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THERAPIES

HEADING: Addictovigilance

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Summary

Objective.- It is essential that health professionals who practice medicine in prison rely on accurate knowledge about their patients to provide them with adapted care. The use of cannabis can influence the health status of prisoners, but data are lacking regarding the potentially related adverse health consequences. The objective of this descriptive study was to describe the cardiovascular outcomes related to cannabis use in prisoners from several detention centres hospitalised in a French hospital. *Methods*.- In France, prisoners who require a longer than 48-hour hospitalisation are admitted in specific secured polyvalent units called inter-regional secured hospital units (ISHU). Hospitalisations in the ISHU of Toulouse University Hospital between 2012 and 2016 for cardiovascular disorders potentially related to the use of cannabis were extracted from the French hospital database and analysed using a previously validated methodology. Included patients were those hospitalised for an inaugural cardiovascular event or deterioration of a pre-existing cardiovascular illness who declared having used cannabis while imprisoned. *Results*.- Overall, 31 cardiovascular outcomes were identified incannabis-using hospitalised prisoners among 411 hospitalisations for cardiovascular disorders (all men, mean age 43+/- SD years old). All used cannabis (daily: 56%) and tobacco (more than 15 PY: 83.3%), 5 used cocaine, and none used alcohol. The most frequent were coronaropathy (n = 13), followed by obliterating arteriopathy of the lower limb (OALL, n = 7), arrhythmic cardiomyopathy (n = 4), venous thrombosis (n = 3), infectious cardiopathy (n = 2), and ischemic stroke (n = 2). *Conclusion*.- This description of serious cardiovascular outcomes in prisoners who use cannabis provides insights into the clinical features possibly observed in this vulnerable population The findings indicate that 7.5% of hospitalizations of prisoners for cardiovascular disorders are potentially linked to cannabis used in prison.

KEYWORDS

Cannabis; Prisons; Cardiovascular diseases; Hospitalisation; Drug-Related Side Effects and Adverse Reactions; Addictovigilance; Harm reduction

Abbrevations

CBR: cannabinoid receptors

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction

FAN: French Addictovigilance Network

GPCR: G-protein coupled receptors

ICD-10: international classification of diseases 10th edition

IQ: interquartile

ISHU: inter-regional secured hospital units

MI: myocardial infarction

MRI: magnetic resonance imaging

NIS: US national inpatient sample

OALL: obliterating artheriopathy of the lower limb

OPPIDUM: observation of illegal drugs and misuse of psychotropic medications

PMSI: *programme de médicalisation des systèmes d'information*

SD: standard deviation

SUD: substance use disorders

THC: tetrahydrocannabinol

WHO: World Health Organization

Introduction

Health professionals who practice medicine in prison need to rely on accurate knowledge about their patients. This knowledge is essential to provide these latter with care adapted to their needs and the problems inherent to the jail environment [1]. One fundamental right of prisoners is to have adequate health care: in practice, however, laws and policies struggle to reach this universal human right and ensure equity towards health care [2].

The use of psychoactive substances by prisoners despite their detained condition is one among factors which can influence their health status. Cannabis, the prevalence of which remains at the highest level in the world, [3] is also of the most used psychoactive substances in prison. Cannabis use was described as part of the prisoners' daily life, even in countries where it is illegal [4]. In France, according to the OPPIDUM (observation of illegal drugs and misuse of psychotropic medications) program, the prevalence of cannabis use in entering prisoners is 45% (versus 40% among free subjects, $p < 0.001$) [5]. Entering prisoners are younger than free subjects, have a worse socioeconomic situation and use more psychoactive (notably, illicit) substances. Other studies conducted in French prisons revealed that 45% of prisoners detained in the area of Toulouse were drug consumers, 73.3% of whom used cannabis on their entry into prison [6] while 83.6% of prisoners detained in the prison of Lyon used psychoactive substances, 36.8% of whom used cannabis; 30.4%, alcohol; 10.3%, cocaine and 7.7%, heroin [7]. In the border country Switzerland, 10.0% of prisoners aged between 20 and 49 years old were estimated to be current cannabis users [8].

Notwithstanding the positive perception and safe image of cannabis throughout the world [9,10], cannabis use has been associated with adverse health effects [11]. In particular, reports on cardiovascular outcomes occurring in cannabis users have arisen in the scientific literature over the last decade [12]. These mainly correspond to cerebrovascular accidents or events [13] and cardiac or peripheral artery disease or disorders [14]. Although they realized an extensive search in the scientific literature, the authors found no data concerning any potential cardiovascular outcomes in prisoners in the context of cannabis use. A review by Wang *et al.* disserts cardiovascular disease in the incarcerated population and identifies drug addiction as one among several risk factors without specifically analysing it [15].

Studies evaluating the use of cannabis and other psychoactive substances in prison or the related health consequences on prisoners are of a limited number, notably because assessing a prohibited practice in a punitive environment is a difficult question [16]. A recent review of the literature investigated morbidity and mortality in several vulnerable populations including prisoners

and individuals with substance use disorders (SUD), but provide no details on SUDs among prisoners [17]. The mortality rate among prisoners was assessed in two different studies; one was conducted in Australia and the other in Scotland [18,19]. Both evidenced similar levels of mortality, and found that mortality was twice as high among detained females as in detained males. These studies provide no details about the causes of deaths, although it would have been interesting to distinguish drug-related suicides from other drug-related deaths. In Sweden, a focus made on fatalities from accidental intoxications highlighted several risk factors, including the use of cannabis [20]. However, this analysis was conducted from a follow-up register of a criminal justice population and not directly among prisoners.

The potential consequences of cannabis use for prisoners' health, especially their cardiovascular health, are of concern. Indeed, cardiovascular diseases remain the leading cause of mortality worldwide in the general population. An increased understanding of risk factors contributes to improving the prevention and medical management of cardiovascular disease. Several predictors of survival after an acute myocardial infarction (MI) were identified among non-incarcerated subjects but unfortunately, use of cannabis and of other psychoactive drugs were not investigated as potential risk factors [21]. In their review, Wang and colleagues emphasize the urge for studies designed to evaluate the cardiovascular risk in the specific population of prisoners [15]. The present study aimed to describe the cardiovascular outcomes in prisoners who use cannabis hospitalised in Toulouse university hospital between 2012 and 2016.

Material and methods

Inter-regional secured hospital unit (ISHU)

Inter-regional secured hospital units (ISHU) were created in 2000 as a consequence of the implementation of law of 18 March 1994 on public health and social protection [22]. In particular, this law defines healthcare treatment of ill prisoners and ISHU enhanced the quality of care provided to prisoners. They also enabled to solve several problems raised by the increasing number of hospitalisations of prisoners such as the organisation of medical extractions and the risks of evasion [23].

ISHUs are short stay hospitalisation units intended to receive, with their consent, ill prisoners older than 13 years old, incarcerated in a penitentiary inter-region, and who require hospitalisation longer than 48 hours, scheduled, or following admission in a specialised or an emergency department. ISHUs are polyvalent units. Only illnesses which require very specific treatment (e.g., obstetric or resuscitation care) are not treated. Among the 8 ISHUs in France, that of Toulouse University Hospital receives a maximum of 16 prisoners from the entire Occitanie region (South of France). During the study period, there were 2,545 admissions including 411 for cardiovascular disorders (16.1%) [Table 1].

Study process

This descriptive study has a cross-sectional design.

In France, all data related to hospitalisations are administratively recorded in every public or private health institutions in a national database called programme de *médicalisation des systèmes d'information* (PMSI) [24]. PMSI records data of different types, including the patient characteristics (gender, date of birth, permanent identification number), the days of admission and discharge, all medical units of admission, and the exhaustive list of diagnoses recorded according to the World Health Organization's (WHO) international classification of diseases, 10th edition (ICD-10).

All hospitalisations potentially related to cannabis use were extracted from PMSI using ICD-10 codes indicative of possible cannabis abuse/addiction, without restriction on any potential associated diagnoses. The diagnosis codes and the strategy algorithm applied in the present study has been validated previously [25,26]. These ICD-10 codes corresponded to "Mental and behavioral disorders due to cannabis use" (F12). All extracted hospitalisations were then reviewed based on defined inclusion/exclusion criteria to identify cardiovascular outcomes. These latter were firstly identified from a list of ICD-10 codes indicative of cardiovascular events and secondly confirmed by the medical elements reported in the corresponding medical charts (Fig. 1).

Inclusion/exclusion criteria

The target population was that of patients hospitalised at Toulouse ISHU from 2012 to 2016 for the occurrence of an inaugural cardiovascular event or deteriorating from a pre-existing cardiovascular

illness who declared having consumed cannabis while imprisoned were included. The French method of causality assessment used to evaluate drug safety was applied to measure cannabis causal involvement and select only those patients with a higher causal involvement (Fig. 1) [27]. “Cardiovascular diseases” corresponded to arrhythmia-related, infectious or coronary heart diseases, cerebrovascular accidents, obliterating arteriopathy of the lower limbs (OALL) and thromboembolic accidents. Patients hospitalised for follow-up care, a check-up or the discovery of cardiovascular disease found stable without specific decline's care were excluded, along with those hospitalised for a cardiovascular motive whose check-up was negative.

Statistical analysis

All data related to the included hospitalisations were described using mean, standard deviation (SD), median and the corresponding first and third interquartiles (IQ1 and IQ3) for quantitative variables, percentages for qualitative variables.

The proportion of cannabis exposure among all hospitalizations for cardiovascular disorders was calculated by dividing the number of included hospitalisations by the total number of hospitalisations for cardiovascular disorders during the study period. Besides, a t-test was applied to compare the mean age of included patients with that of patients admitted for cardiovascular outcomes without cannabis exposure.

Ethics

The French data protection authorities approved the study process including the access to the data recorded in the hospital database PMSI (CNIL approval number 909236v2).

Results

Among 411 hospitalizations for cardiovascular disorders over the study period, 31 (7,5%) were observed in 30 prisoners who used cannabis (Tables 1 and 2). All patients were males. They were significantly younger than the patients admitted for cardiovascular outcomes without cannabis exposure (mean age: 43 versus 55 years old, $p < 0.001$). All of them used cannabis (daily use: 56.7%) and tobacco (more than 15 PY: 83.3%); 5 used cocaine, and none used alcohol (Table 2).

The most frequent events identified in our sample were coronaropathy (Table 3). All the 13 concerned patients underwent a coronarography. MI were diagnosed in nine patients (out of 13), only two of which had a history of coronaropathy disease. Ten patients presented stenosis and required treatment by angioplasty and stenting. Among the five patients who were diagnosed troponin-elevated and ST-elevated MI, three had thrombotic damage having required thrombectomy and stenting. One patient diagnosed with non-troponin-elevated and non-ST-elevated MI had a normal coronarography. However, the magnetic resonance imaging (MRI) favoured blood emboli from a branch of the circumflex coronary artery causing an embolic infarct of the left ventricle. This patient was 50 years old, was an occasional cannabis user and the strongest tobacco user of our sample (60 PY) without other cardiovascular risk factors. The etiologic check-up returned negative, notably for thrombophilia and heart rhythm disorders.

Coronaropathies were followed by OALL. Among the seven patients concerned, six had histories of known OALL and presented a decompensation to a type of stenosis or occlusion which could be on vessels or material (intra-stent, occlusion of bypass). Also, five patients required a vascular intervention during the hospitalisation, and one patient within a period of three months. The remaining patient had no history of OALL and presented subacute ischemia of the lower limb having required a vascular procedure as a matter of urgency.

Then, the four cases of arrhythmic cardiomyopathy included two Wolff-Parkinson-White's syndromes, one of which required coverage by ablation of the accessory pathway and the other, a simple supervision because of an intermittent symptomatology. A third patient was diagnosed with a low-grade second-degree atrioventricular block. These three patients had no history of heart rhythm problems. The last one presented a history of atrial fibrillation and presented an intermittent second-degree atrioventricular block having required to change the drug management.

The other five cardiovascular outcomes identified were venous thrombosis (one thrombosis of the hepatic vein, one phlebitis of the lower limb in a context of pneumonitis and one pulmonary embolism without identified aetiology), infectious cardiopathy (one case of pre-tamponade in the context of pericarditis of unclear aetiology and one case of endocarditis caused by *Streptococcus mutans* and *Enterococcus faecalis*).

Finally, there were two ischemic cerebral strokes in regular and daily cannabis users. A 36-year-old man presented a middle cerebral artery occlusion complicated by cerebral haemorrhage. The other was a 38-year-old man who presented a pontine stroke. For both, angioscan showed no atheroma or stenosis in cerebral arteries. The etiologic check-up found no etiologic factor (including thrombophilia and heart rhythm disorders).

Discussion

Main results

This descriptive study identified that 30 prisoners were hospitalised in the context of cannabis use for thirty-one cardiovascular outcomes in Toulouse University Hospital between 2012 and 2016, the most frequent of which was coronaropathy.

Cardiovascular events identified and associated risk factors

The outcomes identified in this study cohere with the described complications of cannabinoids, especially tetrahydrocannabinol (THC), on the cardiovascular system [28]. The endocannabinoid system has two receptors called type-1 and type-2 cannabinoid receptors (CBR1 and CBR2) [29]. CBRs are heptahelical G-protein coupled receptors (GPCR). They are ubiquitous with a wide distribution and have a variety of effects. Activated CBR1s lead to hypotension and decreased cardiac function associated with various pathologies such as shock, cardiomyopathies and heart failure. They also promote inflammatory and contribute to the development of vascular inflammation and atherosclerosis and induce stimulation or inhibition of sympathetic or parasympathetic activity. In contrast, the stimulation of CBR2s decreases the acute inflammatory response and oxidative stress and might exert beneficial effects on cardiomyocytes. Chronic treatment with CBR2 agonists has antiatherosclerotic and antifibrotic effects in animal models. CBR2 stimulation has no direct cardiovascular effect. Under pathological conditions, the role of cannabinoids in cardiovascular pathology is complex and might depend on the disease and stage of progression.

Clinical studies have described cardiovascular adverse effects of cannabis use. The review by Pacher and colleagues describes cardiomyopathies, acute heart failures, arrhythmias, orthostatic

hypotension, acute coronary syndrome, acute myocardial infarction, sudden cardiac death, vasospasm, vasculitis, artery dissection, coronary thrombosis, myocarditis, pericarditis and stroke [29]. Coronaropathy, which was the most frequent cardiovascular pathology in our study, is also the cardiovascular disorder most reported in the scientific literature [12]. Some of them occur in very young subjects [30,31]. Overall, the level of evidence appears low concerning these disorders as only few studies have investigated the possible association between cannabis use and cardiac outcomes. A cohort of nearly 4 000 patients initially admitted for myocardial infarctions has been followed-up for several years [32–34]. These studies identified cannabis as a triggering factor for myocardial infarctions and highlighted over-mortality in the medium but not in the long term. Several other studies assessed a possible association between cannabis use and strokes [35,36], some of which remained significant even after adjustment on tobacco use [37,38]. Also, individual cases of strokes are described in cannabis users [39,40]: however, only two cases of strokes were observed in the present study. Transient ischemic attacks are usually managed in specialised neurology intensive care units during 48 to 72 hours and then directly return to the prison. This organisation is likely to explain the relatively low proportion of stroke in our sample because the concerned patients usually come to ISHU significantly after the outcome to undergo a complete cardiovascular assessment. The corresponding hospitalisations may have fallen outside our inclusion criteria because follow-up care and check-up after the discovery of cardiovascular disease were excluded. In contrast, patients with a developed stroke are supposed, unless they refuse, to pass in the service systematically. The distribution of diseases described in this study is comparable to that retrieved in the analysis of cases reported to the French Addictovigilance Network (FAN), with three strokes and 20 acute coronary syndromes [14]. In the present study, the two patients who have experienced a stroke had no diagnosed atheroma nor stenosis. There were young patients, with significant consumption of cannabis and tobacco, one of them also using cocaine. They were much younger than the mean age of patients admitted for stroke to emergency departments in the same region (37 years old versus 72) [37] and younger than the overall prisoners admitted to ISHU (Table 1). However, their age was similar to that of cannabis users suffering from strokes as reported in the literature (35 years old) [12].

Cases of venous thromboses were included in our study. Indeed, from a metabolic point of view, cannabis generates an increased rate of factor VII, a platelet hyperactivation greater oxidation of the particles of LDL and activation of the inflammation [12]. No data was found in the literature concerning the possible association between cannabis and venous thromboses. The patients having presented an event of OALL were relatively young for this type of pathology (48 years on average). Furthermore, in most of these cases, the disease pre-existed: this indicates that the onset of disease

occurred at an even earlier age. To finish, cases of Wolff-Parkinson-White's syndromes were included in this study: however, no such syndrome is reported in the literature in relation with cannabis use.

A low proportion of the patients included in our study presented pre-existing cardiovascular risk factors, except for tobacco (systematic) or dyslipidemia (in 16 patients; Table 2). The latter is likely to be overestimated in this study. Indeed, the report of dyslipidemia in the patients' discharge summaries can result from the patients' clinical interview or the list of prescribed medicines. Yet, the prescription of lipid-lowering agents may constitute a primary or secondary prevention treatment in patients with no constitutional dyslipidemia as an initial risk factor. The prevalence of lipid-lowering agents is also very high in other studies conducted among the French population [21].

In this study, the choice for not excluding tobacco use relied on the observation that the association of tobacco and cannabis is almost systematic among cannabis smokers in France. Excluding tobacco users would have induced a selection bias likely to exclude the most frequent patterns of cannabis users.

Most patients used cannabis daily. When the data on cannabis exposure lacked details (n = 9), patients were classified as occasional users, thus potentially introducing a classification bias. The cardiovascular outcomes observed in this study corresponded to 7.5% of all cardiovascular disorder admissions, above the estimated prevalence of regular (2.8%) and daily (1.4%) cannabis use in France [41]. Thirty prisoners were hospitalised in the context of cannabis use in Toulouse University Hospital between 2012 and 2016, the most frequent of which was coronaropathy.

The rate of other psychoactive substances was lower, notably that of cocaine. Also, no current use of alcohol during the detention was declared. Cannabis, cocaine and alcohol are forbidden in prison. The large packaging of alcohol complicates its accessibility to prisoners. Besides, access to cocaine is restricted because it is an expensive substance with a two-fold higher price than outside. The latter point may contribute to explaining the reduced prevalence of cocaine in prison [42]. On the contrary, cannabis use increases during incarceration.

Health status of prisoners

This descriptive study detailing cardiovascular occurrences in hospitalised prisoners who used cannabis in prison contributes to filling gaps in the knowledge about the health status of prisoners. The finding that the outcomes described in this study cohere with the cardiovascular disorders

observed in other contexts is, in itself, new. Indeed, the health status of prisoners has rarely been studied. In the scientific literature, most articles dealing with drugs and prisoners aim to measure the prevalence of drug abuse in prison using several approaches: recourse to questionnaires [7,42–44], interviews [4,45], or retrospective explorations of routine data [8] or even of wastewater analysis [46,47]. Except for one such study published in 1974 and which concluded on the absence of drug abuse in prison [43], all others describe drug use in prison. Among the factors associated with drug use during incarceration were the large size of prison, the longer duration of incarcerations and the older age of prisoners [48–50]. Plourde and Brochu highlighted a rise in the frequency of drug use within the prison, mainly represented by the high prevalence of cannabis [42]. This latter is also described elsewhere, including in France [4,44,45].

Besides, very few data concerning prisoners' morbidity are available in the scientific literature. Several studies assessed the prevalence of the viral HCV and HIV infections, including the risk behaviours among HIV-infected prisoners [51,52]. In 2014, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published a report on drug use in European prison to build a common European basis for data collection on drug use and prison [53]. Overall, all these studies are of limited interest because they depict drug use in prison without evaluating the consequences of drug use on the prisoners' health [54]. Nevertheless, they provide helpful information contributing to improve viral prevention strategies [55].

Limitations and strengths

High level of tobacco smoking was the foreground risk factor identified and constituted a systematic confusion bias. The studies having evaluated cannabis-related strokes found divergent results after adjustment on the patients' tobacco status. Falkstedt and colleagues used a population-based cohort of 49,321 Swedish men born between 1949 and 1951 to investigate the association between cannabis use and early onset stroke [36]. Although the risk of ischemic stroke was almost doubled in subjects with heavy cannabis use, this risk was no longer significant when adjusted for smoking. By contrast, among a cohort of 153 patients with stroke or transient ischemic attack from the general Australian community, individuals who had used cannabis in the past year had a 2.3 fold higher rate than nonusers after further adjustment for covariates related to stroke, including tobacco smoking [38]. Moreover, the exploration of the US national inpatient sample (NIS) found a significant association between use of cannabis and myocardial infarction despite the adjustment on confounding including tobacco smoking and cocaine or amphetamine abuse [56]. Also, cannabis

users more frequently die than non-users [57].Assessment of cannabis exposure was approximate because the collection method was based on the content of discharge summaries, which report a synthesis of each patient's hospital stay. Drug exposure was evaluated by medical interviews, rarely by urine analyses. An assumption was that diseased patients were likely to admit cannabis exposure to improve their medical management. Nevertheless, they may have underreported their consumption. Cannabis is illicit in France and, *a fortiori*, in detention. The type of cannabis preparations used, the exposure level and the THC concentration remained out of reach. This latter characteristic is of importance, as the last WHO expertise on the health and social effects of nonmedical cannabis use report the increase of THC in cannabis preparations up to 20% [11].

Furthermore, the identification of cardiovascular history and risk factors from the information reported in the patients' discharge summaries may have been subject to approximations. For example, dyslipidemia was mentioned in 16 patients without details on the type of dyslipidemia and in the absence of biological values of HDL/LDL cholesterol. Despite its small size, the studied sample includes the most serious cardiovascular events only, at the exception of death occurring before admission, as hospitalisation constitutes a seriousness criterion [14]. Unlike most studies in which data is focused on substance use before or close after incarceration, our study targeted cardiovascular disease in all prisoners without restriction, provided they used cannabis. The ISHU of Toulouse university hospital covers $1/8^{th}$ of the total population of prisoners incarcerated in France. Moreover, the exhaustive character of hospital databases is useful to detect potential drug-related complications, complementing the other data sources traditionally explored in addictovigilance [58]. Indeed, based on a 25-year-experience, the FAN has developed and routinely applies a multidimensional approach to comprehend the adverse disorders related with the use of substances with abuse potential, including the exploration of hospital data [59,60]. This approach has proven useful in clinical practice [61] and to identify addictovigilance signals [62]. Nevertheless, this exploratory study constitutes the first explicit examination of hospital data in a population of hospitalised prisoners. Also, a drastic process was applied to select the patients, with a systematic rejection of all questionable cases. Disorders with borderline characteristics regarding our inclusion/exclusion criteria are likely to have occurred: in such situation, the patients may have been admitted in services different from ISHU. For example, venous thrombosis or transient ischemic stroke, which require short medical care, are most probably not managed in ISHU as this structure receives patients for hospitalisations longer than 48 hours. Also, some cardiovascular outcomes remained out of reach, as rhythm cardiopathy which required no specific medical management.

This study is most probably an under-estimation of the target population of cardiovascular outcomes in hospitalised detained cannabis-users, but it is highly relevant to the initial objective and provides precious information on the health status of prisoners, which lacked to the scientific knowledge. Furthermore, this exploratory study constitutes the first approach to a broader project aiming at assessing the general health of prisoners; it will serve as a helpful basis to implement future studies.

Conclusion

To our knowledge, we provide the first description of serious cardiovascular outcomes described in the context of cannabis use in prison. Despite their vulnerable character, the disorders which occur in these patients have rarely been studied in such a comprehensive way. Cannabis use appears a risk factor which should be systematically investigated at the patients' admission. A sharpened awareness of any health providers involved in prisoners' care is crucial to improving their clinical management. This descriptive study included only the cases corresponding to the first occurrence in patients with no prior cardiovascular history, or to pre-existing disease decompensation which led to introduce specific management or to modify the existing treatment. Other more silent cases are likely to have happened during the study period: further investigations should be conducted to assess them, together with cases affecting systems different from the cardiovascular system, to understand (and manage) better them. This exploratory study constitutes a basis for the future implementation of enlarged investigations.

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Disclosure of interest

Authors have no competing interest to declare

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Table 1. Toulouse Inter-regional secured hospital unit (ISHU) activities from 2012 and 2016 classified by reason for admission. There were 411 admissions for cardiovascular disorders, representing 16.1% of all hospital stays over the period.

Year	**Mean duration (days)**	**Mean age (years)**	**Number of stays**	**Reasons for admission: n (%)**				
				Cardiovascular disorders	Musculoskeletal disorders	Respiratory disorders	Digestive disorders	Tumors of unspecified site
2012	5.32	46	479	80 (16.7%)	57 (12.0%)	46 (9.7%)	44 (9.2%)	-
2013	6.29	47	545	85 (15.6%)	70 (12.9%)	47 (8.6%)	65 (12.0%)	-
2014	6.43	46	481	91 (19%)	70 (14.5%)	47 (9.7%)	40 (8.3%)	-
2015	6.95	46	532	81 (15.2%)	68 (12.7%)	57 (10.8%)	60 (11.2%)	-
2016	6.76	48	508	74 (14.6%)	59 (11.6%)	-	51 (10.0%)	50 (9.8%)
Total			**2545**	**411 (16.1%)**	**383 (15.0%)**	**197 (7.7%)**	**261 (10.2%)**	**50 (2.0%)**

Table 2. Characteristics of the included patients (total and classified by type of cardiovascular outcome).

Characteristics	**Total**		**Cerebral stroke**		**Obliterating arteriopathy of the lower limb***		**Infectious cardiopathy**		**Arrhythmic cardiomyopathy**		**Coronaropathy***		**Venous thrombosis**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
N	**30**	**100%**	**2**	**6,7%**	**7**	**23,3%**	**2**	**6,7%**	**4**	**13,3%**	**13**	**43,3%**	**3**	**10,0%**
Age														
Mean ± SD	43 ± 10		37 ± 1		48 ± 4		38 ± 3		29 ± 4		48 ± 8		34 ± 10	
Median (IQ1;IQ3)	44 (36;50)		37 (36;38)		47 (46;52)		38 (36;41)		28 (25;32)		47 (42;56)		30 (26;46)	
Age ≥50	8	26.7%	0	0.0%	3	42.9%	0	0.0%	0	0.0%	5	38.5%	0	0.0%
Male gender	30	100.0%	2	100.0%	7	100.0%	2	100.0%	4	100.0%	13	100.0%	3	100.0%
Familial cardiovascular history	5	16.7%	0	0.0%	1	14.3%	0	0.0%	0	0.0%	4	30.8%	1	33.3%
Diabetes	1	3.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	7.7%	0	0.0%
Hypertension	4	13.3%	0	0.0%	0	0.0%	1	50.0%	0	0.0%	3	23.1%	0	0.0%
Dyslipidemia	16	53.3%	2	100.0%	5	71.4%	1	50.0%	0	0.0%	8	61.5%	1	33.3%
BMI														
Mean ± SD	23.9 ± 3.2		26.3 ± 0.9		23.6 ± 2.1		21.5 ± 4.9		21.8 ± 2.5		24.5 ± 3.7		26.3 ± 2.1	

Median (IQ1;IQ3)	24.8 (21.5;26.0)		26.3 (25.7;27.0)		24.0 (21.5;25.5)		21.5 (18.0;25.0)		22.1 (20.0;23.6)		25.1 (21.0;26.0)		26.3 (24.8;27.8)	
Missing data (n)	1		0		0		0		0		0		1	
Cannabis														
Occasional	9	30.0%	0	0.0%	4	57.1%	1	50.0%	0	0.0%	4	30.8%	1	33.3%
Regular	4	13.3%	1	50.0%	0	0.0%	0	0.0%	0	0.0%	3	23.1%	0	0.0%
Daily	17	56.7%	1	50.0%	3	42.9%	1	50.0%	4	100.0%	6	46.2%	2	66.7%
Tobacco (Packs.year)														
<15	5	16.7%	0	0.0%	0	0.0%	0	0.0%	2	50.0%	2	15.4%	1	33.3%
[15 - 25[	12	40.0%	2	100.0%	3	42.9%	1	50.0%	2	50.0%	3	23.1%	1	33.3%
[25 - 35[	10	33.3%	0	0.0%	3	42.9%	1	50.0%	0	0.0%	6	46.2%	1	33.3%
≥35	3	10.0%	0	0.0%	1	14.3%	0	0.0%	0	0.0%	2	15.4%	0	0.0%
Current cocaine	5	16.7%	1	50.0%	1	14.3%	0	0.0%	1	25.0%	2	15.4%	0	0.0%
Current alcohol	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

*One patient was diagnosed coronaropathy and obliterating arteriopathy of the lower limb (OALL): the corresponding characteristics are included in both types of outcomes, but the patient was counted once to describe the total sample.

BMI: body mass index ; IQ: interquartile ; SD: standard deviation

Table 3. Detailed presentation of coronaropathies.

Age	BMI	Diabetes	Hypertension	Dyslipidemia	Personal cardiovascular history	Familial cardiovascular history	Cannabis exposure	Tobacco (Pack-Year)	Cocaine	Event	ST	Troponin	LVEF	Management	CAS
49	**28.0**		Yes	Yes			Occasional	30		Unstable angina			50%	Angioplasty and stenting of stenosis	I1
47	**32.0**			Yes		Yes	Occasional	30		MI		+	45%	Angioplasty and stenting of stenosis	I1
60	**27.0**			Yes	Coronaropathy		Regular	52		Check-up for CAD			40%	Stenting of stenosis	I1
37	24.0			Yes			Daily	18	Yes	MI	+	+	Normal (n.a.)	Aspiration of thrombosis and stenting	I1
50	20.7						Occasional	60		MI		+	60%	Normal coronarography	I1

45	**25.1**			Yes	OALL	Yes	Occasional	30		Pre-surgical screening			52%	Medical treatment of stenosis	I1
56	25.0		Yes			Yes	Daily	20		MI	+	+	Normal (n.a.)	Angioplasty and stenting of stenosis	I1
39	21.0						Daily	25		MI		+	55%	Angioplasty and stenting of stenosis	I1
57	19.6			Yes		Yes	Daily	10		MI		+	50-55%	Angioplasty and stenting of stenosis	I1
35	**26.0**						Daily	20	Yes	MI	+	+	45-50%	Thrombectomy and stenting	I2
63	**26.0**	Yes	Yes	Yes			Regular	0		Check-up for diabetes			69%	Medical treatment of stenosis	I1
41	19.1						Daily	30		MI	+	+	45-50%	Angioplasty and stenting of	I2

														stenosis	
45	**25.6**			Yes	Coronaropathy		Regular	30		MI	+	+	35%	Angioplasty and stenting of thrombosis and stenosis	I1

BMI: body mass index; CAS: causality assessment score; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; OALL: obliterating arteriopathy of the lower limbs.

Figure 1. Flow-chart of included patients.