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Clinical Research

Prevalence of psychoactive drug use in patients hospitalized for acute cardiac events: Rationale and design of the ADDICT-ICCU trial, from the Emergency and Acute Cardiovascular Care Working Group and the National College of Cardiologists in Training of the French Society of Cardiology☆

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Abbreviations: EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; FACE, Fast Alcohol Consumption Evaluation; ICCU, intensive cardiac care unit; MACE, major adverse cardiovascular events; QFR, quantitative flow ratio.

☆ Tweet: The ADDICT-ICCU trial, an original prospective study about the prevalence of physchoactive drug use in patients admitted to intensive cardiac care unit! Twitter address: @PezelT.

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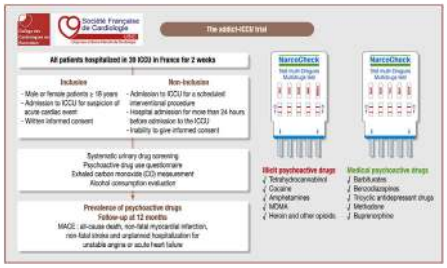
HIGHLIGHTS

- Psychoactive drug use is a public health concern.
- Psychoactive drug use is prevalent and increases the risk of CV events.
- Psychoactive drug use can induce acute CV events.
- Prevalence of psychoactive drug use in patients hospitalized in an ICCU is unknown.
- ADDICT-ICCU will assess this prevalence by systematic urinary drug screening.
- Consecutive patients hospitalized in ICCU for an acute CV event will be screened.

GRAPHICAL ABSTRACT

Study design of the ADDICT-ICCU study, a nationwide prospective multicentre study involving 39 centres throughout France, evaluating the prevalence of psychoactive drugs detected in consecutive patients hospitalized in an intensive cardiac care unit (ICCU) for an acute cardiovascular event. Detection of illicit (cannabinoids, cocaine, amphetamines, ecstasy, heroin and other opioids) and non-illicit (barbiturates, benzodiazepines, tricyclic antidepressant drugs, methadone and buprenorphine) psychoactive drugs will be performed through urine analysis using NarcoCheck® (Kappa City Biotech SAS, Montluçon, France) within 2 hours of admission to the ICCU. MACE: major adverse cardiovascular events.



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SUMMARY

Background: Psychoactive drugs, including illicit drugs, are associated with an increased rate of cardiovascular events. The prevalence and outcome of patients using these drugs at the time of admission to an intensive cardiac care unit is unknown.
Aim: To assess the prevalence of psychoactive drugs detected in consecutive patients hospitalized in an intensive cardiac care unit for an acute cardiovascular event.
Methods: This is a nationwide prospective multicentre study, involving 39 centres throughout France, including all consecutive patients hospitalized in an intensive cardiac care unit within 2 weeks. Psychoactive drug use will be assessed systematically by urine drug assay within 2 hours of intensive cardiac care unit admission, to detect illicit (cannabinoids, cocaine, amphetamines, ecstasy, heroin and other opioids) and non-illicit (barbiturates, benzodiazepines, tricyclic antidepressants, methadone and buprenorphine) psychoactive drugs. Smoking will be investigated systematically by exhaled carbon monoxide measurement, and alcohol consumption using a standardized questionnaire. In-hospital major adverse events, including death, resuscitated cardiac arrest and cardiogenic shock, will be recorded. After discharge, all-cause death and major adverse cardiovascular events will be recorded systematically and adjudicated at 12 months of follow-up.
Results: The primary outcome will be the prevalence of psychoactive drugs detected by systematic screening among all patients hospitalized in an intensive cardiac care unit. The in-hospital major adverse events will be analysed according to the presence or absence of detected psychoactive drugs. Subgroup analysis stratified by initial clinical presentation and type of psychoactive drug will be performed.
Conclusions: This is the first prospective multicentre study to assess the prevalence of psychoactive drugs detected by systematic screening in consecutive patients hospitalized for acute cardiovascular events.

1. Background

Recent studies have highlighted the increasing rates of psychoactive drug use around the world [1–4], causing an increased risk of mortality, in particular as a result of acute cardiovascular events: sudden cardiac death; acute coronary syndrome; acute heart failure; thromboembolic events; and arrhythmias [5–10].

Beyond alcohol and tobacco, these drugs include prescription psychoactive drugs (e.g. benzodiazepine or opioids) and illicit drugs. Cannabis, cocaine, ecstasy and amphetamines are the most common illicit drugs used by European adults, with a prevalence in recent years of 7.6%, 1.3%, 0.8% and 0.6%, respectively [2]. In France, the prevalence of use of any illicit drug is estimated at 11.4% of the population, ahead of Italy (10.6%), the UK (8.7%) and Germany (7.8%) [2]. Further, in France, more than 100,000 deaths per year result from the use of drugs, including alcohol, tobacco and illicit drugs [11].

Whereas previous studies regarding psychoactive drug use were generally population based [1–3], we sought to determine the frequency of such use among patients hospitalized in an intensive cardiac care unit (ICCU), knowing its implication in acute cardiovascular events. Interestingly, the current guidelines recommend a declarative survey to investigate psychoactive drug abuse, but no systematic urine or plasma screening [12,13]. However, patients may under-report psychoactive drug use when presented with a questionnaire, and self-reporting may be limited by recall bias

Table 1
ADDICT-ICCU study inclusion and non-inclusion criteria.

Inclusion criteria	Male or female patients aged ≥ 18 years Admission to an ICCU, whatever the medical reason Written informed consent obtained at enrolment into the study
Non-inclusion criteria	Admission to an ICCU for a scheduled interventional procedure Admission for > 24 hours at any hospital facility before ICCU admission Inability to give informed consent or high likelihood of being unavailable for follow-up

ICCU: intensive cardiac care unit.

[14,15]. These limitations may have attenuated the accuracy of prevalence data in previous studies, because of the lack of systematic drug screening [16].

To our knowledge, no study has ever assessed consecutively the prevalence of psychoactive drug use with systematic urine or plasma screening at the time of an acute cardiovascular event.

The ADDICT-ICCU study is designed to assess the prevalence of recent use of psychoactive drugs in all consecutive patients admitted to an ICCU for acute cardiovascular events in several French centres.

2. Methods

2.1. Study design and population

We will conduct a French multicentre cohort study (39 centres), with prospective enrolment of all consecutive patients admitted to an ICCU, to assess the prevalence of psychoactive drug use by systematic urinary screening (Central illustration). The list of participating centres is provided in Table A.1. The inclusion and non-inclusion criteria are presented in Table 1. The numbers of excluded patients and of those who decline participation will be collected to build the study flowchart. The management of each patient will be at the discretion of the treating physicians, following the current European Society of Cardiology guidelines. The study has been approved by the ethics committee (Committee for the Protection of Human Subjects, Île de France-7, France). Written informed consent will be obtained from all participants. Anonymized data supporting the findings of this study will be collected using Cleanweb™ software (Telemedicine Technologies, Boulogne-Billancourt, France), and will be available from the corresponding author upon reasonable request. The study has been registered on the ClinicalTrials.gov website (http://clinicaltrials.gov/) under the identifier NCT05063097, and study data and results will be added on completion of the study. All authors and investigators of this study have read and approved the manuscript as written (the full list of ADDICT-ICCU investigators is available in Table A.2).

2.2. Detection of psychoactive drug use

The presence of psychoactive drugs will be determined through urine analysis using a dedicated drug assay (NarcoCheck®; Kappa City Biotech SAS, Montluçon, France) within 2 hours of admission to the ICCU. The following illicit drugs will be screened for all consecutive patients: cannabinoids (tetrahydrocannabinol [THC]), including cannabis and hashish; cocaine and metabolites, including crack; amphetamines; 3,4-methylenedioxy-methylamphetamine (MDMA or ecstasy); and heroin and other opioids. In addition to the analysis of illicit drug use, the NarcoCheck® urine drug assay will detect the following medical psychoactive drugs: barbiturates; benzodiazepines; tricyclic antidepressant drugs; methadone; and buprenorphine (Fig. 1). Depending on the type of drug incriminated, the test remains positive for 3–5 days after its last consumption. A table giving the different information for each drug is available in Table A.3. The reliability of the NarcoCheck® device as evaluated in the laboratory is 97–99%, depending on the substance measured. Moreover, in a random subgroup of 60 patients, detection of illicit psychoactive drug will be assessed by high-performance liquid chromatography to evaluate the specificity and sensitivity of the NarcoCheck® urine drug assay. Of note, morphine and other opioids administered for pain sedation during the initial management of patients before admission to the ICCU will be recorded, and their urine tests for opioids will be considered negative. To assess the rate of self-reported use of psychoactive drugs, a standardized questionnaire will be used.

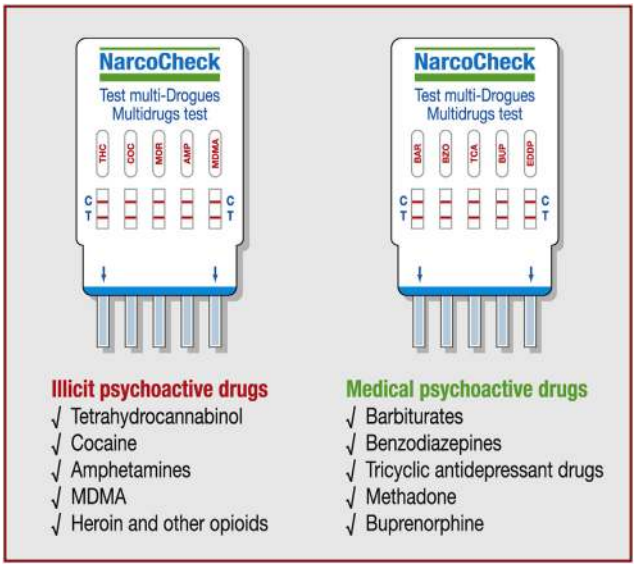

Fig. 1. Presentation of the urine drug assay (NarcoCheck®; Kappa City Biotech SAS, Montluçon, France). The following illicit or medical psychoactive drugs will be evaluated by NarcoCheck®: cannabinoids (tetrahydrocannabinol [THC]), including cannabis and hashish; cocaine and metabolites, including crack; amphetamines; 3,4-methylenedioxy-methylamphetamine (MDMA); heroin and other opioids; barbiturates; benzodiazepines; tricyclic antidepressant drugs; methadone; and buprenorphine.

Tobacco smoking will be evaluated for each patient using a standardized questionnaire with three items: “no smoker”, “past smoker” (specifying the number of years since cessation) or “current smoker”. In addition, we will quantify the tobacco consumption in pack-years, and we will also assess e-cigarette use. Nicotine dependence will be assessed using the Fagerström test, marked on a scale of 0–10 (Appendix A) [17]. In all patients, a standardized exhaled carbon monoxide measurement will be performed systematically with a CO Check Pro device (Micro Direct Diagnostics Ltd, Chatham, Kent, UK) immediately on arrival in the ICCU [18]. The threshold of > 10 parts per million will be used to signify active smoking [19–21]. Then, we will assess the prognostic value of the level of exhaled carbon monoxide on clinical outcomes.

Alcohol dependence will be assessed using the Fast Alcohol Consumption Evaluation (FACE), marked on a scale of 0–24 (Appendix B). A FACE score ≥ 9 indicates high alcohol dependence, whereas scores between 5 and 8 and < 5 indicate moderate alcohol dependence and low alcohol dependence, respectively [22]. The impact of alcohol consumption on prognosis will be also assessed in the study. Each patient will be informed of the urine drug assay and

exhaled carbon monoxide measurement, and trained investigators will conduct the tests.

2.3. Collection of baseline characteristics

Baseline data will include clinical characteristics (date of birth, sex, height, weight, temperature, systolic and diastolic blood pressure, heart rate, Glasgow score, Killip score, oxygen saturation and ventilation mode), reason for hospitalization, list of medications (especially cardiovascular drugs) at admission, history of cardiovascular disease, psychiatric illness or other significant clinical histories. In all centres, the first electrocardiogram performed upon ICCU admission, and all clinically significant electrocardiogram results will be collected prospectively using the same touchpad with a camera and dedicated scanner function of 12 megapixels (4032 × 3024 pixels; Samsung Galaxy Tab S7; Samsung, Seoul, South Korea). Electrocardiogram analysis will be performed at the end of the study by a core laboratory composed of independent blinded experts (a list of electrocardiogram variables to be evaluated is presented in Table A.4). Transthoracic echocardiography will be performed systematically within the first 24 hours of admission for all patients (all standardized echocardiographic variables to be assessed bare presented in Table A.5). Biological data will be collected systematically upon admission, including haemoglobin, serum potassium, creatinine, the peak of high-sensitivity troponin I, N-terminal prohormone of B-type natriuretic peptide or B-type natriuretic peptide. All diagnostic cardiovascular imaging or invasive angiography reports, as well as all treatment introduced during hospitalization will be collected. For all patients with invasive coronary angiography, baseline and procedural coronary angiograms will be collected and sent anonymously to the angiographic core laboratory at Lariboisière Hospital (Fernand Widal Clinical Research Unit) for secondary analyses. The coronavirus disease 2019 (COVID-19) status of each patient will be assessed systematically at ICCU admission using real-time polymerase chain reaction, following current World Health Organization guidelines [23]. Final diagnosis at the end of hospitalization will be adjudicated by two independent experts, and divided into several large main categories (Appendix C and Table A.6). In the event of a discrepancy in the diagnosis, a third expert will be requested to jointly discuss the final diagnosis.

2.4. Angiographic core laboratory

As the ADDICT-ICCU registry is a prospective and recent multicentre database of patients admitted to ICCU, the angiographic data will be collected for additional analyses on the current management of patients with acute coronary syndrome. For all patients referred to ICCU for invasive coronary angiography, baseline and procedural coronary angiograms will be collected and sent anonymously to the angiographic core laboratory at Lariboisière Hospital (Fernand Widal Clinical Research Unit). The ADDICT-ICCU angiographic core laboratory will constitute independent experienced interventional cardiologists not involved in the trial, all blinded to clinical, biological and psychoactive drug detection results. For each patient, two independent experienced interventional cardiologists will perform a comprehensive angiographic and haemodynamic analysis, including description of coronary lesions, periprocedural complications and the measurement of the quantitative flow ratio (QFR) and the non-invasive index of microvascular resistance. The QFR and the non-invasive index of microvascular resistance will be computed using the Medis Suite XA/QAngio XA 3D/QFR software (Medis, Leiden, The Netherlands). Notably, in case of significant discrepancy between two experts, a third expert will perform the analysis.

2.5. Outcomes

The primary outcome will be the prevalence of the different psychoactive drugs (illicit or medical) among all consecutive patients hospitalized in an ICCU. The secondary outcomes assessed during hospitalization will be: in-hospital major adverse events, defined by all-cause mortality, cardiogenic shock (requiring medical or mechanical haemodynamic support) and resuscitated cardiac arrest (severe ventricular arrhythmia requiring defibrillation or antiarrhythmic agents); use of mechanical ventilation; use of intravenous diuretics; non-invasive ventilation; and use of catecholamines or inotropic agents. In addition, the duration of ICCU and in-hospital stays will be recorded.

The secondary outcomes assessed at 12 months of follow-up will be: a composite endpoint of major adverse cardiovascular events (MACE), including all-cause death, non-fatal myocardial infarction, non-fatal stroke and unplanned hospitalization for unstable angina or acute heart failure; each criterion of the combined MACE; and unplanned cardiovascular hospitalizations. Using the standardized definitions [24], the definition of each MACE is provided in Table A.7.

2.6. Follow-up

A centralized follow-up of all patients included in the ADDICT-ICCU study will be organized during the first year of follow-up at the Unité de Recherche Clinique Fernand-Widal, Assistance Publique–Hôpitaux de Paris, and performed by dedicated research technicians or nurses. Hospital discharge reports will be sought for each reported event leading to hospitalization or death, and will be analysed by two independent adjudication experts blinded to drug use. All cases of cardiovascular events in which the final diagnosis appears debatable will be reviewed by a third expert.

2.7. Statistical analysis

2.7.1. Sample size calculation

The sample size calculation was performed to determine the minimum sample size for an expected prevalence of illicit psychoactive drug use with a margin of error in the confidence interval. Based on recently available data published by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [2], we consider that the expected prevalence of use of at least one illicit psychoactive drug will be 11% among the overall population for the primary outcome. The calculation was performed with a level of precision of 2% and with a confidence level of 95% of this result. A two-tailed P value < 0.05 will be considered statistically significant. Under these assumptions, and with a 5% urine drug assay refusal or failure rate, we estimate a sample size of 990 patients to attain a specified confidence interval width of 4% and to assess this prevalence accurately [25]. During the 2-week period of inclusion in the 39 French centres, we plan to include approximately 1500 patients.

2.7.2. Statistical methods

Demographic and clinical characteristics collected at baseline, as well as severity variables and procedures performed during ICCU hospitalization will be summarized and compared between patients in the “psychoactive (illicit or medical) drug use group” and the “no psychoactive drug use group.” Continuous data will be reported as means ± standard deviations for normally distributed data or as medians (interquartile ranges) for non-normally distributed data, as assessed through graphical methods and the Shapiro-Wilk test for normality. Categorical data will be reported as counts and percentages. Between-group comparisons will be performed using Student’s t test or the Mann-Whitney test for

continuous variables, and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Regarding the analysis of the clinical outcomes, four analyses will be performed: (1) the propensity score method, using a doubly robust estimator with augmented inverse propensity score weighting (R package "gbm", version 2.1.8) [26]; (2) a multivariable logistic regression analysis with the following co-variables, based on clinical input: co-morbidities as known predictors of in-hospital severity and the main admission diagnosis (model 1: age, sex, diabetes, current smoking status, history of cardiovascular disease before hospitalization, known chronic kidney disease with a glomerular filtration rate < 90 mL/min, history of cancer and the main admission diagnosis), and the baseline clinical variables of in-hospital severity and the main admission diagnosis (model 2: age, sex, the main admission diagnosis, systolic blood pressure, Killip class and heart rate); (3) a multivariable logistic regression analysis with adjustment for the propensity score in the overall population; and (4) a separate multivariable logistic regression analysis using the propensity score with a propensity score-matched population (with versus without illicit drugs detected).

To create the propensity score, a logistic regression analysis will be used to balance baseline characteristics in patients with versus without illicit drugs detected [27]. To minimize any potential selection bias, the effects of the illicit drugs detected on outcomes will be assessed using a 2:1 propensity score-matched population (with versus without illicit drugs detected; R package "MatchIt", version 3.0.2). The probit model with 2-to-1 nearest neighbour matching and without replacement will be used to identify two patients without illicit drugs detected for each patient with illicit drugs detected. Variables used to calculate the propensity score include baseline characteristics and the main admission diagnosis. To assess the performance of the propensity score, we will use the area under the receiver operating characteristic (ROC) curve (or C-statistic) as a measure of the adequacy of a propensity score. In addition, imbalances between groups will be considered to be small when the absolute standardized difference for a given covariate is less than 10% [28].

For multivariable logistic regression analysis, two prespecified models will be used to verify that patients with psychoactive drugs use do not have more co-morbidities or a more serious condition on admission. Moreover, we will use two separate models to avoid a risk of overfitting by adding too many covariates in the final model because of the limited number of outcomes already described in this population. As a sensitivity analysis, a stepwise forward regression logistic strategy to select the strongest parsimonious set of clinical covariates for outcomes, considering all clinical covariates with a P value ≤ 0.2 on univariate screening, will be performed and added to the supplementary files.

The cumulative incidence rates of MACE after discharge will be estimated using the Kaplan-Meier method, and compared with the log-rank test. The data of patients lost to follow-up will be censored to the time of last contact. Cox proportional hazards methods will be used to identify the predictors of outcomes among patients with and without psychoactive drug use. The proportional hazards ratio assumption will be verified visually using Schoenfeld residuals. Martingale residuals will be used to detect non-linearity in continuous variables.

Prespecified subgroup analyses will be performed according to clinical characteristics, final cardiovascular diagnosis and psychoactive drug use (no drug, one drug, multiple drug use). As cannabis is the most prevalent drug, only this drug will be analysed separately in a subgroup analysis. A two-tailed P value < 0.05 will be considered statistically significant. All data will be analysed using R software, version 3.6.3 (R Project for Statistical Computing, R Foundation, Vienna, Austria).

3. Discussion

This study will provide a broad overview of 10 classes of illicit or medical psychoactive drugs screened systematically in a prospective cohort of consecutive patients hospitalized in an ICCU for an acute cardiovascular event. The association of recent illicit or medical psychoactive drug use with major cardiovascular adverse events during hospitalization and 1-year follow-up will be assessed.

Previous studies have used both self-reporting and registry-based data to assess substance use among acutely hospitalized patients. A major strength of our study is the addition of urine sample analysis. The use of psychoactive substances is increasing in Europe, particularly in France, according to the latest data from the EMCDDA [2]. In the USA, the 2019 National Survey on Drug Use and Health reports similar results, with increasing prevalence over the years [4]. Among the drugs, two categories can be distinguished: (1) illicit psychoactive drugs, the most common of which are cannabis, cocaine, amphetamines, ecstasy and heroin; and (2) medical psychoactive drugs that are not in accordance with prescribing guidelines or procured illicitly (e.g. barbiturates, tricyclic antidepressants, opioids and benzodiazepines).

Regarding illicit drugs, all the substances have cardiovascular and haemodynamic effects, and can cause various acute cardiovascular events, including sudden cardiac death, acute coronary syndrome, acute heart failure, aortic dissection, thromboembolic events, myocarditis and cardiac arrhythmias [9,29,30]. The pathophysiological mechanisms are multiple, and include prothrombotic effects with increased platelet activity and aggregation, sympathomimetic effects with blood pressure variation and increased heart rate, myocardial oxygen demand and temperature [7,13,31].

Regarding medical psychoactive drugs, the use of barbiturates, meprobamates and phenothiazines has been associated with an increased risk of myocardial infarction [32]. Similarly, both overdose and opioid withdrawal can trigger major adverse cardiovascular events [33]. Other psychoactive substances, such as tricyclic antidepressants, have significant effects on heart rate, as well as having the propensity to cause a prolonged corrected QT interval [34]. Moreover, these drugs are used to decrease anxiety, which has been linked to adverse cardiovascular outcomes [35].

Whereas several studies have shown that these psychoactive substances cause acute cardiovascular disease [7–9,36], no study has assessed the prevalence of psychoactive drug use upon ICCU admission using systematic screening drug tests. This study will provide an overall prevalence of psychoactive drug use, detailed by type of drug. In line with the current guidelines [12,13], screening for the use of illegal substances is crucial to initiate the appropriate treatment for addiction, and to limit the risk of cardiovascular event recurrence as a result of the persistence of favouring factors. Although drug screening upon ICCU admission would be crucial for public health, current guidelines do not propose systematic screening because of a lack of evidence [12]. We believe that this study, including consecutive patients, regardless of the medical reason for admission and regardless of age, will identify a particular ICCU population with a higher psychoactive drug use risk. In the future, the results may help cardiologists to improve screening for drug use at ICCU admission, allowing for an earlier weaning programme to reduce the risk of recurrent cardiovascular events.

Current screening relies primarily on questioning, without systematic screening by urine or plasma testing, which has a significant risk of under-reporting, causing a recall bias. Although this risk of under-reporting is well known to practitioners in clinical practice [37], it has not yet been published in such large cohorts. In one study, in patients undergoing cardiac rehabilitation after an acute coronary event, 25% of those who declared stopping smoking were positive for urine cotinine detection [38]. The current study will provide an accurate prevalence of under-reporting of

psychoactive drug use, as both questioning and urinary screening will be performed.

Interestingly, the prevalence of any psychoactive drug is different in terms of sex, whatever the country (in France, 15.8% for males and 7.3% for females) [2]. Therefore, this study will also explore any sex difference concerning psychoactive drug use.

Finally, polyintoxication with multiple drugs, illicit or not, is frequent [37,39,40]. For example, benzodiazepines have been reported to be used to prolong the intensity and duration of the effect of opioids, or to alleviate adverse effects following the use of alcohol or cocaine [41].

Multiple drug use can potentiate side effects, and may increase the risk of adverse consequences, including engaging in self-harm or other risky behaviours, fatal and non-fatal overdose or acute cardiovascular events [10]. By performing systematic drug screening at admission, this study will also provide novel findings on the prevalence of drug combinations, and on the short- and mid-term cardiovascular prognostic impacts of multiple drug use from a large sample.

3.1. Study limitations

This study will have some limitations. First, urinary screening upon admission to the ICCU may give false negatives in cases of drug use several days before hospitalization. However, the urine drug test used continues to show positives 2–6 days after substance use. In addition, to reduce the risk of false negatives, we will exclude all patients hospitalized for more than 24 hours at any hospital facility. Second, the evaluation of drug use will only be performed upon admission to an ICCU, and this study will not aim to evaluate the evolution of drug use or possible cessation as a result of addiction treatment during or after hospitalization. Moreover, for medical psychoactive substances, it will be difficult to differentiate between misuse and use of the drug in the context of medical prescription. Third, the study will be conducted in France, where the general prevalence of illicit drug use is high. The results cannot be extrapolated to other developed countries, but may nevertheless provide interesting information about prevalence in ICCUs. Fourth, this study will not be carried out in all ICCUs of France. However, the recruitment of 39 centres from all regions of France (including large metropoles and medium-sized towns), including public university hospitals, non-university hospitals and private hospitals, should allow for an accurate representation of psychoactive drug use, despite probable geographical variations. Fifth, the study will include patients regardless of age and whatever the reason for admission, creating a certain heterogeneity. However, this choice seemed relevant to us to avoid creating a selection bias by studying a single pathology or a targeted population. Finally, residual confounding factors cannot be eliminated from this study, as with all epidemiological studies.

4. Conclusions

This French multicentre prospective study will assess the prevalence of psychoactive drug use in consecutive patients admitted to ICCUs, and its association with cardiovascular outcomes. In addition, this study will highlight the value of psychoactive drug screening in patients hospitalized for an acute cardiovascular event, to improve the screening and management of these patients.

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Disclosure of interest

J.-G. D. Consulting and lecture fees from the companies AstraZeneca, Bayer, Boehringer Ingelheim, BMS/Pfizer and Sanofi. Grants from the companies Bayer, Bristol Myers Squibb/Pfizer and Biosensors.

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The other authors declare that they have no conflicts of interest concerning this article.

Online Supplement. Supplementary data

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