Carbon monoxide and prognosis in smokers hospitalised with acute cardiac events: a multicentre, prospective cohort study

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eClinicalMedicine
2024;67: 102401

Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.102401

Summary

Background Smoking cigarettes produces carbon monoxide (CO), which can reduce the oxygen-carrying capacity of the blood. We aimed to determine whether elevated expiratory CO levels would be associated with a worse prognosis in smokers presenting with acute cardiac events.

Methods From 7 to 22 April 2021, expiratory CO levels were measured in a prospective registry including all consecutive patients admitted for acute cardiac event in 39 centres throughout France. The primary outcome was 1-year all-cause death. Initial in-hospital major adverse cardiac events (MAE; death, resuscitated cardiac arrest and cardiogenic shock) were also analysed. The study was registered at ClinicalTrials.gov (NCT05063097).

Findings Among 1379 patients (63 ± 15 years, 70% men), 368 (27%) were active smokers. Expiratory CO levels were significantly raised in active smokers compared to non-smokers. A CO level >11 parts per million (ppm) found in 94 (25.5%) smokers was associated with a significant increase in death (14.9% for CO > 11 ppm vs. 2.9% for CO ≤ 11 ppm; p < 0.001). Similar results were found after adjustment for comorbidities (hazard ratio [HR] [95% confidence interval (CI)]): 5.92 [2.43–14.38]) or parameters of in-hospital severity (HR 6.09, 95% CI [2.51–14.80]) and propensity score matching (HR 7.46, 95% CI [1.70–32.8]). CO > 11 ppm was associated with a significant increase in MAE in smokers during initial hospitalisation after adjustment for comorbidities (odds ratio [OR] 15.75, 95% CI [5.56–44.60]) or parameters of in-hospital severity (OR 10.67, 95% CI [4.06–28.04]). In the overall population, CO > 11 ppm but not smoking was associated with an increased rate of all-cause death (HR 4.03, 95% CI [2.33–6.98] and 1.66 [0.96–2.85] respectively).

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Translation: For the French translation of the abstract see Supplementary Materials section.

Interpretation Elevated CO level is independently associated with a 6-fold increase in 1-year death and 10-fold in-hospital MAE in smokers hospitalized for acute cardiac events.

Funding Grant from Fondation Coeur & Recherche.

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Keywords: Carbon monoxide; Smoking; Tobacco; Acute cardiac events; Death; Cardiovascular events

Research in context

Evidence before this study

The impact of smoking on the prognosis of patients presenting with acute cardiac events remains controversial (described as 'Smoker's Paradox').
Expiratory CO measurement is an objective parameter of smoking severity, reflecting the number of cigarettes smoked but also the intensity of inhalation and the delay since last cigarette consumption.

Added value of this study

In this multicentre, prospective registry of 1379 patients hospitalized for acute cardiac events, active smoking was associated with elevated levels of expiratory Carbon Monoxide (CO) on admission in some smokers.
Elevated CO level were independently associated with a 6-fold increase in 1-year death and 10-fold increase in in-hospital major adverse events in smokers.
In the overall population of patients, elevated expiratory CO levels—but not smoking—were associated with a higher rate of death.

Implications of all the available evidence

Elevated CO levels could play a major role in the burden of smoking in patients with acute cardiac events.

Introduction

The tobacco epidemic is one of the biggest public health threats the world has ever faced.[1] While smoking continues to be a major risk factor for cardiovascular disease, its impact on the prognosis of patients presenting with acute cardiac events remains controversial. In acute myocardial infarction, some studies have shown either decreased, either improved survival in smokers after acute coronary syndrome described as 'Smoker's Paradox'.[2] This concept can be explained by several hypotheses. One hypothesis suggests that smoking may have some protective effects (for example through preconditioning). However, it could also be explained by differences between smokers and non-smokers; smokers are generally younger with fewer comorbidities and therefore with a better prognosis regardless of the occurrence of cardiac events. After adjustment for confounders, smoking remains an important predictor of adverse outcomes.[3]

The combustion of cigarettes or cigars produces carbon monoxide (CO). CO is rapidly absorbed from the smoke into the bloodstream, and a high concentration of CO can be found in smokers. CO dramatically reduces the oxygen-carrying capacity of the blood, and its impact on the cardiovascular system has been largely described.[4] Expiratory CO level is commonly used as a marker for smoking status[5] and is correlated with Fagerström score.[6] Expiratory CO measurement is an objective parameter of smoking severity, reflecting the number of cigarettes smoked but also the intensity of inhalation and the delay since last cigarette consumption.[6]

We hypothesised that elevated CO levels due to smoking would be associated with a worse prognosis in patients presenting with acute cardiac events.

Expiratory CO testing is an easy-to-use technique to measure the percent of carboxy-haemoglobin and to determine the amplitude of smoking in smoking cessation strategies.[5] The aim of this study was to assess the impact of expiratory CO levels on 1-year all-cause death in consecutive patients admitted to the intensive cardiac care unit (ICCU) for acute cardiac events included in the Addiction in Intensive Cardiac Care Units (ADDICT-ICCU) study.

Methods

Study population

Details about the design of the ADDICT-ICCU study have been published.[7] Briefly, the ADDICT-ICCU study is a multi-centre, prospective, observational study of all consecutive patients aged ≥18 years who were admitted to ICCUs in 39 centres across France (representing all administrative regions in the country (including large, medium-sized but also much smaller areas and overseas islands) from 7 to 22 April 2021 (eTable 1). The main exclusion criteria were hospitalisation for a planned interventional procedure and hospitalisation for more than 24 h at any hospital facility before admission to the ICCU. The methodology of the collection of baseline characteristics is detailed in eMethod 1. The main admission diagnoses were adjudicated by two independent experts at the end of the hospitalisations

(eMethod 2). The treatment of each patient was at the discretion of the treating physicians and was in accordance with the current European Society of Cardiology guidelines. Sex of participants was defined based on self-report. To assess the socio-economic status of patients, we divided the population of smokers into 5 classes according to the patient's residence address: upper class (15%), upper middle class (26%), middle class (25%). %), lower middle class (19%) and lower class (15%). To address the interaction with the different regions of the hospitals in the propensity-score matching, we classified the centres into 5 regions: centre (Paris), north west, south west, south east and north east.

Ethics

The study was registered at ClinicalTrials.gov (NCT05063097) and approved by the Committee for the Protection of Human Subjects, Ile de France-7, France. All patients provided written informed consent for participation. The trial was conducted in compliance with Good Clinical Practice guidelines, French law and French data protection law.

Data source

The anonymised data supporting the findings of this study were collected using Cleanweb™ software and are available from the corresponding author upon reasonable request. The sponsor of the trial was the « Délégation à la Recherche Clinique et au Développement, Assistance Publique-Hôpitaux de Paris, Paris, France ».

Measurement of CO levels

CO level was measured within 2 h of admission to the ICCU, using a standardised expiratory CO measurement device (CO Check Pro, Micro Direct Diagnostic Ltd, UK [eFigure 1]). The characteristics of this device have been published previously; it measures up to a sensitivity of 1 part per million (ppm) ±2%.[5] Smoking assessment was performed using a standardised questionnaire, which offered the following choices: non-smoker (no history of smoking), former smoker (smoking stopped more than one week prior) or active smoker. The Fagerström scale and the time of last cigarette were also recorded. Concerning the number of packs-year, we asked to the patients the average number of cigarettes per day and the duration of consumption and calculated as follows (number of cigarettes smoked per day/20) × (number of years smoked). If smoking consumption varied over different periods, we evaluated the average value by taking the sum of the averages for each of these periods. When the patient claimed to have reduced his consumption very recently, we used the prior number of cigarettes before reduction. When patients smoked cigars, we considered that a small cigar was equivalent to 3 cigarettes and a large cigar to 10 cigarettes.

Outcome measures and definitions

The primary outcome was the rate of 1-year all-cause death. The adjudication of all-cause death was performed using the electronic French national registry of death (Institut National de la Statistique et des Etudes Economiques, INSEE registry). To investigate the initial prognostic impact of CO levels, we also used an 'initial outcome' corresponding to the rate of in-hospital major adverse events during the initial hospitalisation after inclusion (MAE: in-hospital death, resuscitated cardiac arrest [severe ventricular arrhythmia requiring defibrillation or intra-venous anti-arrhythmic agents] and cardiogenic shock that required pharmacological or mechanical haemodynamic support).[8] All events, including in-hospital MAE, were adjudicated by an independent committee of experts who reviewed anonymised medical documents according to the standardised definitions.[9]

Statistics

Patient characteristics were summarised as means ± standard deviations (SD) for normally distributed data or, as medians and interquartile ranges (IQRs) for non-normally distributed data. Group comparisons for quantitative and qualitative variables were carried out using the Student t-test, the Mann–Whitney test or the Pearson chi-squared test.

To select the optimal cut-off value of CO-level associated with the occurrence of 1-year mortality, we used three different methods (eMethod 4): i) Youden index method, ii) Euclidean indicator method, and iii) product method. The primary outcome was analysed using cox proportional hazards regression (HR). To assess the independent association between the CO levels measured and the occurrence of all-cause death, three analyses were performed.

A cox proportional hazards regression analysis with the following covariables, based on clinical input[10]: 'comorbidities' (model 1: age, sex, diabetes, history of cardiovascular disease before hospitalisation, known chronic kidney disease with a glomerular filtration rate <60 mL/min, history of cancer and main admission diagnosis); 'in-hospital severity' (model 2: age, sex, main admission diagnosis, systolic blood pressure, Killip class and heart rate); 'respiratory parameters' (model 3: age, sex, main admission diagnosis, body mass index, previous chronic obstructive pulmonary disease or asthma, oxygen flow rate at admission, oxygen saturation at admission, haemoglobin level at admission and intravenous diuretic treatment). Data are presented as HR [95% confidence interval (CI)].

A logistic regression analysis was used to create the propensity score to balance the baseline characteristics in active smokers (R package MatchIt, v3.0.2).[11] A 1:1 propensity score-matched population (with CO levels ≤11 ppm vs. CO levels >11 ppm) was created. The probit model with 1:1 nearest neighbour matching and,

without replacement was used to identify one patient with CO levels ≤11 ppm for each patient with a CO level >11 ppm. The variables used to calculate the propensity score were age, sex, previous diabetes, previous hypertension, previous dyslipidaemia, atrial fibrillation, heart rate (first measurement), systolic blood pressure (first measurement), oxygen saturation (first measurement), Killip score, final diagnosis, and geographic regions of the centres. An imbalance between the groups was considered to be small when the absolute standardised difference for a given covariate was <10%.[12]

A logistic regression was performed to analyse the impact of CO level on MAEs during initial hospitalisation. Data are presented as odds ratio (OR) [95% confidence interval (CI)].

A two-tailed p-value <0.05 was considered statistically significant. All data were analysed using R software, version 3.6.3 (R Project for Statistical Computing, R Foundation, Vienna, Austria).

Role of funding source

Fondation "Coeur & Recherche" gave an unrestricted grant to conduct this work (purchase of NarcoCheck® kit, eCRF, monitoring) but had no part in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study population

From 7 to 22 April 2021, 1904 patients were admitted to the ICCUs in the 39 participating centres. Among the 1575 patients recruited, 1379 (87.6%) were screened using expiratory CO measurement (eFigure 2). The reasons for failure to perform an expiratory CO assay are mentioned in eMethod 3.

Among those 1379 patients (mean age 63 ± 15 years, 70% men), 52% had hypertension, 39% had dyslipidaemia and 21% had diabetes mellitus (Table 1). This population did not significantly differ from the overall population (eTable 2). Regarding cardiovascular morbidities, 61% had a history of cardiac disease and 36% known coronary artery disease. The most common final diagnoses are presented in eTable 3. Briefly, 314 (23%) had ST elevation myocardial infarction, 409 (30%) non-ST elevation myocardial infarction, 187 (14%) acute heart failure and 469 (34%) other diagnoses. The median [IQR] duration of hospitalisation was 5.0 [3.0–7.0] days.

Follow-up ended on May 1, 2022. The primary outcome status was known in 1379 (100.0%) patients. During follow-up, there were 95 (6.9%) all-cause deaths. The median [IQR] duration of follow-up for the patients who died was 88 [15–231] days.

Distribution of CO levels

Among the 1379 patients screened using expiratory CO measurement, 469 (34%) were non-smokers, 542 (39%) were former smokers and 368 (27%) were active smokers. Active smokers were younger, more frequently men and less frequently had diabetes, hypertension and known renal failure compared to non-smokers (Table 1). Among active smokers, the mean number of cigarettes smoked was 28 ± 20 packs-year and the mean Fagerström score was 3.8 ± 2.4.

In the overall population, the mean CO level was 5 ± 5 ppm, and the median [IQR/min–max] was 3 [2–6/0–50] parts per million (ppm). Fig. 1 shows the distribution of the patients' CO levels by smoking status. The CO levels were low (according to the literature[3]) and similar in non-smokers and former smokers (median [IQR]; 3 [2–4] ppm and 3 [2–4] ppm respectively; $p = 0.57$) and significantly raised in active smokers (7 [5–12] ppm; $p < 0.001$). The CO levels were correlated with the Fagerström score ($R^2 = 0.32$, $p < 0.001$) but not the number of packs-years ($R^2 = 0.06$, $p = 0.26$) and, inversely correlated with the delay between CO measurement and the time of the last cigarette ($R^2 = 0.54$: $p < 0.001$) (eFigure 3).

Associations between CO levels and death in active smokers

In the 368 active smokers, CO levels were significantly associated with the occurrence of death (HR [95% CI]: 1.07 [1.02–1.13] for each unit of CO in ppm and, 1.90 [1.27–2.85] for each 10 ppm CO, eTable 4). Using the three following methods: Youden index, Euclidean indicator, and product methods, the optimal cut-off value associated with the occurrence of 1-year mortality was CO level >11 ppm (eMethod 4). CO levels >11 ppm were found in 94 (25.5%) active smokers. In these active smokers, death was 14.9% in patients with CO levels >11 ppm vs. 2.9% in patients with CO levels ≤11 ppm ($p < 0.0001$). Smokers with CO levels >11 ppm had similar characteristics compared to smokers with CO ≤ 11 ppm except a higher Fagerström score, a lower mean systolic blood pressure and lower oxygen saturation at admission (Table 1).

Fig. 2 shows the Kaplan Meier survival analysis of active smokers with CO levels >11 ppm compared to CO levels ≤11 ppm. As shown in Table 2, Cox proportional-hazards regression analysis demonstrated that CO levels >11 ppm were associated with a significantly higher rate of death after adjustment for age and sex (HR [95% CI]): 6.09 [2.54–14.6], $p < 0.001$). Similar results were found after adjustment for comorbidities (model 1; HR [95% CI]): 5.92 [2.43–14.4]), clinical parameters of in-hospital severity (model 2; HR [95% CI]): 6.09 [2.51–14.8]) and, respiratory parameters (model 3; HR [95% CI]): 6.57 [2.62–16.5]) (Table 2 and eTable 5 for other parameters). Similar results were obtained with the survival curve of 1-year death according to both the smoking status and the optimal CO-level threshold (eFigure 4). Using propensity score matching 1:1 in smokers, CO

Characteristics	Overall population	Non or former smokers	Smokers before propensity matching			Smokers after propensity matching		
	N = 1379	N = 1011	CO ≤ 11 N = 274	CO > 11 N = 94	p-value[b]	CO ≤ 11 N = 94	CO > 11 N = 94	p-value[b]
Age, years[a]	63 ± 15	66 ± 14	55 ± 13	55 ± 12	0.51	55 ± 11	55 ± 12	0.97
Male, n (%)[a]	959 (69.5%)	669 (66,2)	214 (78.1%)	76 (80.9%)	0.57	76 (80.9%)	76 (80.9%)	>0.99
Body mass index, kg/m^2	27.3 ± 5.4	27.4 ± 5.5	27.1 ± 5.1	26.5 ± 5.1	0.22	26.3 ± 4.3	26.5 ± 5.1	0.95
History of								
Diabetes mellitus[a]	294 (21.3%)	239 (23.6%)	43 (15.7%)	12 (12.8%)	0.49	12 (12.8%)	12 (12.8%)	>0.99
Dyslipidaemia[a]	532 (38.6%)	425 (42.0%)	79 (28.8%)	28 (29.8%)	0.86	24 (25.5%)	28 (29.8%)	0.51
Hypertension[a]	723 (52.4%)	585 (58.0%)	109 (39.8%)	29 (30.9%)	0.12	30 (31.9%)	29 (30.9%)	0.87
Asthma	22 (1.6%)	17 (1.7%)	4 (1.5%)	1 (1.1%)	>0.99	0 (0.0%)	1 (1.1%)	>0.99
COPD	62 (4.5%)	48 (4.7%)	12 (4.4%)	2 (2.1%)	0.53	6 (6.4%)	2 (2.1%)	0.28
Cancer					0.56			0.50
Active	57 (4.1%)	47 (4.6%)	6 (2.2%)	4 (4.3%)		1 (1.1%)	4 (4.3%)	
Previous	81 (5.9%)	68 (6.7%)	10 (3.6%)	3 (3.2%)		3 (3.2%)	3 (3.2%)	
Family history	226 (16.4%)	153 (15.1%)	52 (19.0%)	21 (22.3%)	0.48	12 (12.8%)	21 (22.3%)	0.084
Known CVD	842 (61.1%)	613 (60.6%)	171 (62.4%)	58 (61.7%)	0.90	55 (58.5%)	58 (61.7%)	0.65
CAD	493 (35.8%)	325 (32.1%)	123 (44.9%)	45 (47.9%)	0.62	40 (42.6%)	45 (47.9%)	0.46
Renal failure	138 (10.0%)	115 (11.4%)	20 (7.3%)	3 (3.2%)	0.16	4 (4.3%)	3 (3.2%)	>0.99
Smoking								
Active smokers	368 (26.7%)	NA	274 (100.0%)	94 (100.0%)	NA	94 (100%)	94 (100%)	NA
Packs-year	8 ± 16	NA	27 ± 20	29 ± 20	0.52	28 ± 18	29 ± 20	0.82
Fagerström score	3.65 ± 2.49	NA	3.55 ± 2.35	4.64 ± 2.45	**<0.001**	4.42 ± 2.21	4.64 ± 2.45	0.36
Admission parameters								
Heart rate (bpm)[a]	83 ± 24	82 ± 24	85 ± 23	83 ± 21	0.36	86 ± 23	83 ± 21	0.35
Atrial fibrillation[a]	152 (11.0%)	136 (13.4%)	12 (4.4%)	4 (4.3%)	>0.99	3 (3.2%)	4 (4.3%)	>0.99
SBP (mmHg)[a]	136 ± 27	137 ± 26	134 ± 26	127 ± 26	**0.017**	124 ± 23	127 ± 26	0.51
O2 sat (%)[a]	97 ± 5	97 ± 5	97 ± 2	96 ± 10	**0.018**	97 ± 3	96 ± 10	0.44
Hb (g/dl)	13.6 ± 1.9	13.4 ± 2.0	14.1 ± 1.7	14.3 ± 1.5	0.49	14.2 ± 1.7	14.3 ± 1.5	0.74
GFR (ml/min m^2)	98 ± 93	91 ± 57	112 ± 146	127 ± 164	0.52	115 ± 116	127 ± 164	0.86
Killip score[a]					0.73			0.65
1	1155 (83.8%)	836 (82.6%)	238 (86.9%)	81 (86.2%)		81 (86.2%)	81 (86.2%)	
2	149 (10.8%)	122 (12.1%)	21 (7.7%)	6 (6.4%)		8 (8.5%)	6 (6.4%)	
3	64 (4.6%)	43 (4.3%)	14 (5.1%)	7 (7.4%)		4 (4.3%)	7 (7.4%)	
4	11 (0.8%)	10 (1.00%)	1 (0.4%)	0 (0.0%)		1 (1.1%)	0 (0.0%)	
Glasgow score					0.15			0.62
<15	16 (1.2%)	13 (1.3%)	1 (0.4%)	2 (2.2%)		1 (1.1%)	2 (2.2%)	
≥15	1337 (98.8%)	979 (96.8%)	270 (99.6%)	88 (97.8%)		92 (98.9%)	88 (97.8%)	
Geographic regions								0.38
Centre (Paris)	312 (22.6%)	219 (21.6%)	71 (25.8%)	22 (23.4%)		23 (24.5%)	22 (23.4%)	
North west	150 (10.9%)	112 (11.1%)	31 (11.3%)	7 (7.4%)		11 (11.7%)	7 (7.4%)	
South west	568 (41.2%)	426 (42.2%)	111 (40.6%)	31 (33.0%)		38 (40.4%)	31 (33.0%)	
South east	112 (8.1%)	86 (8.5%)	17 (6.2%)	9 (9.6%)		6 (6.4%)	9 (9.6%)	
North east	237 (17.2%)	168 (16.6%)	44 (16.1%)	25 (26.6%)		16 (17.0%)	25 (26.6%)	
ICA <2 h	374 (27.1%)	232 (22.9%)	101 (36.9%)	41 (43.6%)	0.25	41 (43.6%)	41 (43.6%)	>0.99
ICA >2 h	553 (40.1%)	409 (40.5%)	111 (40.5%)	33 (35.1%)	0.35	32 (34.0%)	33 (35.1%)	0.88
PCI	454 (32.9%)	292 (16.0%)	118 (43.1%)	44 (46.8%)	0.53	37 (39.4%)	44 (46.8%)	0.30
Ejection fraction (%)	52 ± 13	52 ± 13	50 ± 13	51 ± 14	0.93	51 ± 13	51 ± 13	0.96
Main final diagnosis (4 groups)[a]					0.28			0.60
STEMI	314 (22.8%)	185 (18.3%)	89 (32.5%)	40 (42.6%)		34 (36.2%)	40 (42.6%)	
NSTEMI	409 (29.7%)	297 (29.4%)	85 (31.0%)	27 (28.7%)		26 (27.7%)	27 (28.7%)	
Acute heart failure	187 (13.6%)	152 (15.0%)	29 (10.6%)	6 (6.4%)		5 (5.3%)	6 (6.4%)	
Other diagnosis	469 (34.0%)	377 (37.3%)	71 (25.9%)	21 (22.3%)		29 (30.9%)	21 (22.3%)	

(Table 1 continues on next page)

Characteristics	Overall population	Non or former smokers	Smokers before propensity matching			Smokers after propensity matching		
	N = 1379	N = 1011	CO ≤ 11 N = 274	CO > 11 N = 94	p-value[b]	CO ≤ 11 N = 94	CO > 11 N = 94	p-value[b]
(Continued from previous page)								
Events								
All-cause death	95 (6.9%)	73 (7.2%)	8 (2.9%)	14 (14.9%)	**<0.001**	2 (2.1%)	14 (14.9%)	**0.002**
In-hospital MAE	58 (4.2%)	31 (3.1%)	7 (2.6%)	20 (21.3%)	**<0.001**	3 (3.2%)	20 (21.3%)	**<0.001**

Data are presented as n (%) or mean ± SD. Abbreviations: Family history: family history of cardiovascular diseases; CV: Cardiovascular; CAD: Coronary artery disease; GFR: Glomerular filtration rate; Hb: Hemoglobin; LV: Left ventricular; CO: Carbon Monoxide; ppm: parts per million; COPD: chronic obstructive pulmonary disease; SBP: Systolic blood pressure; ICA: invasive coronary angiography (for acute myocardial infarction); O2 sat: Oxygen saturation; PCI: percutaneous coronary intervention; CABG: Coronary artery bypass grafting; ST + MI: ST elevation myocardial infarction. In hospital MAE: in hospital major adverse events (initial hospitalisation) including in-hospital death, resuscitated cardiac arrest (severe ventricular arrhythmia requiring defibrillation or intra-venous anti-arrhythmic agents), and cardiogenic shock that required pharmacological or mechanical haemodynamic support. [a]Variables used for propensity score. [b]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. Significant p-values (p<0.05) are presented in bold.

Table 1: **Main characteristics of the overall population and smokers according to CO level threshold before and after propensity matching.**

levels >11 ppm were associated with an increased risk of death (HR [95% CI]: 7.46 [1.70–32.8], Table 2).

In multivariable analysis including all smoking consumption parameters (delay between last cigarette, the number of packs-year, the Fagerström score and CO level), CO level was the only parameter independently associated with the occurrence of 1-year mortality in the overall population (eTable 6) and in active smokers (eTable 7). Similar results were obtained after adjustment for socio-economic status (eTable 8) or after adjustment for the geographic regions of the inclusion centres (eTable 9).

Associations between CO levels and initial acute cardiac events in smokers

To investigate the impact of CO at the time of the initial acute cardiac event, we studied the in-hospital major adverse events (MAEs: death, resuscitated cardiac arrest and cardiogenic shock) during the initial hospitalisation for acute cardiac event. During hospitalisation, there were 58 (4.2%) in-hospital MAEs, including 23 (1.7%) in-hospital deaths, 23 (1.7%) cardiac arrest events and 12 (0.9%) cardiogenic shocks that required pharmacological and/or mechanical haemodynamic support. As shown in Table 2, smokers with CO > 11 ppm had a significantly higher rate of in-hospital MAEs than smokers with CO ≤ 11 ppm (21.3% vs. 2.6% respectively, p < 0.0001). There was a significant trend between CO level and MAE (p < 0.0001, Fig. 3). Using logistic regression, we found that CO level >11 ppm was independently associated with an increased rate of in-hospital MAE OR [95% CI]): 11.37 [4.54–28.5]) after adjustment for age and sex. Similar results were found after adjustment for comorbidities (model 1: OR [95% CI]: 15.8 [5.56–44.6]), clinical parameters of in-hospital severity (model 2: OR [95% CI]: 10.7 [4.06–28.0]) and respiratory parameters (model 3: OR [95% CI]: 20.6 [6.40–66.1]). Relationship between MAE and smoking habits (packs year, Fagerström score and delay since last cigarette) according to CO thresholds is presented in eTable 10. After adjustment for cofounders including smoking behaviours, CO-level remains independently associated with MAE (eTable 11).

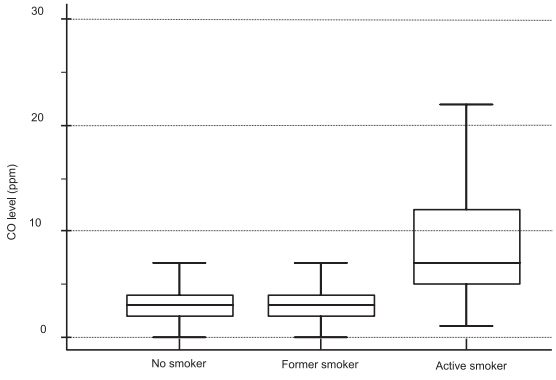

Fig. 1: **Distribution of CO levels by smoking status**. Concentration of expiratory CO levels in the population according to smoking status. Data are presented as box and, whisker plot. Abbreviations: CO: carbon monoxide; ppm: parts per million.

Comparison of smoking and CO to determine death and comparison of prognostic value of smoking and CO levels in the overall population.

In the overall population of the study, using a Kaplan Meier analysis, CO > 11 ppm but not smoking was associated with an increased rate of all-cause death (HR [95% CI]: 4.03 [2.33–6.98] and 1.66 [0.96–2.85] respectively, Fig. 4) after adjustment on age and sex. Interestingly, we found that smokers with a CO ≤ 11 ppm had a lower rate of events compared to non-smokers and former smokers (HR [95% CI]: 0.40 [0.19–0.83]). Such a lower rate of events found in smokers with CO ≤ 11 ppm compared to non-smokers became non-significant after adjustment for age (HR [95% CI]: 0.79 [0.37–1.69]).

In the overall population, for the prediction of death compared to model 1, the addition of active smoking exhibited a better likelihood of the model in terms of prognostic value compared to traditional risk factors of 1.7 (Global $\chi 2$: 76.6–78.3; LR-test with p = 0.002). Then, the addition of CO > 11 ppm also showed a better

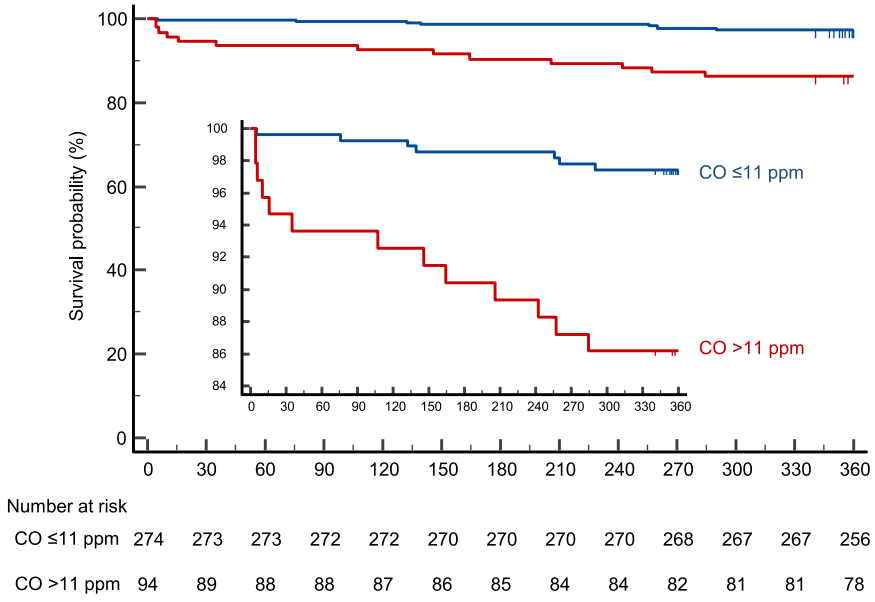

Fig. 2: **Kaplan Meier curves of all-cause death in active smokers according to CO level cut off**. Data are presented according to CO levels: CO level >11 ppm (red line) vs. CO level ≤11 ppm (blue line). Abbreviations: CO: carbon monoxide; ppm: parts per million; HR: Hazard ratio; CI: confidence interval.

Panel A: 1-year death	HR	95% CI	p-value
Univariable analysis[a]	6.1	2.5–14.6	<0.001
Multivariable analysis			
Model 1	5.9	2.4–14.4	<0.001
Model 2	6.1	2.5–14.8	<0.001
Model 3	6.6	2.6–16.5	<0.001
Propensity-matched population analysis	7.5	1.7–32.8	<0.001
Panel B: Intra-hospital MAE (initial hospitalisation)	**OR**	**95% CI**	**p-value**
Univariable analysis[a]	11.4	4.5–28.5	<0.001
Multivariable analysis			
Model 1	15.7	5.6–44.6	<0.001
Model 2	10.7	4.1–28.0	<0.001
Model 3	20.6	6.4–66.1	<0.001

Model 1: age, sex, main admission diagnosis, diabetes, history of cardiovascular disease before hospitalisation, known chronic kidney disease with a glomerular filtration rate <60 mL/min (yes/no), and history of cancer (yes/no). Model 2: age, sex, main admission diagnosis, systolic blood pressure, Killip class, and heart rate. Model 3: age, sex, main admission diagnosis, BMI, previous COPD or asthma (yes/no), oxygen flow rate at admission, oxygen saturation at admission, haemoglobin level at admission, and intravenous diuretic treatment (yes/no). Intra hospital MAE: Intra hospital major adverse events (initial hospitalisation): death, resuscitated cardiac arrest and cardiogenic shock. Abbreviations: HR: Hazard ratio; OR: Odds ratio; CI: confidence interval; CO: carbon monoxide; BMI: body mass index; COPD: chronic obstructive pulmonary disease; MAE: in-hospital major adverse event. Panel A: HR (95% CI) of CO level >11 ppm and, 1-year death in univariable and multivariable analysis with model 1, 2 and, 3 and, propensity-matched population 1:1. Panel B: OR (95% CI) of CO level >11 ppm and intra hospital MAE (initial hospitalisation) in univariable and, multivariable analysis with model 1, 2 and, 3. [a]Adjusted on age and sex.

Table 2: **Univariable and multivariable analysis of CO level >11 ppm and 1-year death and MAE.**

likelihood of the model compared to traditional risk factors of 16.3 (Global $\chi 2$: 76.6–92.9; LR-test with $p < 0.001$). Notably, the addition of both CO > 11 ppm and smoking together exhibited the same likelihood of the model compared to a model including only CO > 11 ppm (Global $\chi 2$: 92.9 for both).

Discussion

In this prospective study of a multi-centre cohort of consecutive patients admitted to ICCUs for acute cardiac events with systematic assessment of expiratory CO level on admission, we found that elevated expiratory CO levels were strongly and independently associated with a 6-fold increase of 1-year death in active smokers with a cut-off value of CO > 11 ppm. Elevated CO levels were associated with a 10-fold increase in-hospital MAEs. In the overall population of patients, a CO > 11 ppm but not smoking was associated with a significant increase in 1-year death. Finally, the incremental prognostic value of CO was better than smoking for determining death in the overall population. There was no interaction for this association with geographic regions of the centres, socio economic status or other parameters of smoking consumption.

This is the first study to describe the association between elevated CO level and the prognosis of smokers hospitalised for an acute cardiac event. A potential relationship between elevated CO levels and the prognosis of cardiac events has been suggested in 3 previous studies; Cohen et al. found an increased rate of fatalities among cases of myocardial infarction during periods of

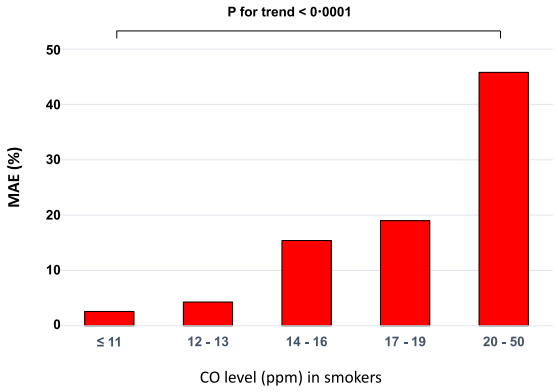

Fig. 3: **Rate of in-hospital MAE in active smokers according to CO level**. First bar is smokers with CO level ≤11 ppm (threshold found–n = 260). The other bars are quartiles of the population of smokers with CO > 11 ppm: 12–13 ppm; 14–16 ppm; 17–19 ppm; 20–50 ppm. Abbreviations: CO: Carbon monoxide; MAE: in-hospital major adverse event.

high CO pollution[13]–Leikin et al. correlated carboxyhaemoglobin levels with acute cardiac complaints in patients presenting at an emergency department.[14] Finally, Elsasser et al. found that patients with myocardial infarction and elevated carboxyhaemoglobin have more arrhythmias and higher creatine kinase levels.[15]

CO's affinity for haemoglobin is more than 200 times that of oxygen.[4] CO causes hypoxia by forming carboxy-haemoglobin and shifting the oxy-haemoglobin dissociation curve to the left with even relatively low amounts of inhaled carbon monoxide.[4] The World Health Organisation has indicated that a CO level >50 ppm for 30 min, >25 ppm for 1 h or >10 ppm for 8 h can be associated with significant medical damage.[16] Our CO level threshold >11 ppm is in the range of CO poisoning.

The effect of CO poisoning on the cardiovascular system have been largely described; elevated CO levels are associated with myocardial injury, reduced left ventricular function and cardiovascular death.[17–19] The excess of mortality found in our study in patients with elevated CO levels could result in myocardial injury from CO poisoning with tissue hypoxia as well as damage at the cellular level. Then, the coexistence of CO poisoning with an acute cardiac event could easily explain the initial excess of events found in our study. It is important to notice that there was a strong relationship between CO level, MAE and the delay of last cigarette but not with the number of packs year suggesting that CO has a direct role more than smoking history. Indeed, we found that CO level was the only "smoking related parameter" associated with 1-year mortality.

The increased rate of death during the months following the initial event could be explained in many ways: first, a greater severity of the initial event linked to CO poisoning could be followed with a higher rate of subsequent events during follow-up. Second, it has been shown in several studies that the rate of tobacco abstinence after discharge for an acute event is low ranging from 16 to 45%.[20,21] Patients with elevated CO levels also have the highest dependence scores—they probably find it harder to stop and likely continue to smoke more heavily after discharge, leading to an even higher death rate in the longer term. The occurrence of a new event could also be associated with a higher rate of death due to another concomitant CO poisoning. Third, we cannot exclude that chronic CO poisoning could induce myocardial injury per se and subsequent events in patients with previous cardiac disease. For all those mechanisms, it is important to remember that changing smoking behaviour after an acute cardiac event in those patients would have a strong impact to reduce death during follow-up.

It is important to notice that we found no significant difference in the prognosis of active smokers vs. non- or former-smokers. It is important to remember that smokers have a lower risk profile (Table 1): active smokers are younger and have less diabetes, hypertension and known renal failure compared to non-smokers. Interestingly, we found (eFigure 4) that smokers with a CO ≤ 11 ppm had a lower rate of events compared to non-smokers. The direct impact of smoking on the prognosis of patients presenting with acute cardiac events remains controversial; in acute myocardial infarction, some studies have shown either decreased, either improved survival in smokers after acute coronary syndrome described as "Smoker's Paradox".[2] Our results could provide a better understanding of this "smoker's paradox" phenomenon. First, we confirm that in our study active smokers are younger with less comorbidities including diabetes, dyslipidaemia, hypertension, and chronic kidney disease. On the other hand, elevated CO levels could be associated with more events in some smokers. The population of smokers could therefore be divided into 2 groups: i) active smokers with a low CO level who have a better prognosis, and ii) active smokers with a high CO level who have a poorer prognosis. These results highlighting potentially two patterns of active smokers could explain some discrepancies observed in the prior studies concerning the impact of smoking on the prognosis in patients with acute myocardial infarction. However, the concept of "smoker's paradox" remains complex and other additional studies will need to continue to investigate these hypotheses.

Expiratory CO testing measures the amount of CO in expired breath in ppm corresponding to the percent of carboxy-haemoglobin. It is commonly used as a marker for smoking status.[6] Although environmental sources of CO exist (e.g., from the incomplete combustion of carbon, such as motor vehicle exhaust, pollution or malfunctioning furnaces during the winter), tobacco smoking is the primary source of elevated CO levels in

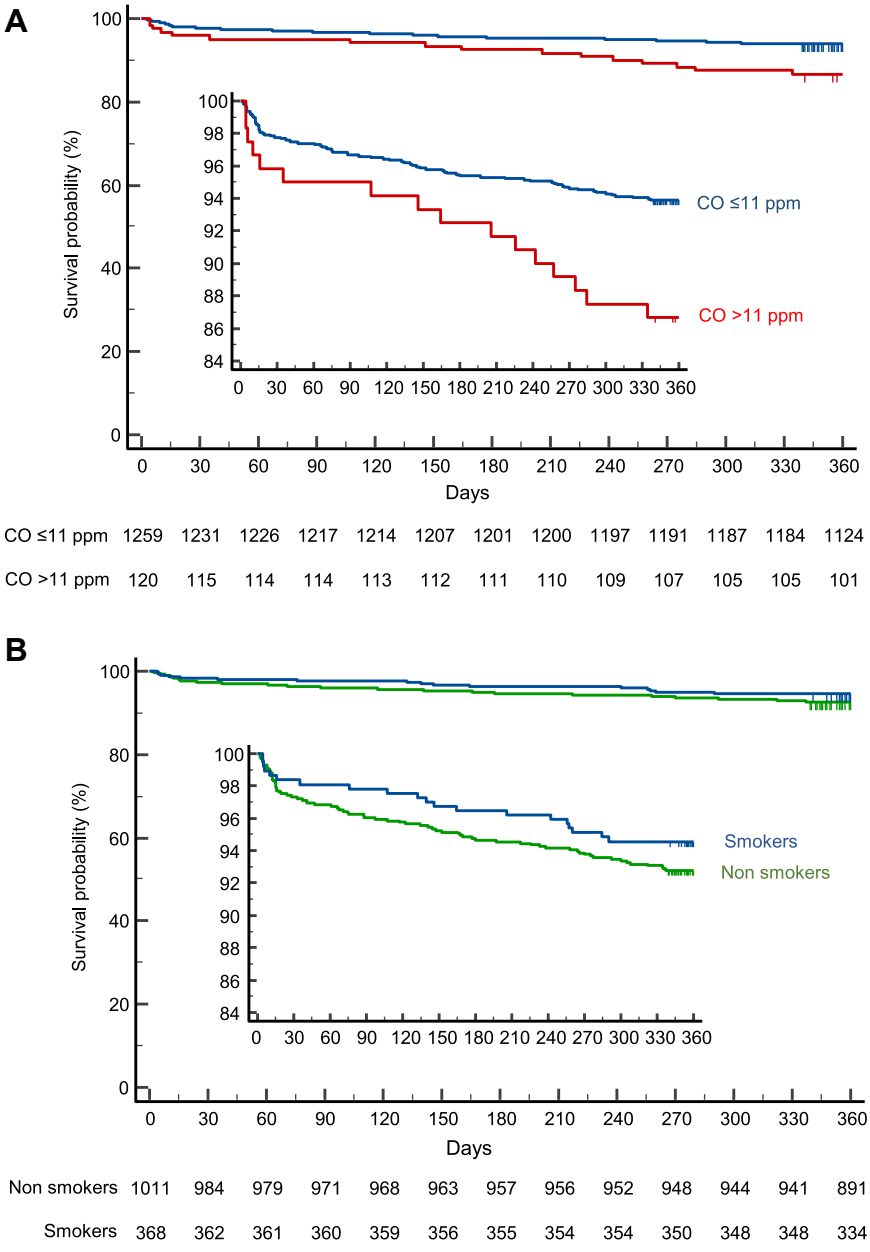

***Fig. 4:* Kaplan Meier curve of all-cause death in the overall population according to CO level cut off and, smoking status**. Panel A: CO level >11 ppm vs. CO level ≤11 ppm. Panel B: Active smokers vs. non or former smokers. Abbreviations: CO: carbon monoxide; ppm: parts per million; HR: Hazard ratio; CI: confidence interval.

the bloodstream.[4,5] CO level in expired air is correlated with Fagerström score and the delay of last cigarette but interestingly not the number of packs year.[6] Active smokers can also demonstrate low CO levels.[22,23] Interestingly, expiratory CO measurement is very easy to perform just after admission to ICCU and is certainly a more objective parameter concerning heaviness of smoking than self-reported consumption. Smoking habits can vary greatly—individuals can inhale smoke deeply or not; they can smoke the cigarettes from beginning to end or let them burn in the ashtray; they can smoke in a small, non-ventilated room or outside.[24] Therefore, expiratory CO value reflects the number of cigarettes smoked but also the intensity of inhalation and the delay since last cigarette consumption. Moreover, in our study, although CO measurements were performed within 2 h after entry to the ICCU, the patients may have spent several hours in the emergency

department before admission in cardiology. Indeed, we found that elevated CO levels were associated with shorter times since the last cigarette and CO measurement. Finally, patients who experienced cardiological symptoms before hospitalisation may have reduced their consumption in the days before hospitalisation.[19]

Regarding therapeutic opportunities apart from quitting smoking, an initial treatment with oxygen could be discussed in the population of smokers with CO > 11 ppm. The half-life of carboxyhaemoglobin is 4–6 h when a patient is breathing room air, 40–80 min when breathing 100% oxygen and only 15–30 min when breathing hyperbaric oxygen.[4] However, oxygen therapy in this setting must be carefully evaluated.[25,26] Finally, smokers with elevated CO levels may need a more significant follow-up due to their excess risk of subsequent events and we can imagine that changing smoking behavior after an acute cardiac event through CO measurement could have a strong impact to reduce death during follow-up.

This study has some limitations. First, the mean burden of missing data on all of the collected variables was 2.5%, which did not seem to necessitate the use of a missing data imputation method for the analyses. Second, we cannot exclude the theoretical possibility that the knowledge of elevated CO levels could change the medical management of patients, although such a possibility appears extremely unlikely. Notably, the rate of patients treated with oxygen (median flow 3 l/min) at admission was similar in patients with CO levels ≤11 ppm and those with CO levels >11 ppm (17.2% and 16.5% of patients, respectively; p = 0.90) and there was no interaction of oxygen treatment with prognosis. Third, residual confounding factors cannot be eliminated in an observational study. We did not identify other external factors that may affect the development of acute cardiovascular events or smoking behaviour during the inclusion period. However, we cannot exclude some seasonal variations in tobacco consumption. In addition to CO, other compounds are released in large amounts during smoking including reactive oxygen species, reactive aldehydes, and ketones. Although that the timing of CO measurement could have influenced the results, we did not collect the time between arrival in ICCU and CO measurement to carefully investigate this interaction. While the CO level varies over time, it is important to emphasize that this study only allows us to evaluate the prognostic value of the initial CO measurement based on the assumption of a constant CO level throughout the period at risk. This therefore represents a limitation in the interpretation of the results of this study. The analysis was performed on smokers because elevated values of CO (>95% percentile of the values of non-smokers) were only found in smokers. Moreover, we found that, in the population of smokers, there was a large distribution of CO levels. We analysed the comparative effect of CO and smoking in the last part in the general population to compare the respective effect of smoking and CO. Although smoking behaviour after hospital discharge constitutes a known prognostic factor, in this study we did not collect data related to smoking behaviours during the follow-up which constitutes an important limitation to the conclusions of this study. We cannot exclude that smokers who continue to smoke are probably physically or genetically more resistant to the harms of smoking. Of note, the number of females in the active smokers group is too small to perform gender difference analysis regarding the prognostic impact of the expiratory CO level. Finally, given that the data on nation-wide activity in ICCUs in France indicated an average ICCU admission rate of 45 patients per centre over the 15-day inclusion period of the study, the theoretical recruitment would have been 1755 patients across 39 centres.[27] Therefore, our screening of 1904 patients was consistent with a systematic and consecutive selection.

In conclusion, this prospective multi-centre observational study of consecutive patients admitted to ICCUs for acute cardiac events shows that elevated CO levels is strongly and independently associated with a 6-fold increase of all-cause death and 10-fold increase of in-hospital MAE. CO level >11 ppm has an incremental prognostic value above smoking, improving model discrimination and reclassification for death. Further randomised clinical trials are warranted to assess the possibility of a more aggressive management strategy in active smokers hospitalised in the ICCU with a high CO level.

Contributors

Concept and design: Jean-Guillaume Dillinger; Théo Pezel, Patrick Henry.

Data collection: Clément Delmas, Guillaume Schurtz, Antonin Trimaille, Nicolas Piliero, Claire Bouleti, Benoit Lattuca, Stéphane Andrieu, Julien Fabre, Reza Rossanaly Vasram, Jean-Claude Dib, Victor Aboyans, Charles Fauvel, Francois Roubille, Edouard Gerbaud, Albert Boccara, Etienne Puymirat.

Data curation: Solenn Toupin, Theo Pezel, Eric Vicaut.

Data analysis and interpretation: Jean-Guillaume Dillinger, Théo Pezel, Solenn Toupin, Eric Vicaut, Patrick Henry. Jean-Guillaume Dillinger and Patrick Henry have verified the underlying data.

Writing: Jean-Guillaume Dillinger; Théo Pezel, Patrick Henry.

All authors read and approved the final version of the manuscript.

Data sharing statement

The anonymised data supporting the findings of this study were collected using Cleanweb™ software and will be available from the corresponding author upon reasonable request.

Declaration of interests

Jean-Guillaume Dillinger, Théo Pezel, Clément Delmas, Guillaume Schurtz, Antonin Trimaille, Nicolas Piliero, Claire Bouleti, Benoit Lattuca, Stéphane Andrieu, Julien Fabre, Reza Rossanaly Vasram, Jean-Claude Dib, Charles Fauvel, Albert Boccara, Etienne Puymirat, Solenn Toupin, Eric Vicaut and Patrick Henry report no conflict of interests.

Victor Aboyans reports consulting fees from Astra-Zeneca, honoria for lectures or presentations from Boehringer, Bayer and Novonordisk, participation on a DSMB for Bayer, member of a committee of the European Society of Cardiology and of the French Society of Cardiology.

Francois Roubille reports honoria for lectures or presentations from Astra Zeneca, Boehringer, Astra Zeneca, Vifor, Bayer, Pfizer, Novartis, Servier, Novo-Nordisk, Air liquid, Abbott, QuidelOrtho, GSK.

Edouard Gerbaud reports consulting fees from Terumo Corporation, Abbott vascular and honoria for lectures from Servier.

Authors had full access to all the data in the study and, accept responsibility to submit for publication.

Acknowledgements

Fondation "Coeur & Recherche" gave an unrestricted grant for this work.

The authors would like to thank all the patients and, investigators of the centres (eTable 12) for their participation and, the team of the "Unité de Recherche Clinique Fernand-Widal" (in particular, Brahim Mohamed Elarbi, Lise Schaub, and, Nadhira Bennacer) for their help in the design and, implementation of this study. We would like to thank Manveer Singh, Simon Pamart, Emmanuel Gall, and, Antoine Lequipar for their useful participation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102401.

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