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Trends in prevalence and outcomes of acute coronary syndrome associated with cocaine consumption: The RUTI-cocaine study

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ABSTRACT

Background: The use of cocaine as a recreational drug has increased over recent years. In this study, we aimed to analyze the prevalence, and in-hospital and long-term outcomes of acute coronary syndrome (ACS) associated with cocaine consumption (ACS-ACC).
Methods: A prospective observational registry of young patients hospitalised with ACS from 2001 through 2015, we analysed ACS-ACC temporal trends, clinical characteristics, and major adverse cardiovascular events (MACE) during long-term follow-up.
Results: There were 8153 admissions with ACS, of whom 864 patients were ≤50-years-old; 59 patients (6.8%) presented with ACS-ACC. The prevalence of patients with a history of cocaine consumption increased to maximum of 18% in 2008 with no variations thereafter ($r = 0.74$, $p < 0.001$). The ACS-ACC incidence increased over time from 5% to 9% ($r = 0.25$, $p = 0.07$). Compared to patients with ACS not associated with cocaine consumption, the ACS-ACC exhibited a higher incidence of in-hospital ventricular tachycardia (16.9% *vs* 4.7%, $p < 0.001$) and trends to in-hospital mortality (3.4% *vs* 1.0%, $p = 0.097$); during a median follow-up of 5.6 years, ACS-ACC had higher risk of MACE (HR 1.83; 95% CI 1.04–3.25, $p = 0.038$), higher risk of myocardial infarction (HR 2.39, 95% CI 1.02–5.60, $p = 0.045$), and higher risk of cardiovascular mortality (HR 6.26; 95% CI 1.67–23.43, $p = 0.006$).
Conclusion: Young patients with ACS-ACC carry a high risk of short and long-term major adverse cardiovascular events. Over the 15-year study period, we observed an increasing prevalence of this entity. This trend and its outcomes underscore the need for increased awareness and improved management strategies.
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1. Introduction

Over recent years, Europe has witnessed a rise in the use of cocaine as a recreational drug, such that it is now the most consumed drug after cannabis. Data from the European Monitoring Centre for Drugs and Drug Addiction indicate that 15.6 million European inhabitants have used cocaine at some point in their lives, and that 3.4 million have done so in the last year [1], respectively representing 10.2% and 3.7% of the Spanish population between 15 and 65 years of age [2].

Extensive research has examined the cardiovascular toxicity of cocaine. Cocaine usage increases the risk of acute myocardial infarction [3], regardless of the consumer's cardiovascular risk factors and extent of coronary artery disease [4]. Additionally, acute coronary syndromes (ACS) associated with recent cocaine use (ACS-ACC) seem to have poorer in-hospital outcomes compared to ACS not related to cocaine consumption [5]. However, no contemporary studies have investigated the prevalence and long-term prognosis in such cases.

In our present study, we aimed to define temporal trends in the prevalence of ACS-ACC over a 15-year period. We further investigated the in-hospital and long-term outcomes in such cases compared to young patients with ACS not related to cocaine consumption.

2. Methods

The RUTI-cocaine Study was a prospective observational study that examined cocaine use among young (≤50-years-old) consecutive ACS patients admitted to our critical cardiovascular care unit between January 2001 and April 2015. Our institute is a tertiary university hospital having the only critical cardiovascular care unit within a well-defined geographical area serving ~850,000 inhabitants in the northern Barcelona metro area. The study protocol included a questionnaire about cocaine use and frequency of use. Additionally, the patients' urine was qualitatively tested for cocaine use within 48–72 h

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of admission using immunoenzyme analysis (Dimension Flex Reagent Cartridge; Siemens Healthcare Diagnostics Ltd., Frimley, Camberley, UK).

The specific protocol at admission has been reported elsewhere [5]. Briefly, demographic and clinical data were collected. If a patient had multiple hospital admissions due to ACS during the study period, only the first admission episode was included in analysis. Two groups were defined based on patients' recent cocaine consumption prior to admission for ACS [6]. The acute coronary syndrome associated with cocaine consumption (ACS-ACC) group included patients with a positive cocaine urine test or who declared they were current users upon admission (irrespective of cocaine urine test result). The acute coronary syndrome not associated with cocaine consumption (ACS-NACC) group included patients with a negative urine test for cocaine and who described themselves as non-users, former users, or occasional users.

We define ventricular tachycardia as the appearance of sustained ventricular tachycardia (30 s) or that requires treatment with cardioversion or antiarrhythmics drugs.

Cardiac Death was defined as documented death by cardiac cause such as myocardial infarction, heart failure, cardiac tamponade or sudden death. Same definition is used for in-hospital and follow-up phase.

The main clinical outcome was the composite of major adverse cardiovascular events (MACE), which included all-cause death, readmission due to myocardial infarction, and revascularization by coronary artery bypass grafting or percutaneous coronary intervention (PCI) during follow-up. Cardiovascular mortality was also analysed. Follow-up events were obtained from searching the patients' electronic clinical records, from death registers, or by contacting the patient's relatives. All participants gave their informed consent, and this study was performed in compliance with the Helsinki Declaration, and was evaluated by the local Ethics Committee.

2.1. Statistical analysis

Categorical variables are presented as number and percentage, while continuous variables are presented as mean ± standard deviation or median and interquartile range based on whether they have a normal distribution. To compare differences between study groups, we performed univariate analysis using the Student's *t*-test for continuous variables, the Mann-Whitney *U* test for non-normal variables, and the chi-squared test or Fisher's exact test for categorical variables.

To identify changes over time in the prevalence of cocaine consumption according to clinical history and the prevalence of ACS-ACC, we constructed a fractional polynomial regression model and a simple linear regression model, using the year of admission as the independent variable [7]. We performed Cox proportional hazards regression analysis in the univariate and multivariate mortality and MACE analyses. To evaluate the proportional hazards assumption, we assessed the Schoenfeld residuals. Considering death from any cause as a competing event of readmission due to ACS and revascularization, we used a multivariate competing risk model to obtain the HRs for readmission due to ACS and revascularization. The regression models incorporated the following variables: age, sex, arterial hypertension, diabetes mellitus, dyslipidaemia, previous myocardial infarction, Killip-Kimball class, frequency of anterior wall myocardial infarction, and left ventricular ejection fraction. We plotted the adjusted Kaplan-Meier and cumulative incidence curves (using the competing risk model). Statistical analyses were performed using the statistical package IBM-SPSS version 22 (SPSS Inc., Chicago, Illinois, United States) and STATA V.13.0 (College Station, Texas, USA). A p value of <0.05 was considered significant.

3. Results

Over the 15-year study period, there were 8153 admissions with ACS. Of these patients, 1002 patients were ≤50-years-old at the moment of the first admission during the study period, and 864 (86.2%) underwent cocaine urine testing. Within this group, 59 patients (6.8%) presented with ACS-ACC; in 52 patients (6.0%) the cocaine urine test was positive and 7 patients (0.8%) declared being current users upon admission. Patient inclusion is shown in a flow-chart (see online Fig. A). A total of 151 patients (17.5%) reported having consumed cocaine at least once in their lifetime. We determined the evolution of cocaine consumption in patients with ACS (Fig. 1A), and trends in ACS-ACC prevalence over the study period (Fig. 1B). Fractional polynomial regression analysis revealed that cocaine use among patients with ACS strongly increased from 2001 to 2008, reaching a maximum prevalence of 18%, and then showed no significant variations from 2009 to 2014 (coefficient 0.015, 95% CI 0.010–0.025; $p = 0.005$).

Overall, the incidence of ACS-ACC increased from 5% to 9% during the 15-year study period ($r = 0.25$, $p = 0.07$).

Table 1 shows the patients' baseline clinical characteristics. Patients with ACS-ACC were younger, and more frequently had a history of smoking, high-risk alcohol consumption, and use of other drugs. This group also showed a higher proportion of patients with ST segment elevation as the initial presentation, and less frequently had a history

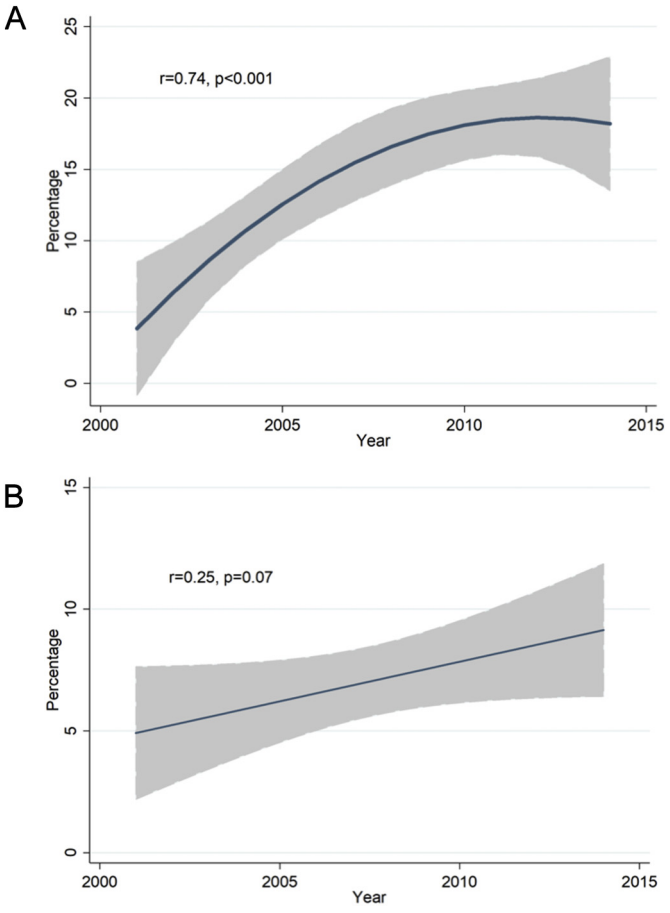

Fig. 1. A: Temporal trends in the prevalence of patients with a previous history of cocaine consumption. Regression line with 95% confidence interval (shaded areas). B: Secular trends in the prevalence of acute coronary syndrome associated with cocaine consumption. Regression line with 95% confidence interval (shaded areas).

of dyslipidaemia. Infarct location and Killip-Kimball classification were similar between patients who were using cocaine before admission and those who were not. During admission, patients with ACS-ACC showed a significantly higher incidence of ventricular tachycardia (16.9% *vs* 4.7%, $p < 0.001$) and trends to in-hospital mortality (3.4% *vs* 1.0%,$p = 0.097$). Patients with ACS-ACC also exhibited higher in-hospital mortality; however, this difference was not statistically significantly different (3.4% *vs* 1.0%, $p = 0.097$). Compared to the ACS-NACC group, the ACS-ACC group less commonly received β-blocker therapy during admission (40.7% *vs* 78.1%, $p < 0.001$) and after discharge (59.6% *vs* 84.2%, $p < 0.001$), and were more frequently treated with calcium channel blockers during admission (30.5% *vs* 8.0%, $p < 0.001$) and at discharge (28.1% *vs* 10.9%, $p < 0.001$). No significant differences were found between other pharmacological treatments (see online Fig. B). Among patients who initially presented with STEMI, reperfusion therapy was performed in 82% of SCA-ACC and 87.5% in SCA-NACC, $p = 0.264$, being primary angioplasty the main reperfusion therapy over fibrinolysis in both groups (70.7% *vs.* 29.3% in ACS-ACC and 78.5% *vs.* 21.5% in ACS-NACC).

Among all patients who underwent coronary angiography, the proportion of PCI was similar between the ACS-ACC and ACS-NACC groups (75.0% *vs* 82.1%, $p = 0.205$) while drug-eluting stents were less commonly used in ACS-ACC patients (17.6% *vs* 34.5%, $p = 0.043$).

Survival and long-term follow-up data were available for 796 of the 864 included patients, with a median follow-up of 5.6 years (interquartile range 2.9–9.2). Compared to the ACS-NACC group, patients with ACS-ACC experienced higher rates of cardiovascular mortality and myocardial infarction, and similar rates of all-cause death

Table 1
Clinical baseline characteristics of patients with ACS-ACC and ACS-NACC.

	ACS-ACC ($n = 59$)	ACS-NACC ($n = 805$)	p value
Male sex	54 (91.5)	694 (86.2)	0.248
Age (years)	42.2 (6.6)	44.1 (4.9)	0.006
History			
Current smokers	57 (96.6)	604 (75.0)	<0.001
Moderate/severe alcohol consumption	26 (44.1)	150 (18.6)	<0.001
Consumption of other drugs	13 (22)	41 (5.1)	<0.001
Hypertension	12 (20.3)	244 (30.3)	0.105
Dyslipidaemia	23 (39)	455 (56.5)	0.009
Diabetes mellitus	6 (10.2)	98 (12.2)	0.648
Peripheral artery disease	2 (3.4)	38 (4.7)	0.639
Stroke/transient ischemic attack	0 (0)	10 (1.2)	0.389
Prothrombotic disorders	1 (1.7)	37 (4.6)	0.294
Infection with HIV and/or HVC	2 (3.4)	29 (3.6)	0.932
Family history of early ischemic heart disease	13 (22)	177 (22)	0.997
Angina	7 (11.9)	117 (14.5)	0.572
Myocardial infarction	6 (10.2)	59 (7.3)	0.425
Previous PCI	5 (8.5)	25 (3.1)	0.030
Previous CABG	0 (0)	3 (0.4)	0.639
ACS characteristics			
STEMI presentation	50 (84.7)	577 (71.7)	0.030
NSTEMI presentation	9 (15.3)	228 (28.3)	0.030
Unstable angina	75 (9.3)	4 (6.8)	0.514
Q wave AMI	47 (79.7)	562 (69.8)	0.109
Anterior localization ($n = 797$)	26 (47.3)	324 (43.7)	0.941
Killip Class ($n = 788$)			0.437
Killip I–II	50 (90.9)	698 (95.2)	
Killip III–IV	5 (9.1)	35 (4.8)	
Total CPK U/L ($n = 738$), median [IQR]	1510.5 [619–4190]	1323 [505–2772]	0.401
CPK-MB U/L ($n = 736$), median [IQR]	175 [43–420]	138 [44–280]	0.310
cTnI (ng/ml) ($n = 740$), median [IQR]	30 [10–68]	22 [7.7–50.2]	0.502
LVEF (%), mean ± SD	49.9 ± 13.7	52 ± 10.9	0.278
In-hospital complications			
Ventricular tachycardia	10 (16.9)	38 (4.7)	<0.001
Ventricular fibrillation	6 (10.2)	58 (7.2)	0.401
Atrial fibrillation	4 (6.8)	22 (2.7)	0.079
Complete atrioventricular block	1 (4.8)	20 (2.5)	0.704
Acute intraventricular conduction disturbances	4 (6.8)	12 (1.5)	0.004
Epistenocardiac pericarditis	5 (8.5)	19 (2.4)	0.006
In-hospital mortality	2 (3.4)	8 (1.0)	0.097

Data are presented as n (%) unless otherwise indicated. ACS = acute coronary syndrome. ACS-ACC = acute coronary syndrome associated with cocaine consumption. ACS-NACC = acute coronary syndrome non-associated with cocaine consumption. HIV = human immunodeficiency virus. HCV = hepatitis C virus. PCI = percutaneous coronary intervention. CABG = coronary artery bypass grafting. STEMI=ST-segment elevation myocardial infarction. AMI = Acute Myocardial Infarction. CK = creatine kinase. CK-MB = creatine kinase MB isoenzyme. cTnI = troponin isoenzim I. IQR = interquartile range.

and revascularization. When these events were considered mutually exclusive, the clinical composite end-point occurred in 24.6% ($n = 14$) of patients with ACS-ACC and 13.9% ($n = 103$) of patients with ACS-NACC (see Table online). Compared to the ACS-NACC group, patients with ACS-ACC showed a significantly higher risk of MACE (HR 1.83; CI 95% 1.04–3.25, $p = 0.038$) after adjustment for age, sex, arterial hypertension, diabetes, dyslipidaemia, previous myocardial infarction, Killip-Kimball class, anterior infarct location, and left ventricular ejection fraction. Similarly, patients with ACS-ACC showed significantly higher risks of myocardial infarction (HR 2.39; CI 95% 1.02–5.60, $p = 0.045$) and cardiovascular mortality (HR 6.26; 95% CI 1.67–23.43, $p = 0.006$) (Figs. 2 and 3).

4. Discussion

Our analysis of the RUTI-cocaine Study revealed that from 2001 to 2015, there was a trend of increasing prevalence of young patients with ACS-ACC, who had a significantly worse adverse prognosis over long-term follow-up compared to patients with ACS-NACC.

Cocaine consumption constitutes a serious health problem with a negative impact on society. A study of the US CARDIA registry reported that 35% of individuals under 45 years of age had used cocaine at some point in their lives, and that 6% had ≥100 lifetime episodes of cocaine exposure and could thus be considered addicts [8]. Likewise, cocaine use appears to be increasing in European countries where the incidence of cocaine-related problems has doubled or tripled since the 1990s [9]. The Spanish Observatory of Drug Addiction conducted the EDADES survey, and reported that subjects of 15–65 years of age in the Spanish population showed a progressive increase in the prevalence of cocaine use up to 2008, with a subsequent plateau [2]. Our present study showed similar trends in cocaine consumption within the young Catalan population treated for ACS.

The relationship between cocaine consumption and myocardial infarction has been extensively investigated, revealing that several pathobiological insults promote the development of myocardial ischemia. Cocaine users have a six-fold greater risk of ACS than non-cocaine users even after adjustment for coronary artery disease [4], indicating that cocaine is one of the most powerful triggers of infarction [10]. Among patients with ACS, there is an estimated 6% prevalence of ACS-ACC [11]. Our present analysis showed that 17.5% of young patients admitted for ACS had a history of cocaine use, with an increasing prevalence over time, and recent cocaine consumption detected in 6% of patients at the time of admission.

Our present results also indicated that compared to ACS patients who had not previously consumed cocaine, patients with ACS-ACC exhibited a higher incidence of habits related to an unhealthy lifestyle (*e.g.* tobacco use, high-risk alcohol consumption, and use of other illicit drugs), lower incidence of classic cardiovascular risk factors, and a lower age. Studies of other series of patients with ACS-ACC also report a lower prevalence of cardiovascular risk factors [11], and a predominance of smoking and dyslipidaemia [12]. The presently observed higher proportion of STEMI among patients with ACS-ACC is also consistent with a previously reported initial clinical profile at admission among young patients with ischemic cardiomyopathy [12].

With regards to cardiovascular complications during admission, ACS-ACC patients showed a higher incidence of acute intraventricular conduction disturbances and epistenocardiac pericarditis, which are both complications traditionally associated with larger infarctions. These results are consistent with the findings of the first ACS-ACC series [13], with ventricular tachycardia being the main complication occurring within the first 12 h of admission [14]. It is hypothesized that the higher ventricular tachycardia incidence may be related to greater adrenergic stimulation by cocaine or to lower use of β-blocker therapy during the acute phase. Our present results also revealed a trend towards higher in-hospital mortality among patients with ACS-ACC, with a rate of almost 4% compared to previously estimated in-hospital mortality of <2% [6], but ranging from 0% [14] to 4.3% [11]. Notably, the greater proportion of in-hospital complications in this population is associated with longer hospital stays and higher cost burdens among young patients with ACS-ACC [15].

Our present analysis also revealed that patients' recent cocaine consumption prompted differential use of conventional anti-ischemic and vasodilator treatment of ACS in this population. During the acute phase, patients with ACS-ACC less commonly received treatment with β-blocker therapy and were more often prescribed calcium channel antagonists. This reduced use of β-blockers is consistent with findings in current series of ACS-ACC patients [11]. Despite the strong evidence favouring the β-blocker therapy in patients with ACS [16], such treatment is discouraged in the setting of recent cocaine consumption [17] due to the risk of coronary vasoconstriction secondary to unopposed α-receptor stimulation [18]. This is a controversial issue due to a lack of contemporary evidence regarding the safety and/or efficacy of β-blocker therapy in this clinical setting [19]. Another striking difference

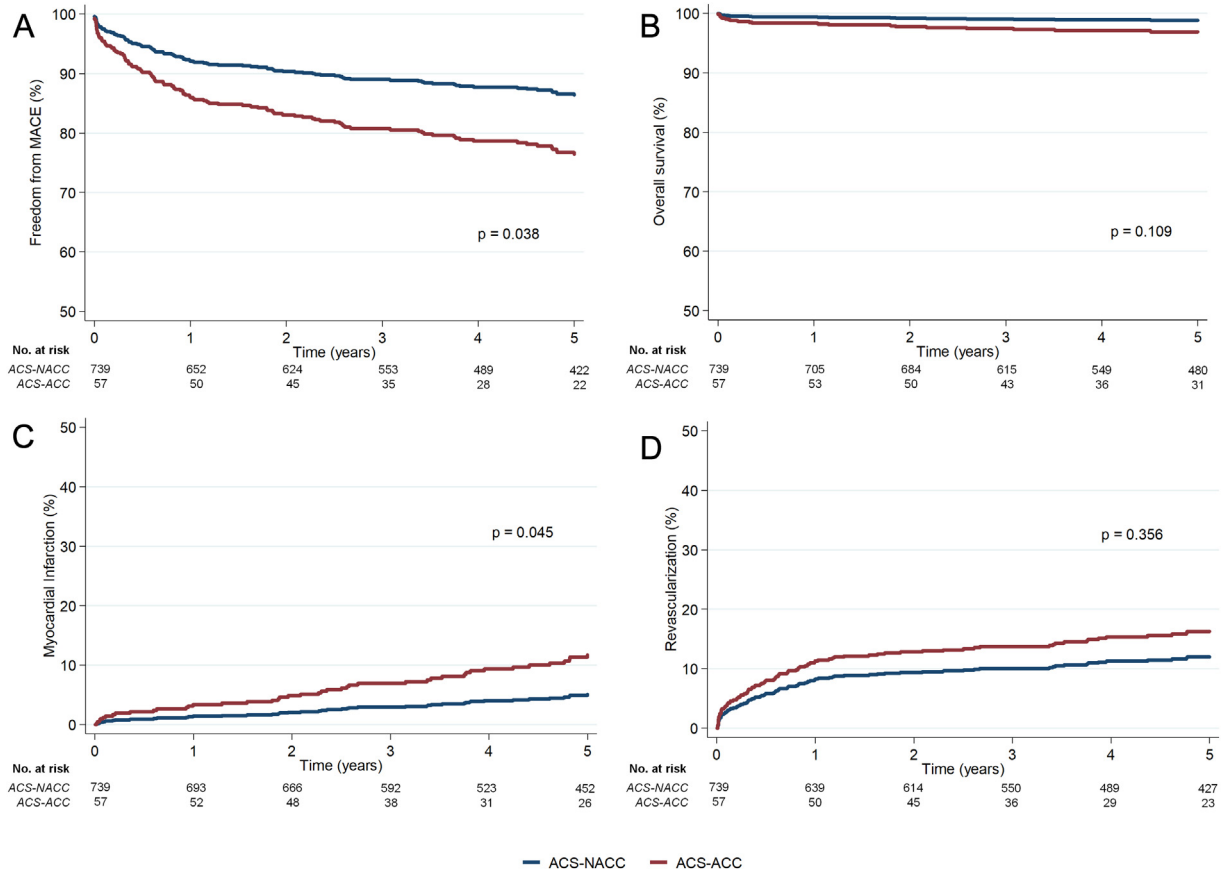

Fig. 2. Clinical outcomes of patients with acute coronary syndrome associated with cocaine consumption (ACS-ACC) and patients with acute coronary syndrome not associated with cocaine consumption (ACS-NACC). (A) Cumulative probability of major adverse cardiovascular events (MACE). (B) Cumulative survival. (C) Cumulative incidence of readmission due to myocardial infarction. (D) Cumulative incidence of revascularization. MACE: composite endpoint of all-cause death, infarction, and revascularization.

in the treatment of this population was the reduced use of drug-eluting stents, which was indicated based on the physician's discretion upon admission [11]. This was likely related to the increased risk of thrombosis in cocaine users [20] or to the propensity of these patients to discontinue medication, including antiplatelet therapy [21].

Our long-term follow-up results showed that subjects with ACS-ACC were exposed to a higher risk of MACE, mainly due to an elevated risk of myocardial infarction. Previous research has also demonstrated this increased risk; they reported 30-day readmission rates of 38% among ACS-ACC patients [22], and higher mortality rates were observed (of 18 to 29%) among subjects with ACS-ACC [11,23]. After confounding factors adjustments double mortality was found in ACC-ACS patients compared to non-consumers for all causes of death and cardiovascular mortality in long follow up [23]. The adverse long-term prognosis for ACS-ACC patients may be partly explained by the early and accelerated development of atherosclerosis secondary to cocaine consumption, as well as by possible low adherence to pharmacological treatment. In registries of cocaine consumption among different populations, the continuation of cocaine use is a recognized risk factor for recurrence and myocardial infarction during follow-up [24] and cardiovascular accident [25]. These hypotheses may also explain the five-fold higher rates of all-cause mortality observed among cocaine users compared to the general population [26].

The major limitations of this study are inherent to its observational nature. Moreover, as this was a single-centre study, our report cannot

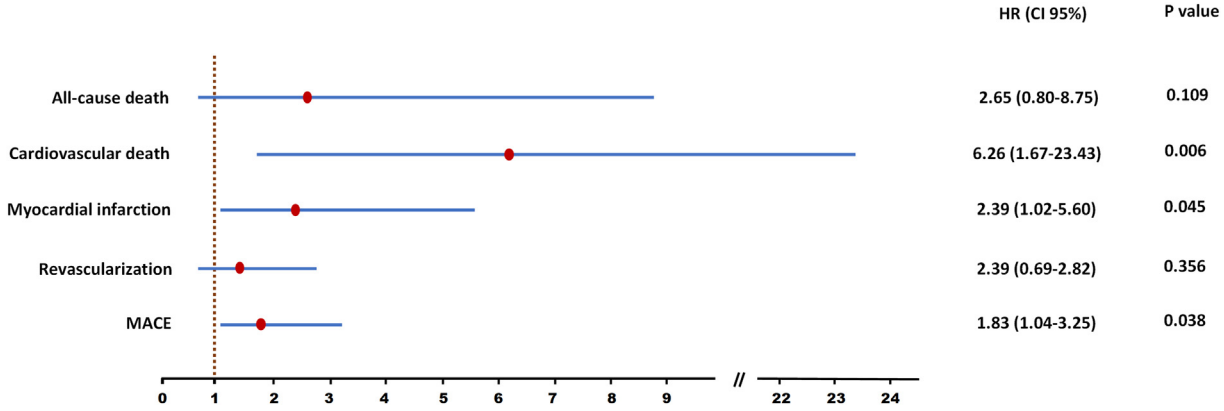

Fig. 3. Forrest plot indicating hazard ratio (HR) and confidence interval (CI) for clinical outcomes in patients with acute coronary syndrome associated with cocaine consumption compared to patients with acute coronary syndrome not associated with cocaine consumption.

provide a comprehensive overview of the magnitude of ACS-ACC. Rather, it reflects our experience in a real-life critical cardiovascular care unit over a 15-year period during which the referral geographical areas have remained stable. While the long recruitment period enabled us to assess the evolution of the disease prevalence over time, it may also introduce bias due to the evolution of cardiac treatments. In order to evaluate the impact of this bias we performed an exploratory analysis and grouping the patients according to the date of admission (during the first 8 years and during the last 8 years of the study period), we analyze the comparative incidence of follow-up untoward cardiac events. For those patients admitted during the first 8 years, MACE rates were higher in ACS-ACC patients (0.32 events/1000 patient-years; 95% CI: 0.19–0.55) compared with ACS-NACC patients (0.08 events/1000 patient-years; 95% CI: 0.06–0.09). In the group of patients admitted during the last 8 years of the study period, MACE rates were also higher in ACS-ACC patients in comparison with ACS-NACC patients (0.11 events/1000 patient-years; 95% CI: 0.05–0.25 and 0.08 events/1000 patient-years; 95% CI: 0.06–0.10, respectively).

Another limitation is based on how we established the patients' recent or previous cocaine use. The prevalence of cocaine use determined by hair testing is reportedly 3- to 5-fold higher than that estimated by population surveys or interviews [27,28]. However, in this study we used a cocaine urine test and anamnesis, as these were most affordable methods for daily clinical practice. Additionally, we could not comprehensively evaluate the rates of discontinuation of cocaine consumption in all patients after the index event, leaving the impact of discontinuation on prognosis unknown as well as the lack of knowledge about medical therapy during follow-up.

Lost patients during the long follow-up can be a limitation when drawing conclusions about long-term events.

Despite these limitations, our present cohort is one of the largest reported to date, and comprises a representative population of young patients with ACS-ACC. The limitations do not preclude easy extrapolation and application of the results to hospitals in the metropolitan areas of large European cities.

5. Conclusions

Overall, our present analysis of the RUTI-cocaine Study revealed an increased prevalence of cases of ACS-ACC across a 15-year period. These patients exhibit a high risk of in-hospital cardiovascular complications, and have an adverse prognosis during long-term follow-up. This new evidence underscores the need to develop appropriate therapeutic and follow-up strategies that can modify this ominous prognosis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.026.

Declaration of interests

All the authors declare not having any conflict of interest.

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