Cardiovascular Revascularization Medicine 69 (2024) 42–49

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

journal homepage: www.sciencedirect.com/journal/cardiovascular-revascularization-medicine

The enigma of the 'smoker's paradox': Results from a single-center registry of patients with STEMI undergoing primary percutaneous coronary intervention

Umberto Paradossi [a], Alberto Ranieri De Caterina [a], Giancarlo Trimarchi [b], Fausto Pizzino [a], Luca Bastiani [a], Filippo Dossi [c], Mario Raccis [c], Giacomo Bianchi [a], Cataldo Palmieri [a], Cesare de Gregorio [b], Giuseppe Andò [b,*], Sergio Berti [a]

[a] Fondazione Toscana G. Monasterio, Ospedale del Cuore, 54100 Massa, Italy
[b] Department of Clinical and Experimental Medicine, University of Messina, 98124 Messina, Italy
[c] Department of Cardiology, Ospedale di Lavagna, 16033 Lavagna, Italy

ARTICLE INFO

Keywords:
Smoker's paradox
Lifestyle risk factors
STEMI
Ischemic time
Primary PCI

ABSTRACT

Background: Smoker's paradox usually refers to the observation of a favorable outcome of smoking patients in acute myocardial infarction.
Methods: From April 2006 to December 2018 a population of 2456 patients with ST segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI) were prospectively enrolled in the MATRIX registry. Ischemic time, clinical, demographics, angiographic data, and 1-year follow-up were collected.
Results: Among 2546 patients admitted with STEMI, 1007 (41 %) were current smokers. Smokers were 10 years younger and had lower crude in-hospital and 1-year mortality (1.5 % vs 6 %, $p < 0.0001$ and 5 % vs 11 %, $p < 0.0001$), shorter ischemic time (203 [147–299] vs 220 [154–334] minutes, $p = 0.002$) and shorter decision time (60 [30–135] vs 70 [36–170] minutes, $p = 0.0063$). Smoking habit [OR:0.37(95 % CI:0.18–0.75)-$p < 0.01$], younger age [OR 1.06 (95%CI:1.04–1.09)-$p < 0.001$] and shorter ischemic time [OR:1.01(95%CI:1.01–1.02)-$p < 0.05$] were associated to lower in-hospital mortality. Only smoking habit [HR:0.65(95 % CI: 0.44–0.9)–$p = 0.03$] and younger age [HR:1.08 (95%CI:1.06–1.09)–$p < 0.001$] were also independently associated to lower all-cause death at 1-year follow-up. After propensity matching, age, cardiogenic shock and TIMI flow <3 were associated with in-hospital mortality, while smoking habit was still associated with reduced mortality. Smoking was also associated with reduced mortality at 1-year follow-up (HR 0.54, 95 % CI [0.37–0.78]; $p < 0.001$).
Conclusions: Smoking patients show better outcome after PCI for STEMI at 1-year follow-up. Although "Smoking paradox" could be explained by younger age of patients, other factors may have a role in the explanation of the phenomenon.

1. Introduction

Primary percutaneous coronary intervention (pPCI) is the preferred reperfusion therapy in patients with ST-segment elevation myocardial infarction (STEMI). Despite an effective coronary flow restoration in a timely fashion, some categories of patients are still at increased risk of death. As a general principle, traditional cardiovascular risk factors are also associated with higher in-hospital or long-term mortality after STEMI. In this context, some evidence [1–3] suggests that smoking habit can be associated with a lower unadjusted risk of all-cause mortality at 1-year as well as a lower rate of death or hospitalization for heart failure (HF) after STEMI. This phenomenon – also known as the smoker's paradox – remains controversial as its evidence are still conflicting. More importantly, no clear pathophysiological mechanism would sustain potential protection conferred by smoking habit to STEMI patients. The purpose of this study was to assess whether smoking could be associated with mortality in patients with STEMI referred to pPCI in one of the largest Hub and Spoke networks for STEMI in Italy in the period 2006–2018.

2. Materials and methods

The Matrix Registry is a single-center non-interventional registry created to evaluate in a prospective fashion demographic, clinical and therapeutic characteristics of all-comers patients presenting to our Institution

* Corresponding author at: Department of Clinical and Experimental Medicine, Università degli Studi di Messina, Messina, Italy.
E-mail address: giuseppe.ando@unime.it (G. Andò).

http://dx.doi.org/10.1016/j.carrev.2024.06.007
Received 9 March 2024; Received in revised form 6 June 2024; Accepted 7 June 2024
Available online 8 June 2024

with STEMI and treated with primary PCI. We thus conducted a subgroup analysis of the Matrix Registry aiming at evaluating the potential relationship between smoking habit and in-hospital cardiovascular death as primary endpoint and all-cause death at 1-year-follow-up after STEMI treated with PCI as secondary endpoint. Moreover, we investigated if ischemic time could influence the outcome of smokers. Our Hub and Spoke network for STEMI in North-western Tuscany, Italy, began in April 2006 with the systematic use of PCI. The population of this 1658 km2 area is roughly 400,000. This program involved one Hub (Ospedale del Cuore di Massa) and five Spoke centers, one medical helicopter and six advanced life support ambulances, with direct transmission of pre-hospital ECG to the catheterization laboratory (24/7 PCI capability within 30 min of notification) activated by a single-call action. All patients presenting within 12 h of the onset of symptoms suggestive of myocardial ischemia and new or presumed-new ST-elevation or left bundle-branch block, who were transferred to our PCI hospital and treated with primary PCI from April 1, 2006, to December 31, 2018, were considered for inclusion in this study. We excluded patients who were transferred and diagnosed with STEMI but not treated with PCI (CABG or medical therapy).

A database dedicated to STEMI patients was created and maintained by the information department of our hospital. Over 200 parameters were included in the data set (medical history, biochemical parameters, as well as clinical, echocardiographic, and angiographic data), collected either manually, through a graphical user interface, or by automatically extracting data from medical records (personal details, time to treatment, outcomes, etc.) [4]. Some of the parameters were defined as mandatory, without which the patient would be excluded from the study. These parameters were the time of 1) symptom onset leading to medical assistance; 2) first medical contact; 3) catheterization laboratory arrival; and 4) first balloon inflation time. The time from symptom onset to first medical contact was defined decision time (DT), the time from symptom onset to first balloon inflation was defined symptom to balloon time (SBT). Based on SBT patients were divided into five groups: ≤2 h, between 2 and 4 h, between 4 and 6 h, be-tween 6 and 8 h, and between 8 and 12 h (Supplementary Table 1).

In 92 % of patients ($n = 2260$), it was possible to pinpoint a specific time of symptom onset. It was difficult to determine an accurate onset in the remaining 8 % ($n = 196$) of patients, most of whom were elderly and diabetic with atypical symptoms or patients with OHCA. For these patients, in order to be as accurate as possible, we collected the clinical information from relatives and from EMS dispatches.

Mortality data within the intervention hospital was taken from the main database, which also provided systematic information on discharge and transferal of patients to their local hospitals. Data about cardiovascular mortality in the patients' local hospitals were systematically collected by telephone. For all patients, 1-year follow-up information was obtained by conducting a direct phone interview with the patient or his/her general practitioner as well as searching in the mortality database. Follow-up was not possible with 25 patients (0.9 %), due to unsuccessful attempts to contact them by phone; they were therefore excluded from the study.

No restrictions on age and sex were applied. Before primary PCI, all patients received intravenous ASA (500 mg) and a P2Y12 inhibitor (clopidogrel [600 mg], ticagrelor [180 mg] prasugrel [60 mg]). Ticagrelor was the standard therapy in patients treated after 2011. Unfractionated heparin (70–100 IU/kg, intra-arterial) was administered in the catheterization laboratory before initiating the diagnostic angiography. From January 2009 onwards, thrombo-aspiration was performed whenever a large thrombus burden was detected [5,6]. The use of glycoprotein IIb/IIIa therapy was left to the operators' discretion in patients with large thrombus burden and/or angiographic complications (distal embolization, no-reflow phenomenon) of primary PCI according to the guidelines [7,8]. STEMI was defined by symptoms of myocardial ischemia accompanied by a persistent elevation of the ST segment on the electrocardiogram according to the 4th Universal MI Definition [9]. Cardiogenic shock was defined as persistent systolic blood pressure ≤ 90 mmHg, unresponsive to fluid administration and requiring vasopressors with echocardiographic evidence of severe dysfunction of the left ventricle, over a large infarction area. The use of intra-aortic balloon pump in cardiogenic shock was encouraged for all suitable patients but was left to operator's discretion. Culprit vessel TIMI flow grade was assessed after the PCI procedure and procedural success was defined as post-procedural TIMI 3 flows. To assess left and right ventricular systolic function, and rule out any mechanical complications, all patients received two-dimensional echocardiographic evaluation upon arrival in the catheterization laboratory before PCI, within the first 24 h after PCI, and every day during their in-hospital stay. Left ventricular systolic function was determined by Left Ventricle Ejection Fraction, calculated using the biplane Simpson's method by a trained cardiologist. Subsequent medical treatment included anti-ischemic, lipid-lowering, and antithrombotic drugs was administered to every patient strictly according to current treatment guidelines [10,11]. Smoking status was defined as patients who were currently smoking or had quit <6 months at the time of the event.

Categorical variables were summarized using frequencies and proportions and compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. The normal distribution of continuous variables was evaluated using the Shapiro-Francia test and Student's *t*-test for independent groups was used to compare data with normal distribution, presented as mean values ± SD (σ). To test for possible differences between non-normally distributed variables, the Mann-Whitney test for independent groups was used and the data are presented as medians and inter-quartile ranges [IQR: 25 %–75 %]. The relationship between general characteristics of the population and SBT groups was assessed by one-way ANOVA and to control for type I error the Scheffe's adjusted significance level was used. Tukey post-hoc analysis was used to determine differences between groups. A linear relationship between two sets of data has been assessed using Pearson's product-moment correlation. The primary and secondary outcomes are respectively in-hospital mortality and 1-year all cause death.

We used logistic regression model to assess association between variables and in-hospital death while Cox-regression model was used for 1-year all-cause death. Kaplan-Meyer curves and Log-rank test was used to describe event-free survival for all-cause death.

In order to reduce the imbalance between covariates in the two groups and further assess the effect of smoking in STEMI patients, a propensity score analysis was performed; a logistic regression was performed to obtain propensity score (covariates: male sex, age, diabetes mellitus type II, hypertension, dyslipidemia, history of coronary artery disease in the family, previous cardiovascular interventions, previous acute coronary syndrome, cardiogenic shock at presentation and degree of left ventricular ejection fraction); a 1:1 nearest neighbor matching was done to obtain two comparable groups.

A *p*-value <0.05 was considered statistically significant for all analyses. All statistical analyses were conducted with STATA® statistical package, version 13.0 (Stata Corp LP). The study protocol was approved by the local Ethics Committee and by the Italian Ministry of Health (http://www.onecare.cup2000.it/telemedicina/percorso-diagnostico-terapeutico-dell'infarto-miocardico-acuto) and was conducted in accordance with the 1975 Declaration of Helsinki. Informed consent was obtained from each patient (or from relatives in case of the patient's inability) before the angiogram for participation in the follow-up.

3. Results

A total of 2456 STEMI patients treated with primary PCI were enrolled until December 2018. Demographic, clinical, and angiographic characteristics according to is-chemic time are reported in Supplementary Table 1.

The median age of our population was 67 years [58–77, range 28–99]. Of note, women were significantly older than men (76 [65–83] vs 64 [56–73] years - $p < 0.0001$).

The prevalence of smoking habit was higher in male patients compared to female patients (47 % vs 24 %, p < 0,001). Similarly, hypertension was more common among males than females (68 % vs 57 %, p < 0,001). Of note that SBT was shorter in male patients than female patients (235 [163–332] vs 201 [146–291] minutes – $p < 0.001$) (Supplementary Table 2 and Table 3).

Table 1
Comparison of main demographic and clinical characteristics between groups.

	Smoking $n = 1007$ (41)	Non-smoking $n = 1449$ (59)	p value
Age, years; median [IQR]	61 [52–69]	72 [63–81]	<0.001
Male n (%)	807 (80)	985 (68)	<0.001
DT, minutes; median [IQR]	60 [30–135]	77 [36–170]	<0.001
Diabetes n (%)	234 (24)	274 (19)	0.781
Hypertension n (%)	698 (69)	793 (55)	0.071
Dyslipidaemia n (%)	477 (47)	508 (35)	0.113
BMI, kg/m^2; median [IQR]	26 [24–29]	26 [24–29]	0.923
Family history of CAD n (%)	301 (30)	355 (25)	0.675
Prior MI (>7 days) n (%)	102 (10)	180 (12)	0.080
Prior PCI/CABG n (%)	150 (15)	116 (8)	0.061
Cardiogenic shock n (%)	47 (5)	103 (7)	0.013
Cardiac arrest pre-PCI n (%)	60 (5)	78 (5)	0.876
LVEF, %; median [IQR] n (%)	50 [31–60]	51 [32–58]	0.123
LVEF < 40 %; n (%)	396 (39)	572 (39)	0.519
In hospital length of stay, days; median [IQR]	5 [3–6]	5 [3–6]	0.812
Culprit artery segment:			
Left Main disease n (%)	18 (2)	13 (1)	0.987
Left anterior descending n (%)	555 (55)	593 (41)	0.065
Circumflex artery n (%)	202 (20)	217 (15)	0.124
Right coronary artery n (%)	417 (41)	419 (29)	0.102
Bypass graft n (%)	9 (1)	12 (1)	0.987
Non culprit stenosis > 50 % n (%)	349 (35)	361 (25)	0.164
Three vessels disease n (%)	94 (8)	142 (9)	0.839
Two vessels disease n (%)	255 (24)	219 (16)	0.118
Single vessels disease n (%)	658 (64)	1088 (73)	0.078
SBT, minutes median [IQR] n (%)	203 [147–299]	220 [154–334]	0.002
Post-procedure TIMI 0–1 n (%)	148 (14)	172 (12)	0.856
Post-procedure TIMI 3 n (%)	838 (83)	1183 (81)	0.381

Abbreviations: CABG: coronary artery bypass graft; DT: decision time; LVEF: Left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; SBT: symptoms to balloon time; STEMI: ST segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction flow.

Table 2
Univariable and Multivariable analysis of in-hospital mortality.

	Univariable odds ratio (95 % confidence interval)	p value	Multivariable odds ratio (95 % confidence interval)	p value
Age	1.08 (1.06–1.10)	<0.001	1.06 (1.04–1.09)	<0.001
Current smoker	0.25 (0.15–0.45)	<0.001	0.37 (0.18–0.75)	<0.01
Hypertension	1.28 (0.84–1.97)	0.8	/	/
Diabetes	0.68 (0.57–0.91)	<0.01	0.91 (0.47–1.11)	0.2
Dyslipidaemia	1.87 (1.78–1.37)	<0.001	1.07 (0.98–1.26)	0.7
BMI	1.42 (0.73–1.65)	0.1	/	/
Cardiogenic shock	2.01 (1.89–2.22)	<0.001	2.01 (1.73–2.13)	<0.01
Cardiac arrest pre-PCI	1.65 (1.21–1.65)	<0.01	1.10 (1.05–1.31)	<0.01
Multivessel disease	0.76 (0.76–1.02)	<0.01	0.86 (0.83–1.12)	0.6
Post-PCI TIMI flow < 2	5.38 (3.42–8.46)	<0.001	5.62 (3.49–9.04)	<0.001
SBT (minutes)	1.01 (1.01–1.02)	<0.01	1.01 (1.01–1.02)	<0.05
Male sex	0.30 (0.20–0.46)	<0.001	0.53 (0.32–0.88)	<0.01
LVEF	0.75 (0.33–0.84)	<0.01	0.81 (0.77–1.07)	0.3

Abbreviations: BMI: body mass index; CI: confidence interval; SBT: symptoms to balloon time.

Median ischemic time for the entire population was 215 [IQR: 150–317] minutes. Again, women experienced significantly longer SBT (239 [163–346] vs 206 [147–305] min - $p < 0.0001$) than men. In the whole population, a shorter SBT was associated with better revascularization; a median of 210 [150–312] min was reported for TIMI flow 3 group while a median of 225 [157–355] min was reported for TIMI flow <2 group with a significant difference ($p < 0.01$). Only 5 % of smoking patients experienced cardio-genic shock versus 7 % of non-smoking patients ($p = 0.013$). No differences appeared among the other Killip class. Complete comparison of demographic and clinical characteristics between groups are reported in Table 1.

Smoking habit was associated with younger age (61 [52–69] vs 72 [63–81] years – $p < 0.001$) and smokers' SBT appears to be shorter than that of non-smokers (203 [147–299] vs 220 [154–334] minutes – $p < 0.002$). Moreover, DT differs among groups, in fact, smoking patients showed less hesitation in seeking medical assistance compared to non-smoking patients in a significant fashion (60 [30–135] vs 77 [36–170] minutes – p < 0.001). No differences in terms of post-procedural TIMI 3 and of history of previous MI between smoking and non-smoking patients were observed.

A total of 95 (4 %) and 201 (8 %) patients died in-hospital and at 1-year follow-up, respectively. In-hospital and one-year follow-up mortality were significantly higher among women than men (8 % vs 2 % - $p < 0.0001$ and 14 % vs 7 % - p < 0.0001 respectively). Patients who experienced higher in-hospital cardiovascular mortality were those with a longer SBT (264 [IQR: 190–420] min vs 212 [IQR: 150–315] min - $p = 0.0038$), while no differences in this relationship appeared at 1-year

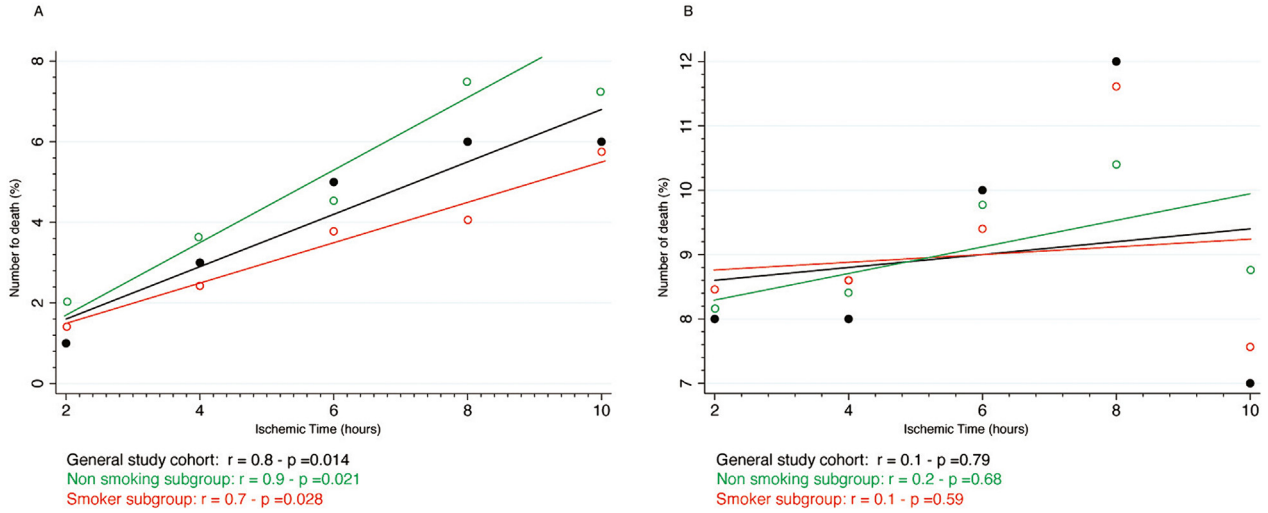

Fig. 1. Mortality and ischemic-time relationship in the general study cohort [black], in the smoker subgroup [red] and in non-smoking subgroup [dark green].
(Panel A): In-hospital mortality and ischemic time. In-hospital mortality appears to increase linearly for every 2 h delay according to ischemic time respectively by 2.5 % [general study cohort - $r = 0.8$ - $p = 0.014$], by 3 % [non-smoker subgroup - $r = 0.9$ - $p = 0.021$], by 1,8 % [smoking subgroup - $r = 0.7$ - $p = 0.028$].
(Panel B): 1-year mortality and ischemic time. 1-year mortality did not appear to increase linearly according to ischemic time. General study cohort: $r = 0.1$ - $p = 0.79$; non-smoker subgroup: r = 0.1 – $p = 0.68$ smoking subgroup $r = 0.2 – p = 0.59$.

Table 3
Univariable and multivariable Cox regression analysis of one-year all-cause mortality.

	Univariable Cox regression	p value	Multivariable Cox regression	p value
	Hazard ratio (95 % CI)		Hazard ratio (95 % CI)	
Age	1.08 (1.06–1.10)	<0.001	1.06 (1.04–1.09)	<0.001
Current smoker	0.25 (0.15–0.45)	<0.001	0.37 (0.18–0.75)	<0.01
Hypertension	1.10 (1.09–1.12)	<0.001	1.10 (1.08–1.12)	<0.001
Diabetes	0.40 (0.29–0.56)	<0.001	0.93 (0.62–1.39)	0.4
Dyslipidemia	1.90 (1.38–2.61)	<0.001	1.15 (0.80–1.65)	0.9
BMI	0.78 (0.65–0.92)	< 0.01	0.93 (0.57–1.21)	0.3
Cardiogenic shock	1.68 (1.59–1.23)	<0.001	1.06 (0.97–1.15)	0.6
Cardiac arrest pre-PCI	1.11 (0.96–1.42)	0.8	/	/
Multivessel disease	1.15 (1.12–1.36)	<0.01	1.04 (0.88–1.22)	0.6
Post-PCI TIMI flow < 2	1.22 (1.09–1.28)	<0.01	1.10 (0.98–1.11)	0.8
SBT (minutes)	0.77 (0.77–1.02)	<0.01	0.84 (0.84–1.22)	0.2
Male sex	1.03 (0.66–1.62)	0.3	/	/
LVEF	1.01 (0.98–1.01)	0.5	/	/

Abbreviation: BMI: body mass index; CI: confidence interval; SBT: symptoms to balloon time.

follow-up (226 [IQR: 165–324] min vs 210 [IQR: 149–214] min - $p = 0.103$).

As shown in Fig. 1, in-hospital mortality increased linearly according to SBT both in smoking and non-smoking subgroup ($r = 0.7$ - $p = 0.028$ and $r = 0.9$ - $p = 0.021$, respectively) whilst such a trend was not observed for mortality at 1-year follow-up among groups ($r = 0.2 - p = 0.59$ for smokers and $r = 0.1 - p = 0.68$ for non-smoking sub-group respectively). Based on this finding, we calculated that in-hospital mortality in-creased by 2.8 % for every 2 h delay.

Univariable and Multivariable Adjusted analysis were used to detect the relationship between variables and in-hospital death (Table 2) and all-cause death at 1-year follow-up (Table 3). After multivariable analysis, SBT [OR:1.01 (95 % CI: 1.01–1.02) - $p < 0.05$] appeared as an independent predictor of in-hospital mortality together with age [OR 1.06 (95 % CI: 1.04–1.09) - $p < 0.001$], cardiogenic shock [OR 2.01 (95 % CI: 1.73–2.13) - $p < 0.01$], cardiac arrest pre-PCI [OR 1.1 (95 % CI: 1.05–1.31) - p < 0.01], post-PCI TIMI flow <2 [OR 5.62 (95 % CI: 3.49–9.04) - $p < 0.001$], whilst smoker status [OR:0.37 (95 % CI: 0.18–0.75) - p < 0.01] and male sex [OR:0.53 (95 % CI: 0.32–0.88) - p < 0.01] emerged as protective variables.

At 1-year follow-up, univariable Cox models showed that age, smoking, hypertension, diabetes, dyslipidemia, BMI, cardiogenic shock, cardiac arrest pre-PCI, multivessel disease, post-PCI TIMI flow <2 and SBT were all associated to death. At multivariable analysis only age [HR:1.06 (95 % CI: 1.04–1.09) – $p < 0.001$] and hypertension [HR:1.1 (95 % CI: 1.08–1.1) – $p = 0.001$] remained positively associated to all-cause death; while smoking-habit [HR:0.37 (95 % CI: 0.18–0.75) – p < 0.001] maintained the protective effect. It is worth noting that SBT [HR:0.77 (95 % CI: 0.77–1.02) – $p = 0.1$] showed no association with the outcome.

Table 4
Post-matching baseline characteristics.

Characteristic	N	Non-smokers N = 886[a]	Smokers N = 886[a]	p-Value[b]
Male	1772	715 (81 %)	696 (79 %)	0.3
Age	1772	65 (57, 73)	64 (57, 72)	0.3
Diabetes type II	1772	168 (19 %)	152 (17 %)	0.3
Hypertension	1772	491 (55 %)	483 (55 %)	0.7
Dyslipidemia	1772	365 (41 %)	363 (41 %)	>0.9
CAD (family)	1772	255 (29 %)	265 (30 %)	0.6
Past ACS	1772	94 (11 %)	91 (10 %)	0.8
Shock	1772	46 (5.2 %)	46 (5.2 %)	>0.9
LVEF (%)	1772	45 (40, 50)	45 (40, 50)	0.5

Abbreviations: ACS: acute coronary syndrome; CAD: coronary artery disease; LVEF: left ventricular ejection fraction.
[a] n (%); Median (IQR).
[b] Pearson's Chi-squared test; Wilcoxon rank sum test.

Kaplan-Meier curves confirmed a better event-free survival of smoking patients (Log-Rank test: $P < 0.0001$) (Fig. 2). It is worth noting that 41 % of all deaths occurred in the first month after STEMI. Incidence of death among non-smokers was significantly higher than smokers in the first month (5.1 % vs 1.2 %; $P < 0.001$) with 43 % of all deaths in non-smokers group occurring in first month vs 32 % in smokers, being this difference mainly driven by in-hospital mortality. After the first month, mortality in smokers is 2.2 times higher while the increase of incidence of non-smokers is only 1.3 times higher (6.8 % vs 2.6 %, P < 0.001).

Propensity score matching yielded two comparable groups (886 smokers vs 886 non-smokers) with no significant differences in baseline characteristics (Table 4). There were no differences (Table 5) regarding symptoms-to-balloon times, door-to-balloon, and decision times, as well as no differences in the immediate reperfusion state; in-hospital death was higher in non-smokers group (3.4 % vs 1.7 %; $p = 0.024$) and remained higher also at 1-year follow-up (9–5 % vs 5.1 %; $p < 0.001$). At univariable analysis (Supplementary Table 4) we found that in-hospital mortality was associated with age (OR 1.04, 95 % CI [1.02–1.07]; $p = 0.001$), previous cardiovascular interventions (OR 2.59, 95 % CI

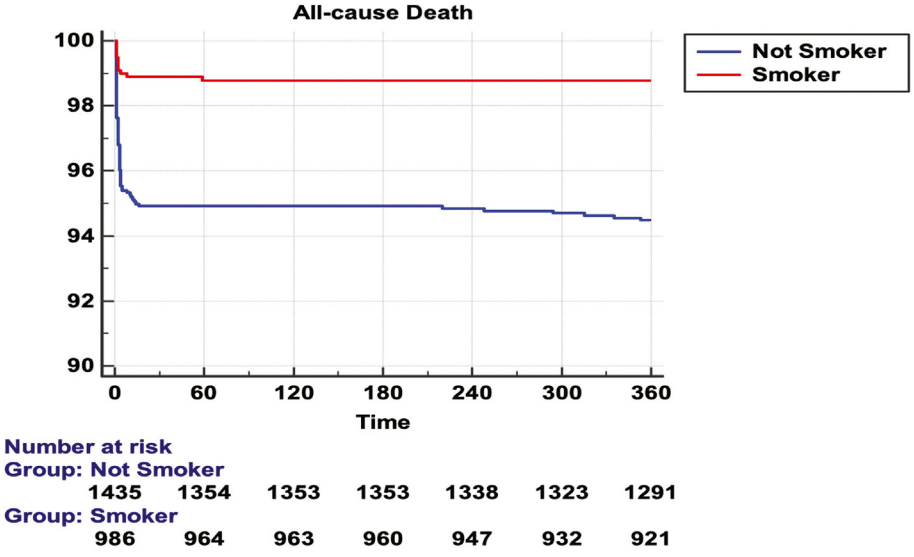

Fig. 2. 1-year Kaplan-Meier survival curves.

Table 5
Operative data and outcomes in propensity-matched patients.

Characteristic	N	Non-smokers N = 886[a]	Smokers N = 886[a]	p-Value[b]
SBT (minutes)	1772	212 (148, 322)	206 (149, 300)	0.4
Decision time	1772	73 (30, 165)	65 (30, 140)	0.3
TIMI 3	1772	701 (79 %)	687 (78 %)	0.4
TIMI 1–2	1772	187 (21 %)	201 (23 %)	0.4
In-hospital death	1772	30 (3.4 %)	15 (1.7 %)	0.024
Death at follow-up	1709	81 (9.6 %)	44 (5.1 %)	<0.001

Abbreviation: SBT: symptoms to balloon time; TIMI: thrombolysis in myocardial infarction flow.
[a] n (%); Median (IQR).
[b] Pearson's Chi-squared test; Wilcoxon rank sum test.

[1.23–5.03]; $p = 0.007$), cardiogenic shock (OR 42.8, 95 % CI [22.5–83.7]; $p < 0.001$), increased symptoms-to-balloon time (OR 1.02, 95 % CI [1.02–1.03]; p < 0.001) and decision time (OR 1.04, 95 % CI [1.01–1.02]; $p = 0.013$), as well as low TIMI flow at the end of the procedure (TIMI 1 or TIMI 2: OR 5.16, 95 % CI [2.84–9.55]; $p < 0.001$). Conversely, smoking habit (OR 0.49, 95 % CI [0.26–0.91]; $p = 0.026$) and TIMI 3 score (HR 0.19, 95 % CI [0.10–0.25]; p < 0.001), were associated with decreased in-hospital mortality. At multivariable analysis (Supplementary Table 5), age (OR 1.04, 95 % CI [1.02–1.07]; $p = 0.015$), cardiogenic shock (OR 42.9, 95 % CI [20.8–92.1]; p < 0.001) and TIMI flow <3 (OR 3.77, 95 % CI [1.86–7.74]; p < 0.001) were associated with in-hospital mortality, while smoking habit was still associated with reduced mortality (OR 0.44, 95 % CI [0.20–0.90]; p = 0.026). At 1-year follow-up, lower age (HR 1.04, 95 % CI [1.02–1.06]; p < 0.001) and smoking (HR 0.54, 95 % CI [0.37–0.78]; p < 0.001) were independently associated with lower mortality.

4. Discussion

The so-called “smoker's paradox” was introduced into scientific arena more than two decades ago [12–15] to describe the counterintuitive phenomenon of lower mortality in smoking patients presenting with STEMI compared to non-smokers. The paradoxical nature of this evidence is in the sight of all and some analyses have tried to deconstruct the evidence of this paradox by showing its inconsisten-cies [16–20]. More in details, while some authors have proposed to explain the counterintuitive beneficial effect of smoking in STEMI with an enhanced myocardial preconditioning – thus being associated with a decreased final infarct size [21–23], others have shown that, among STEMI patients undergoing primary PCI, smoking sta-tus does not affect infarct size [24]. However, some aspects remain nowadays unsolved and there is not a univocal satisfactory explanation. Our data, derived from a large cohort of consecutive STEMI patients, aim at shedding new light on the enigmatic protection related to smoking status in the setting of STEMI and to investigate the relation with ischemic time before revascularization.

4.1. Smoking habit and younger age

One of the most common hypotheses explaining the observed “protection” of smoking patients in the setting of STEMI relates to the importance of a younger age of smokers rather than smoking itself. As previously reported, indeed, smokers are usually younger at the time of their first cardiovascular events, with fewer atherosclerotic risk factors and comorbidities compared with nonsmokers [17]. In our population we confirm that smoking patients were younger and had a better prognosis, both in terms of lower in-hospital and one-year mortality. Specifically, smoking patients develop STEMI about 10 years earlier than non-smoking, as previously reported by Björn Redfors et al. [25]. From a pathophysiologic perspective, smokers have increased platelet aggregation [26,27], increased fibrinogen, and decreased fibrinolytic activity compared with non-smokers [27], creating a state of hypercoagulability that predisposes to acute thrombosis [28]. Smoking also induces endothelial dysfunction [29] and neutrophil acti-vation [28], causes oxidant injury [29], increases fibrinogen levels, and causes platelet activation [27], all of which increase the rate of atherosclerosis and plaque progression by direct or indirect effects [3]. Additionally, smoking can trigger spasms in the coro-nary arteries, further exacerbating the risk of acute coronary syndrome. All these conditions can be related to accelerated atherosclerosis, and the fact that smokers were admitted to the hospital for STEMI about 10 years before non-smokers, indicates that premature coronary atherothrombosis is the high price they pay for smoking [30,31]. Besides, as previously reported, there was no association of smoking with infarct size or microvascular obstruction MVO, and that smoking patients were at greater risk of reinfarction [18,32]. Our multivariable analysis confirmed that, among others, not only younger age but also smoking status were independently associated with both decreased in-hospital death and 1-year-all cause death.

4.2. Smoking habit and lower ischemic time

Animal and clinical studies have shown more myocardial salvage and better out-comes with a reduction in SBT [33]. In fact, as previously reported, SBT could be con-sidered the new gold standard for STEMI care [34]. Stratifying our population, we found a strong relationship between SBT and in-hospital mortality. For every 2-h de-lay, mortality significantly and linearly increased by 2.8 %. Conversely, such a trend was not observed for mortality at 1-year follow-up, which is likely dependent on other factors. SBT is influenced by several factors, such as the patient's ability to promptly recognize signs and symptoms of heart attack [35,36], together with a rapid decision to seek medical care (i.e., short decision time), as well as a fast diagnosis [37] and quick transport to the most appropriate medical facility, to restore coronary blood flow [38–43]. In our study, we observed that decision time and SBT in smokers was significantly shorter than in non-smokers thus, in turn, leading to a benefit of in hospital mortality after STEMI, but not at one year follow-up for all cause death. As specified in the methods, in 92 % of patients it was possible to pinpoint a specific time of symptom onset and in the remaining patients, most of whom were elderly and diabetic with atypical symptoms or patients with OHCA, in order to be as accurate as possible, we collected the clinical information from relatives and from EMS dispatches. One could speculate that, for smokers more than for non-smokers, the awareness of being at risk of coronary artery disease may allow a rapid link of symptoms to heart problem and, consequently, lead the patients to a prompter and quicker seek for help, thus finally leading to a decrease of decision time and the ischemic time. This may explain the shorter decision time that we found in our smoking patients to seek medical care which helps to shorten the ischemic time. Non-smokers are more frequently elderly and diabetics, thus with atypical STEMI presentation or lower chest pain. However, again we underline that multivariable analysis revealed that smoking habit was independently associated with a reduced in-hospital mortality.

4.3. Smoking-related protection in STEMI: beyond younger age

Our study outlined that in patients with STEMI receiving PCI revascularization smoking habit and younger age are independent protective factors for all-cause mortality at 1-year, while diabetes remains a strong negative risk factor.

This result does not take into account for the number of smokers who may have already deceased before being admitted to the hospital for pPCI, considering only those who survive long enough to be hospitalized. Given the perspective of this collider bias, the smoker's paradox should be interpreted within the context of hospitalized patients and does not account for out-of-hospital myocardial infarction deaths.

Evidence from literature support the observation of a lower mortality rate in smokers with STEMI receiving thrombolytic therapy [44–48]. As well as in our study, after adjusting for initial risks, this association remains significant in some studies [49], while others don't show lowered mortality after corrections [44–47]. Even among the most recently published studies,

some support the evidence that smokers had lower crude 1-year rates of all-cause mortality, but this was not maintained after adjusting for age and other risk factors [25,50]. In terms of the impact of smoking on in-hospital mortality, the widest case series was analyzed by Gupta et al. in a nationwide cohort of about 1 million patients [51]. It was demonstrated, similarly to our results, that even after adjusting for age and risk factors, smoking status is associated with reduced in-hospital mortality, a shorter average length of stay, and a lower incidence of in-hospital cardiac arrest [51].

It is hypothesized that smoking's impact on increased blood clotting rather than plaque vulnerability results in better response to this treatment. Smoking can lead to a tenden-cy for clotting caused by endothelial dysfunction, amplified platelet activity, raised fibrinogen levels, and disproportionate thrombin generation [52]. Furthermore, fibrin cross-linking is affected by cigarette components [53]. Thus, in smokers the predominant cause of STEMI could be on thrombogenic basis, making thrombolytic therapy more effective. Consequently, this might influence the effectiveness of various antithrombotic therapies [54]. Notably, an analysis of the HORIZONS-AMI trial revealed that among STEMI patients receiving pPCI, bivalirudin monotherapy resulted in reduced 30-day and 1-year mortality in smokers but not in non-smokers when compared to unfractionated heparin plus glycoprotein IIb/IIIa inhibitors [55].

Some studies have also indicated that nicotine can lead to increased expression of P2Y12 receptors in human platelet lysates, which may elucidate the impact of smoking on platelet inhibition [56]. This could explain a possible greater response to P2Y12 inhibitor such clopidogrel used in acute phase of STEMI and pPCI and a different clinical efficacy in smokers versus non-smokers.

Another aspect to consider in the smoking patient is the composition of coronary plaque. Some studies [57,58] show that in smokers, coronary plaques, evaluated by in-travascular ultrasound (IVUS), have a reduced fibrous component and an increased li-pid content. Furthermore, Bolorunduro et al. [59] evaluated the composition of culprit lesions in smokers, highlighting an increased burden of necrotic core, and showing that smokers have more vulnerable plaques, especially in the presence of other cardiovas-cular risk factors. However, prospective studies on broader cohorts are needed to de-termine the prognostic impact of plaque composition evaluated by intravascular imag-ing in smoking patients with acute coronary syndrome.

4.4. Study limitations

The results of this clinical prospective registry should be considered in light of some limitations. First, this is a single-centre registry with a long period of inclusion and the follow-up time was limited to 1 year after index events. We lost contact with 25 out of our total 2336 patients for a variety of reasons, including unsuccessful attempts to reach patients by phone even after several attempts and due to privacy preferences of the patients concerned. Second, information on smoking status was available only at the time of the STEMI and not during follow-up. Given the beneficial impact of smoking cessation, information on changes in smoking status over the course of the study would have provided additional useful information. Moreover, packs smoked per day, and total pack-years were not available, making a more comprehensive differentiation between patients impossible. Post-discharge pharmcological therapy was not considered among the mandatory fields of the registry.

We do not have detailed information on the completeness of revascularization for patients presenting with multivessel disease. Generally, all patients referred to our center receive complete revascularization based on evidence of significant flow limitation or inducible ischemia. However, we acknowledge that the management of multivessel disease may have varied over the years due to new studies and evolving guidelines [60]. This issue could limit our understanding of patients' ischemic risk status during follow-up and impact long-term mortality.

Mortality is significantly higher in the first month among non-smokers; even though this could be a limit, in particular for follow-up analysis, it is worth noting that the difference between the two groups remains significant during follow-up. In addition, this registry is restricted to STEMI patients treated with pPCI and does not account for those who died prior to coronary angiography. This selection bias, known as collider bias, prevents assessing the effect of smoking habits on all STEMI patients and instead restricts the focus to only those receiving pPCI.

Non smoking patients in our study were significantly older, and older patients are especially at risk of having multiple, undetected health issues that tend to occur together. Since these comorbidities were not propestively collected in the database, they might not be accounted for in the propensity matching process, potentially leading to imprecise results.

5. Conclusions

Our study demonstrated that patients presenting with STEMI are younger and have a lower ischemic time than non-smoking patients. Smoking habit, younger age and shorter ischemic time are associated to lower in-hospital mortality. Smoking-habit and younger age, but not ischemic time, are also independently associated to a better outcome in terms of all-cause mortaliuty at 1-year follow-up. Although the underling mechanism of “smoking paradox” remains uncertain, younger age plays a role in the explanation of this apparent counterintuitive phenomenon.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional review board statement

The study was conducted in accordance with the 1975 Declaration of Helsinki and approved by the Ethics Committee of Fondazione Gabriele Monas-terio – Regione Toscana, Massa, Italy.

Informed consent statement

Informed consent was obtained from each patient (or from rela-tives in case of the patient's inability) before the angiogram for participation in the follow-up.

CRediT authorship contribution statement

Umberto Paradossi: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alberto Ranieri De Caterina:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giancarlo Trimarchi:** Validation, Methodology. **Fausto Pizzino:** Validation, Methodology. **Luca Bastiani:** Writing – original draft, Formal analysis. **Filippo Dossi:** Methodology, Data curation. **Mario Raccis:** Validation, Data curation. **Giacomo Bianchi:** Validation, Methodology, Data curation. **Cataldo Palmieri:** Data curation. **Cesare de Gregorio:** Visualization, Supervision. **Giuseppe Andò:** Visualization, Supervision. **Sergio Berti:** Visualization, Supervision.

Data availability statement

The data that support the findings of this study may be made available from the corresponding author upon reasonable request.

Declaration of competing interest

Sergio Berti is proctor for St. Jude Medical and Edwards Lifesciences LLC. The remaining authors report no financial relationships or conflicts of interest regarding the con-tent herein.

Acknowledgments

The authors would like to thank Roberto Martini for the graphics and the Cath Lab staff of the Fondazione Gabriele Monasterio – Regione Toscana, Massa, Italy for their precious help in collecting data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2024.06.007.

References

[1] National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
[2] Andrikopoulos GK, Richter DJ, Dilaveris PE, Pipilis A, Zaharoulis A, Gialafos JE, et al. In-hospital mortality of habitual cigarette smokers after acute myocardial infarction; the "smoker's paradox" in a countrywide study. Eur Heart J. 2001;22:776–84. https://doi.org/10.1053/euhj.2000.2315.
[3] Symons R, Masci PG, Francone M, Claus P, Barison A, Carbone I, et al. Impact of active smoking on myocardial infarction severity in reperfused ST-segment elevation myocardial infarction patients: the smoker's paradox revisited. Eur Heart J. 2016;37:2756–64. https://doi.org/10.1093/eurheartj/ehv738.
[4] Taddei A, Paradossi U, Rocca E, Carducci T, Mangione M, Dalmiani S, et al. Information system for assessing health care in acute myocardial infarction. Computing in Cardiology. 2012;2012:205–8.
[5] Sardella G, Mancone M, Bucciarelli-Ducci C, Agati L, Scardala R, Carbone I, et al. Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. J Am Coll Cardiol. 2009;53:309–15. https://doi.org/10.1016/j.jacc.2008.10.017.
[6] Miranda-Guardiola F, Rossi A, Serra A, Garcia B, Rumoroso JR, Iñiguez A, et al. Angiographic quantification of thrombus in ST-elevation acute myocardial infarction presenting with an occluded infarct-related artery and its relationship with results of percutaneous intervention. J Interv Cardiol. 2009;22:207–15. https://doi.org/10.1111/j.1540-8183.2009.00464.x.
[7] Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e18–114. https://doi.org/10.1161/CIR.0000000000001038.
[8] Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87–165. https://doi.org/10.1093/eurheartj/ehy394.
[9] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018;72:2231–64. https://doi.org/10.1016/j.jacc.2018.08.1038.
[10] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–77. https://doi.org/10.1093/eurheartj/ehx393.
[11] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88. https://doi.org/10.1093/eurheartj/ehz455.
[12] Helmers C. Short and long-term prognostic indices in acute myocardial infarction. A study of 606 patients initially treated in a coronary care unit. Acta Med Scand Suppl. 1973;555:7–26.
[13] Kelly TL, Gilpin E, Ahnve S, Henning H, Ross J. Smoking status at the time of acute myocardial infarction and subsequent prognosis. Am Heart J. 1985;110:535–41. https://doi.org/10.1016/0002-8703(85)90071-7.
[14] Sparrow D, Dawber TR. The influence of cigarette smoking on prognosis after a first myocardial infarction. A report from the Framingham study. J Chronic Dis. 1978;31:425–32. https://doi.org/10.1016/0021-9681(78)90006-1.
[15] Weinblatt E, Shapiro S, Frank CW, Sager RV. Prognosis of men after first myocardial infarction: mortality and first recurrence in relation to selected parameters. Am J Public Health Nations Health. 1968;58:1329–47. https://doi.org/10.2105/ajph.58.8.1329.
[16] Joner M, Cassese S. The "smoker's paradox": the closer you look, the less you see. JACC Cardiovasc Interv. 2019;12:1951–3. https://doi.org/10.1016/j.jcin.2019.07.028.
[17] Yadav M, Mintz GS, Généreux P, Liu M, McAndrew T, Redfors B, et al. The smoker's paradox revisited: a patient-level pooled analysis of 18 randomized controlled trials. JACC Cardiovasc Interv. 2019;12:1941–50. https://doi.org/10.1016/j.jcin.2019.06.034.
[18] White HD. Deconstructing the paradox of smoking and improved short-term cardiovascular outcomes after myocardial infarction. J Am Coll Cardiol. 2020;75:1755–7. https://doi.org/10.1016/j.jacc.2020.02.044.
[19] Kirtane AJ, Kelly CR. Clearing the air on the "smoker's paradox". J Am Coll Cardiol. 2015;65:1116–8. https://doi.org/10.1016/j.jacc.2015.01.012.
[20] Doi SA, Islam N, Sulaiman K, Alsheikh-Ali AA, Singh R, Al-Qahtani A, et al. Demystifying smoker's paradox: a propensity score-weighted analysis in patients hospitalized with acute heart failure. J Am Heart Assoc. 2019;8:e013056. https://doi.org/10.1161/JAHA.119.013056.
[21] Nakada Y, Canseco DC, Thet S, Abdisalaam S, Asaithamby A, Santos CX, et al. Hypoxia induces heart regeneration in adult mice. Nature. 2017;541:222–7. https://doi.org/10.1038/nature20173.
[22] Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, et al. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol. 2016;67:1674–83. https://doi.org/10.1016/j.jacc.2016.01.069.
[23] Yang X, Cohen MV, Downey JM. Mechanism of cardioprotection by early ischemic preconditioning. Cardiovasc Drugs Ther. 2010;24:225–34. https://doi.org/10.1007/s10557-010-6236-x.
[24] De Luca G, Parodi G, Sciagrà R, Bellandi B, Comito V, Vergara R, et al. Smoking and infarct size among STEMI patients undergoing primary angioplasty. Atherosclerosis. 2014;233:145–8. https://doi.org/10.1016/j.atherosclerosis.2013.12.011.
[25] Redfors B, Furer A, Selker HP, Thiele H, Patel MR, Chen S, et al. Effect of smoking on outcomes of primary PCI in patients with STEMI. J Am Coll Cardiol. 2020;75:1743–54. https://doi.org/10.1016/j.jacc.2020.02.045.
[26] Levine PH. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. Circulation. 1973;48:619–23. https://doi.org/10.1161/01.cir.48.3.619.
[27] Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. J Am Coll Cardiol. 1993;22:1159–67. https://doi.org/10.1016/0735-1097(93)90431-y.
[28] Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol. 1997;29:1422–31. https://doi.org/10.1016/s0735-1097(97)00079-x.
[29] Michael Pittilo R. Cigarette smoking, endothelial injury and cardiovascular disease. Int J Exp Pathol. 2000;81:219–30. https://doi.org/10.1046/j.1365-2613.2000.00162.x.
[30] Ottesen MM, Jørgensen S, Kjøller E, Videbaek J, Køber L, Torp-Pedersen C. Age-distribution, risk factors and mortality in smokers and non-smokers with acute myocardial infarction: a review. TRACE study group. Danish Trandolapril Cardiac Evaluation. J Cardiovasc Risk. 1999;6:307–9. https://doi.org/10.1177/204748739900600506.
[31] Bøttcher M, Falk E. Pathology of the coronary arteries in smokers and non-smokers. J Cardiovasc Risk. 1999;6:299–302. https://doi.org/10.1177/204748739900600504.
[32] Connelly KA, Roifman I. STEMI, the smoker's paradox, and cardiac magnetic resonance imaging: it's all a case of smoke and mirrors. JACC Cardiovasc Imaging. 2019;12:1004–6. https://doi.org/10.1016/j.jcmg.2018.04.029.
[33] Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation. 1977;56:786–94. https://doi.org/10.1161/01.cir.56.5.786.
[34] Denktas AE, Anderson HV, McCarthy J, Smalling RW. Total ischemic time: the correct focus of attention for optimal ST-segment elevation myocardial infarction care. JACC Cardiovasc Interv. 2011;4:599–604. https://doi.org/10.1016/j.jcin.2011.02.012.
[35] Zapka JG, Oakes JM, Simons-Morton DG, Mann NC, Goldberg R, Sellers DE, et al. Missed opportunities to impact fast response to AMI symptoms. Patient Educ Couns. 2000;40:67–82. https://doi.org/10.1016/s0738-3991(99)00065-8.
[36] Hedges JR, Feldman HA, Bittner V, Goldberg RJ, Zapka J, Osganian SK, et al. Impact of community intervention to reduce patient delay time on use of reperfusion therapy for acute myocardial infarction: rapid early action for coronary treatment (REACT) trial. REACT Study Group. Acad Emerg Med. 2000;7:862–72. https://doi.org/10.1111/j.1553-2712.2000.tb02063.x.
[37] Curtis JP, Portnay EL, Wang Y, McNamara RL, Herrin J, Bradley EH, et al. The pre-hospital electrocardiogram and time to reperfusion in patients with acute myocardial infarction, 2000-2002: findings from the National Registry of Myocardial Infarction-4. J Am Coll Cardiol. 2006;47:1544–52. https://doi.org/10.1016/j.jacc.2005.10.077.
[38] De Luca G, Suryapranata H, Zijlstra F, van't Hof AWJ, Hoorntje JCA, Gosselink ATM, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. J Am Coll Cardiol. 2003;42:991–7. https://doi.org/10.1016/s0735-1097(03)00919-7.
[39] Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med. 2006;355:2308–20. https://doi.org/10.1056/NEJMsa063117.
[40] Bradley EH, Curry LA, Webster TR, Mattera JA, Roumanis SA, Radford MJ, et al. Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. Circulation. 2006;113:1079–85. https://doi.org/10.1161/CIRCULATIONAHA.105.590133.
[41] Le May MR, So DY, Dionne R, Glover CA, Froeschl MPV, Wells GA, et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2008;358:231–40. https://doi.org/10.1056/NEJMoa073102.
[42] Khot UN, Johnson ML, Ramsey C, Khot MB, Todd R, Shaikh SR, et al. Emergency department physician activation of the catheterization laboratory and immediate transfer to an immediately available catheterization laboratory reduce door-to-balloon time in ST-elevation myocardial infarction. Circulation. 2007;116:67–76. https://doi.org/10.1161/CIRCULATIONAHA.106.677401.
[43] Ting HH, Rihal CS, Gersh BJ, Haro LH, Bjerke CM, Lennon RJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI Protocol. Circulation. 2007;116:729–36. https://doi.org/10.1161/CIRCULATIONAHA.107.699934.
[44] Barbash GI, Reiner J, White HD, Wilcox RG, Armstrong PW, Sadowski Z, et al. Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytic therapy for

acute myocardial infarction: mechanism of the “smoker’s paradox” from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol. 1995;26:1222–9. https://doi.org/10.1016/0735-1097(95)00299-5.

[45] Zahger D, Cercek B, Cannon CP, Jordan M, Davis V, Braunwald E, et al. How do smokers differ from nonsmokers in their response to thrombolysis? (the TIMI-4 trial). Am J Cardiol. 1995;75:232–6. https://doi.org/10.1016/0002-9149(95)80026-o.

[46] Grines CL, Topol EJ, O’Neill WW, George BS, Kereiakes D, Phillips HR, et al. Effect of cigarette smoking on outcome after thrombolytic therapy for myocardial infarction. Circulation. 1995;91:298–303. https://doi.org/10.1161/01.cir.91.2.298.

[47] Maggioni AP, Piantadosi F, Tognoni G, Santoro E, Franzosi MG. Smoking is not a protective factor for patients with acute myocardial infarction: the viewpoint of the GISSI-2 study. G Ital Cardiol. 1998;28:970–8.

[48] Barbash GI, White HD, Modan M, Diaz R, Hampton JR, Heikkila J, et al. Acute myocardial infarction in the young–the role of smoking. The Investigators of the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. Eur Heart J. 1995;16:313–6.

[49] Barbash GI, White HD, Modan M, Diaz R, Hampton JR, Heikkila J, et al. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. Circulation. 1993;87:53–8. https://doi.org/10.1161/01.cir.87.1.53.

[50] Janjani P, Salehi N, Asadmobini A, Siabani S, Nalini M. Smoker pseudo-paradox in ST-segment elevation myocardial infarction patients. Folia Med (Plovdiv). 2023;65:243–50. https://doi.org/10.3897/folmed.65.e80189.

[51] Gupta T, Kolte D, Khera S, Harikrishnan P, Mujib M, Aronow WS, et al. Smoker's paradox in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. J Am Heart Assoc n.d.;5:e003370. https://doi.org/10.1161/JAHA.116.003370.

[52] Sambola A, Osende J, Hathcock J, Degen M, Nemerson Y, Fuster V, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. Circulation. 2003;107:973–7. https://doi.org/10.1161/01.cir.0000050621.67499.7d.

[53] Galanakis DK, Laurent P, Janoff A. Cigarette smoke contains anticoagulants against fibrin aggregation and factor XIIIa in plasma. Science. 1982;217:642–5. https://doi.org/10.1126/science.6124042.

[54] Gargiulo G, Carrara G, Frigoli E, Vranckx P, Leonardi S, Ciociano N, et al. Bivalirudin or heparin in patients undergoing invasive management of acute coronary syndromes. J Am Coll Cardiol. 2018;71:1231–42. https://doi.org/10.1016/j.jacc.2018.01.033.

[55] Goto K, Nikolsky E, Lansky AJ, Dangas G, Witzenbichler B, Parise H, et al. Impact of smoking on outcomes of patients with ST-segment elevation myocardial infarction (from the HORIZONS-AMI Trial). Am J Cardiol. 2011;108:1387–94. https://doi.org/10.1016/j.amjcard.2011.06.063.

[56] Shanker G, Kontos JL, Eckman DM, Wesley-Farrington D, Sane DC. Nicotine upregulates the expression of P2Y12 on vascular cells and megakaryoblasts. J Thromb Thrombolysis. 2006;22:213–20. https://doi.org/10.1007/s11239-006-9033-4.

[57] Buljubasic N, Akkerhuis KM, de Boer SPM, Cheng JM, Garcia-Garcia HM, Lenzen MJ, et al. Smoking in relation to coronary atherosclerotic plaque burden, volume and composition on intravascular ultrasound. PLoS One. 2015;10:e0141093. https://doi.org/10.1371/journal.pone.0141093.

[58] Kumagai S, Amano T, Takashima H, Waseda K, Kurita A, Ando H, et al. Impact of cigarette smoking on coronary plaque composition. Coron Artery Dis. 2015;26:60–5. https://doi.org/10.1097/MCA.0000000000000168.

[59] Bolorunduro O, Cushman C, Kapoor D, Alexander K, Cuellar-Silva J, Giri S, et al. Comparison of coronary atherosclerotic plaque burden and composition of culprit lesions between cigarette smokers and non-smokers by in vivo virtual histology intravascular ultrasound. J Invasive Cardiol. 2015;27:354–8.

[60] Biscaglia S, Guiducci V, Escaned J, Moreno R, Lanzilotti V, Santarelli A, et al. Complete or culprit-only PCI in older patients with myocardial infarction. New Engl J Med. 2023;389:889–98.