model were Killip class ≥II on admission (OR 5.92, 95% CI 3.69 to 9.47), age (1-year increment [OR 1.05, 95% CI 1.03 to 1.08]), diabetes (OR 2.05, 95% CI 1.31 to 3.19) and invasive coronary procedures (angiography, coronary angioplasty or bypass surgery [OR 0.54, 95% CI 0.29 to 1.00]).

The cumulative 6-month crude mortality rate was significantly lower in smokers than nonsmokers (7.9% vs. 21.5%, respectively, $p < 0.0001$) (Table 4, Fig. 1A). This difference in mortality in favor of smokers persisted after direct age adjustment (11.0%, 95% CI 6.9% to 15% vs. 18.6%, 95% CI 15.8% to 21.4%, respectively, $p < 0.01$) (Table 4). However, after multivariate analysis adjusting for age and other baseline characteristics, thrombolytic therapy and invasive coronary procedures (see Methods), the lower 6-month mortality rate in smokers was no longer statistically significant (HR 0.84, 95% CI 0.54 to 1.30, $p = 0.42$) (Table 4, Fig. 1B). Other variables entered (in decreasing order) into the final stepwise model were congestive heart failure during the hospital period (HR 3.61, 95% CI 2.48 to 5.24), age (1-year increment [HR 1.05, 95% CI 1.03 to 1.06]), Killip class ≥II on admission (HR 2.08, 95% CI 1.42 to 3.03), diabetes (HR 1.47, 95% CI 1.06 to 2.02) and systolic blood pressure on admission <100 mm Hg (HR 1.83, 95% CI 1.06 to 3.13).

Comparison between smokers with and without thrombolysis. Among active smokers (n = 367), 181 patients (49%) were treated with thrombolysis. The baseline characteristics and in-hospital complications (Table 5) of smokers with (n = 181) and without thrombolysis (n = 186) were comparable. Smokers with thrombolysis more often had a Q wave infarction and complex ventricular arrhythmias (ventricular tachycardia or fibrillation), whereas a previous infarction and paroxysmal atrial fibrillation were more frequent among smokers ineligible for thrombolysis. Peak CK levels were higher among smokers with thrombolysis. Medical treatment and rate of invasive coronary procedures performed during the index hospital period were similar in both groups except for heparin, which was given more frequently to smokers with thrombolysis (Table 6).

Thirty-day mortality rates were similar in smokers with and without thrombolysis (6.1% and 5.9%, respectively). The cu-

Table 3. Management of Smokers and Nonsmokers After Acute Myocardial Infarction

	Smokers (n = 367)		Nonsmokers (n = 632)		
	No.	%	No.	%	p Value
Nitrates	303	83	497	79	0.14
Beta-blockers	165	45	262	41	0.28
Heparin	297	81	478	76	0.05
Aspirin	328	89	503	80	<0.0001
ACE inhibitors	118	32	247	39	<0.03
Calcium antagonists	93	25	126	20	<0.05
Diuretic drugs	87	24	226	36	<0.0001
Digitalis	21	6	83	13	0.0004
Thrombolysis	181	49	254	40	0.005
Coronary angiography	111	30	164	26	0.14
PTCA	68	19	70	11	0.001
CABG	19	5	27	4	0.51

ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

Table 4. Crude Age-Adjusted Mortality Rates and Multivariate Relative Risk of Dying in Smokers and Nonsmokers at 30 Days and 6 Months After Acute Myocardial Infarction

	30-Day Mortality					6-Month Mortality				
	Smokers (n = 367)		Nonsmokers (n = 632)			Smokers (n = 367)		Nonsmokers (n = 632)		
	No.	%	No.	%	p Value	No.	%	No.	%	p Value
Age (yr)										
≤50 (n = 181)	3/126	2.4	1/55	1.8		3/126	2.4	2/55	3.6	
51–60 (n = 208)	4/95	4.2	11/113	9.7		7/95	7.4	15/113	13.3	
61–70 (n = 291)	8/99	8.1	28/192	14.6		11/99	11.1	36/192	18.8	
71–80 (n = 252)	4/39	10.3	39/213	18.3		5/39	12.8	51/213	23.9	
>80 (n = 67)	3/8	37.5	20/59	33.9		3/8	37.5	32/59	54.2	
All (n = 999)*	22/367	6.0	99/632	15.7	< 0.0001	29/367	7.9	136/632	21.5	< 0.0001
Age-adjusted (%)	8.8		13.5			11.0		18.6		
95% CI (%)	5.0–12.5		11.0–16.0			6.7–15.0		15.8–21.4		
Relative risk†	0.75					0.84				
95% CI	0.43–1.29					0.54–1.30				

*Crude mortality. †The 30-day mortality odds ratio and 6-month hazard ratio by multivariate analysis when comparing the risk of dying between smokers and nonsmokers after adjusting for age and pertinent variables (see Methods). CI = confidence interval.

mulative 6-month crude mortality rate among both groups of patients was 7.2% and 8.6%, respectively (p = 0.53 by log-rank test) (Fig. 2).

Discussion

The main finding of the present study is that the seemingly better prognosis of smokers after acute myocardial infarction may be attributed to their more favorable risk profile and that after adjusting for age and other confounding variables, smoking was no longer an independent predictor of better prognosis.

Previous studies. Our findings from a nationwide survey are in accordance with some recent clinical trials (10,13–15). In the Gruppo Italiano per lo Studio Della Sopravvivenza nell'Infarto Miocardico (GISSI-2) study (14) including 9,720 patients, smokers had a better in-hospital and 6-month post-discharge prognosis, which disappeared after multivariate adjustment for clinical variables (age, gender, number of hours between symptoms onset to hospital admission, Killip class, infarct location, diabetes, hypertension, previous angina, body mass index, peak CK levels and number of ECG leads with ST segment elevation). Data from the Myocardial Infarction Triage and Intervention (MITI) Project (15), in which two-thirds of the patients did not receive thrombolysis, also did not identify smoking as an independent predictor of low mortality after adjustment (age, reinfarction, congestive heart failure, cardiogenic shock and recurrent chest pain).

In contrast to these findings, a number of studies conducted in the prethrombolytic and thrombolytic eras found that the higher in-hospital mortality among nonsmokers remained significant even after adjustment for baseline characteristics (4–7,16,17). Molstad et al. (5) studied 484 patients with a first myocardial infarction in the prethrombolytic era. The 90-day mortality of smokers was lower than that of nonsmokers and

Figure 1. Cumulative 6-month actuarial survival curves for smokers and nonsmokers: **A,** Unadjusted Kaplan-Meier curves; p < 0.0001 (log-rank test) for between-group differences. **B,** Adjusted survival curves predicted from the best selected Cox model. The relative risk for smokers was not significantly different from that for nonsmokers (p = 0.42).

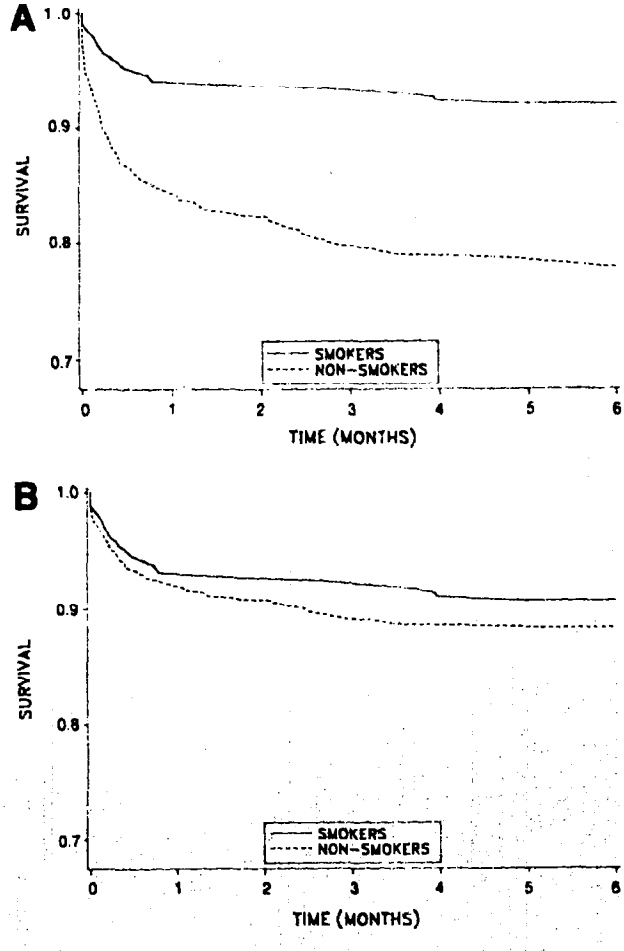

Table 5. Characteristics, Hospital Complications and Follow-Up Mortality in Smokers Treated With and Without Thrombolysis

	Thrombolytic Treatment		
	Yes (n = 181)	No (n = 186)	p Value
Men	165 (91)	169 (91)	0.92
Age (yr)	57 ± 11	58 ± 12	0.46
Prior MI	34 (19)	52 (28)	0.04
Prior angina	37 (21)	35 (19)	0.70
Hypertension	53 (29)	54 (29)	0.96
Diabetes	31 (17)	37 (20)	0.50
Hypercholesterolemia	43 (24)	56 (30)	0.17
Family history of CAD	36 (20)	43 (23)	0.45
Prior CABG	9 (5)	1 (< 1)	0.01
Q wave MI	144 (80)	105 (57)	< 0.0001
On admission			
Systolic BP <100 mm Hg	11 (6)	10 (5)	0.77
Heart rate >100 beats/min	21 (12)	31 (17)	0.16
Killip class ≥II	39 (22)	44 (24)	0.63
Peak CK (IU)	1,476 ± 1,357	1,021 ± 1,168	< 0.001
Complications			
PAF	4 (2)	13 (7)	0.03
Advanced AVB	18 (10)	11 (6)	0.15
VT/VF	33 (18)	11 (6)	< 0.001
CHF/PE	17 (9)	21 (11)	0.55
Cardiogenic shock	6 (3)	5 (3)	0.73
Recurrent MI	8 (4)	3 (2)	0.12
Recurrent ischemia	17 (9)	19 (10)	0.79
Stroke	1 (< 1)	1 (< 1)	0.99
Mortality			
30 day	11 (6.1)	11 (5.9)	0.95
6 mo	13 (7.2)	16 (8.6)	0.61

Data presented are mean value ± SD or number (%) of patients. Abbreviations as in Tables 1 and 2.

remained so after adjustment for baseline differences, ECG findings, laboratory data and drugs at entry (relative risk 0.55, 95% CI 0.33 to 0.93). Similar findings were noted by Kelly et al.

Table 6. Treatment and Management of Smokers After Acute Myocardial Infarction According to Thrombolytic Treatment

	Thrombolytic Treatment				
	Yes (n = 181)		No (n = 186)		
	No.	%	No.	%	p Value
Nitrates	156	86	147	79	0.07
Beta-blockers	86	48	79	42	0.33
Heparin	162	90	135	73	< 0.0001
Aspirin	165	92	161	87	0.15
ACE inhibitors	55	30	63	34	0.48
Calcium antagonists	49	26	44	24	0.65
Diuretic drugs	37	21	50	27	0.15
Digitalis	6	3	15	8	0.05
Coronary angiography	60	33	51	28	0.23
PTCA	37	21	31	17	0.35
CABG	10	6	9	5	0.77

Abbreviations as in Tables 1 and 3.

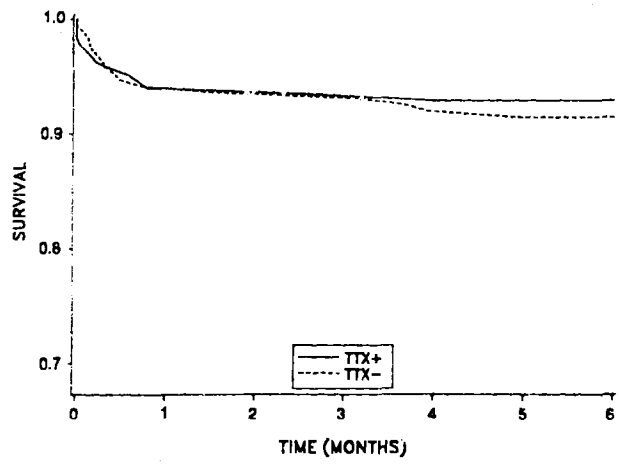

Figure 2. Cumulative 1-year actuarial survival curves for smokers treated with and without thrombolysis; p = 0.53 (log-rank test) for between-group differences. TTX+ = thrombolysis-treated patients; TTX− = non-thrombolysis-treated patients.

(4) in 2,955 patients (excluding ex-smokers) with an acute myocardial infarction, where adjusting for age and other variables (blood urea, history of heart failure, angina, myocardial infarction and pulmonary congestion on admission) reduced but did not cancel the survival differential favoring smokers at 1 month, but did eliminate the mortality differences at 6 and 12 months. In two recent large thrombolytic trials (6,7), the mortality rate of smokers was lower than that of ex-smokers or nonsmokers even after adjustment for baseline characteristics. In the study by Barbash et al (6), including 2,366 nonsmokers, 2,244 ex-smokers and 3,649 active smokers from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial, a 1.4-fold increase in in-hospital and 6-month mortality rates was demonstrated for nonsmokers after adjusting for baseline characteristics similar to those in our study. Similar findings for 30-day mortality, were reported from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study (7) in 41,021 patients treated with thrombolysis but not in the angiographic substudy (18). In this subgroup, adjustment for clinical and angiographic variables, including coronary anatomy, TIMI grade 3 flow and left ventricular function, yielded similar mortality in smokers and nonsmokers (OR 0.93 for smokers). Similar findings were observed by Grines et al. (9) in patients from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials. Smokers had a better 42-day survival after adjustment for baseline clinical variables (age, systolic blood pressure and infarct location) but not after adjustment for acute angiographic variables, including number of diseased vessels, left ventricular ejection fraction and TIMI flow grade. Thus, a partial explanation for the discrepant findings in the different studies may be related to the different variables controlled for, in particular the angiographic data. Furthermore, because TIMI grade 3 flow is more prevalent among smokers after thrombolysis (9–11) and may explain in

part their improved survival, it may be inappropriate to control for this variable in the multivariate analysis.

The most likely explanation for the discrepancy between our study and previous studies (6,7,9,18) is that those studies did not include consecutive patients as was done in our survey. Rather, they included only patients eligible for a thrombolytic trial, who are generally younger and have better baseline characteristics and prognosis than those ineligible for thrombolytic therapy, a limitation recognized by Barbash et al. (18) for the GUSTO-I study and by others (8). Although our study is much smaller than the two aforementioned ones (6,7,18), it is based on a consecutive series of unselected patients admitted to all coronary care units in Israel during a 2-month period, including peripheral, secondary and tertiary hospitals; therefore, its results may be more generally applicable to patients with acute myocardial infarction in the community.

Possible mechanisms for better outcome in smokers. Several factors may explain the paradox of a seemingly better early prognosis of smokers after acute myocardial infarction. In our study, as in most others, age was a strong independent predictor of mortality after myocardial infarction. In the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) Registry (19), a 10-year increment of age was associated with a twofold increase in in-hospital mortality. In the GUSTO-I trial (7), age was the most significant factor influencing 30-day mortality and provided nearly half the prognostic information in the multivariate logistic model. In all previous studies, smokers experienced myocardial infarction at a younger age than nonsmokers (4–6,10,11,13,18,20). In the present study, smokers were 10 years younger than nonsmokers. It was also shown (20) that the adjusted age for a first nonfatal infarction progressively declined with increasing smoking exposure. Thus, the younger age of smokers favors a better prognosis during the early phase of acute myocardial infarction.

Smokers also have a more favorable risk profile other than age (4–6,9,11,13,18,20). In the present study, the frequency of previous infarction, diabetes and hypertension (7,13,21,22) was lower among smokers than nonsmokers.

Smoking is arrhythmogenic (23), increases the incidence of late potentials on the signal-averaged ECG and may increase the risk of ventricular tachycardia and sudden death (24). Therefore, smokers may be more prone to prehospital sudden death than nonsmokers (25,26), thus artificially reducing the in-hospital mortality after acute myocardial infarction.

The hospital course of nonsmokers was more complicated than that of smokers, probably due to their older age and worse baseline characteristics. In our study, congestive heart failure and cardiogenic shock were 3-times more common in nonsmokers than in smokers. Nonsmokers more frequently received digitalis and diuretics. Similar findings were noted in previous studies (6,13,18).

A smaller infarction may lead to better survival in smokers. Infarct size was smaller in smokers at 90 min after initiation of thrombolytic therapy (9,18) but not at hospital discharge (9,10,20). In our study, peak CK levels were similar in smokers and nonsmokers. Similar findings were noted in some studies (10,20) but not in others (5,11). Smokers had a higher frequency of inferior infarction than nonsmokers (5,6,10,11,13,18), usually associated with a smaller infarction. Nonetheless, even if the infarct size is similar in smokers and nonsmokers, nonsmokers might have developed more often heart failure on admission and during the hospital course as a result of diastolic dysfunction associated with advanced age, hypertension and diabetes.

In our study, smokers were treated more frequently with thrombolysis and invasive coronary interventions, probably because they were younger and had less contraindications for these modes of therapy. Thus, smokers may have benefited more from these innovative therapies than nonsmokers.

Smokers have higher fibrinogen, hematocrit and Factor VII levels (9,11,27,28), impaired endothelial function (29) and vasospasm (30), predisposing them to thrombus formation and myocardial infarction (31). Thus, coronary obstruction in smokers might be more thrombogenic and less atherosclerotic in nature. A large thrombotic component in smokers may be more amenable to vasodilation and thrombolysis and hence to more complete reperfusion, leading to improved early infarct-related coronary artery flow and less residual atheromatous stenosis after thrombolysis. Smoking precipitates myocardial infarction at an earlier age with a lesser degree of coronary artery disease (13,18,32). In the Coronary Artery Surgery Study (CASS) registry (33), a negative correlation was noted between the extent of coronary disease and smoking. McKenna et al. (34) found that normal coronary arteries were more frequently found among smokers than nonsmokers after acute myocardial infarction, suggesting a higher rate of vasospastic or thrombotic occlusion. Recently, several studies pointed out that the patency rate (TIMI grade 3 flow) (9–11,18) and lumen diameter measured early after thrombolytic therapy are greater in smokers than nonsmokers (9), supporting the thrombogenic mechanism of infarction among smokers. Consequently, smokers may have a smaller infarction and may be left with less severe underlying narrowing than nonsmokers (9), which may explain, at least in part, their better survival.

Uniqueness of the study. This survey of consecutive, unselected patients with acute myocardial infarction confirms observations made earlier in randomized clinical trials, and its findings may be more generally applicable than those obtained from selected patients entered in clinical trials. In addition, previous studies compared the prognosis of smokers with that of nonsmokers after acute myocardial infarction, either in the prethromolytic or current thrombolytic era. The present survey allowed us to compare the outcome between smokers with and without thrombolysis; two groups with similar low risk profiles who were otherwise managed similarly (Tables 5 and 6). Remarkably, mortality was similar and low in both groups of smokers, suggesting that the favorable outcome of smokers after myocardial infarction is probably related to their better baseline characteristics and their younger age. The lack of

observed mortality difference between smokers treated versus not treated with a thrombolytic agent may also be related to the small number of patients in the present study and to the low mortality rate of young patients with myocardial infarction (35). Our finding is in contrast to that observed in the APSAC Intervention Mortality Study (AIMS) trial (36), where the mortality was significantly lower among smokers treated with thrombolysis than in those not treated with thrombolysis. The reason for this discrepancy with our study seems to be due to differences in the patient groups of the two studies. Whereas AIMS was a randomized trial in which all patients ≤70 years old treated within 6 h of symptoms were eligible for thrombolysis, our nationwide survey included all patients admitted with an acute myocardial infarction. Patients not given thrombolysis were those who were not eligible for it. It is also conceivable that major differences in the use of aspirin, which was much lower in the AIMS study than in our study (2% vs. 85%, respectively), influenced differently the response to thrombolysis and the outcome in smokers.

Limitations of the study. We could not differentiate between past-smokers and those who had never smoked. The prognosis of ex-smokers after acute myocardial infarction is intermediate between that of current smokers and nonsmokers (6,7,10,13,14). Thus, the mortality rate in our nonsmoking patients may be diluted with ex-smokers and, thus, underestimated. We cannot exclude the possibility that patients with a more adverse risk profile, and thus a worse prognosis, quit smoking before the index infarction because of worsening of their cardiac condition.

We do not have information regarding cessation of smoking after the acute event, and therefore we could not evaluate its impact on outcome after the acute infarction. However, in general, posthospital period cessation rates exceed 50% (37).

The present study includes data on in-hospital complications and 6-month mortality but no information on nonfatal cardiac events during the follow-up period. Even though the difference in mortality rates between smokers and nonsmokers was not significant, we cannot exclude the possibility that the postdischarge morbidity of smokers may differ from that of nonsmokers, especially among those who continued smoking (38,39).

Summary. The present study in unselected, consecutive patients with acute myocardial infarction suggests that smokers have an early survival advantage over nonsmokers. However, the seemingly better early prognosis could be attributed to the younger age, lower risk profile and less eventful hospital course of smokers. Smokers present with acute myocardial infarction about a decade earlier than past or nonsmokers. Efforts to discourage smoking should continue. Larger community-based studies in patients with acute myocardial infarction from different countries, assessing classical and new risk factors [lipoprotein(a), polymorphism in the angiotensin-converting enzyme gene] and angiographic and hemostatic data may shed further light on the mechanism of the seemingly better prognosis of smokers.

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Appendix

Participating Centers, Directors of Cardiac Departments and Responsible Physicians for the Israeli Thrombolytic National Survey

Coordinating center: Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Israel

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