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ORIGINAL ARTICLE

Cardiovascular disease among people with drug use disorders

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Abstract
Objectives To present the prevalence and incidence of cardiovascular disease (CVD) in a national cohort of patients seeking treatment for drug use disorders (DUD).
Methods This is a longitudinal record linkage study of consecutive DUD treatment admissions between 2000 and 2006 from Denmark.
Results Of 17,642 patients seeking treatment for DUD, 828 individuals (4.53 %) had a history of CVD at treatment entry. Among the remaining patients, 16,820 were traced and 1535 new incident cases of CVD were observed during a mean follow-up time of 7.5 years. The incidence of CVD was associated with intravenous drug use [subhazard ratio (SHR) = 1.41, $p < 0.001$], not responding to injection question (SHR = 1.23, $p = 0.005$), older age (SHR = 1.04 per year, $p = 0.000$), use of prescription methadone (SHR = 1.32, $p < 0.001$), use of benzodiazepines (SHR = 1.21, $p = 0.005$), and being referred to methadone treatment (SHR = 1.15, $p = 0.022$). The use of amphetamines was negatively associated with the risk of CVD within this cohort (SHR = 0.75, $p = 0.001$).
Conclusions Patients injecting drugs using prescribed methadone were at elevated risk for cardiovascular disease and should be monitored for CVD. Opioid medications should be evaluated in terms of their cardiovascular sequelae.

Keywords Cardiovascular disease · Methadone · Injection drug use · Substance abuse treatment · Opioids · Amphetamine

Introduction

Cardiovascular disease (CVD) constitutes a significant burden on healthcare systems and is a significant cause of premature death (Danaei et al. 2011a, b; Farzadfar et al. 2011). People with drug use disorders (DUD) are at risk of premature death from a range of causes (Degenhardt and Hall 2012; Nordstrom et al. 2013; Nyhlén et al. 2011), but little is known about the specific burden of CVD in this patient group.

Although people with DUD form a heterogeneous group, particular risk factors exist, and illicit drug use may lead to CVD in multiple ways. Injection use may lead to venous disease (Pieper et al. 2007), and thrombosis, septicaemia or endocarditis (Salmon et al. 2009), involving both infectious and inflammatory mechanisms. Additionally, lifetime opioid exposure is associated with increased arterial stiffness and vascular age (Reece and Hulse 2014) in a dose-dependent fashion (Reece and Hulse 2013). High doses of methadone may cause QT interval prolongation (Kao et al. 2013; Roy et al. 2012). In clinical practice with people with long-standing opioid use, this raises the question of whether long-term opioid maintenance treatment adds to the risk of CVD, or whether other factors

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associated with opioid substitution such as decreased illicit drug use and injection, increased contact with services, and better social stability offset the risk associated with cumulative opioid exposure. If the former is the case, this would suggest a need to develop treatments for opioid use disorders that are effective, but which would ideally have lower levels of cardiovascular risk compared to the current alternatives in opioid maintenance treatment.

Besides opioids, several other drugs have been shown to or are suspected of causing CVD. For instance, high doses of cocaine and amphetamine are associated with acute vascular events, typically arrhythmias and elevated blood pressure (De Giorgi et al. 2012; Figueredo 2011), and there is evidence that amphetamine use may increase the risk of acute myocardial infarction (Westover et al. 2008) and prolonged corrected QT interval (Mooney et al. 2009). Benzodiazepines have occasionally been shown to be associated with risk of CVD among patients with depression or anxiety (Lapane et al. 1995; Seldenrijk et al. 2015); however, this association is difficult to disentangle from the severity of mood and anxiety disorders (e.g., Jaussent et al. 2013). Further, case reports have indicated that cannabis use may be associated with acute myocardial infarction (Desbois and Cacoub 2013).

Since CVD is a leading cause of mortality and lowered quality of life (McKenna et al. 2005), it is important to identify groups at high risk for CVD, to prevent and adequately treat new cases. Little is currently known about the prevalence and incidence of CVD in DUD populations, and clinicians would benefit from more nuanced knowledge on the prevention and treatment of CVD in diverse patient populations in clinical practice.

The aims of this study were to assess the prevalence of CVD in a Danish national cohort of people who had sought treatment for a DUD during the years from 2001 to 2007, and new incidences of CVD until the end of 2011. Predictors of new incidence CVD in this treatment seeking population were investigated using competing risks regression.

Methods

Setting

The setting was all Danish public outpatient drug use treatment centers between January 1st 2000 and December 31st 2006. All treatments in these institutions are free of charge.

Participants

This study included 17,642 patients aged between 18 and 75 years old who were consecutively admitted for public outpatient treatment for DUD. All admissions and the dates of patient's first admission for treatment during this period were included.

Registers

Data were retrieved from six national registers and were stored at a server in Statistics Denmark. The Danish Substance Abuse Treatment Register (DSATR) includes data on drugs used before seeking treatment for illicit drug use problems. The DSATR contains dummy codes for each drug, including illicit and prescribed methadone, benzodiazepines, heroin, buprenorphine, other opioids, cannabis, amphetamine, cocaine, alcohol, MDMA, LSD, and solvents. Only for methadone does the data base report both illicit and prescribed methadone. When admitting patients, staff members ask if the substance has been used within the past year and about injection drug use. Additionally, the register includes basic demographic characteristics such as age, gender, level of education, living conditions, and information about previous treatment.

Patients are identified by a unique identification number that allows linking patients with other public registers. A total of 99.8 % of entries in the database could be matched with other registers and could be included. For this study, illicit methadone and prescribed methadone were entered as separate variables, whereas other opioid agonists and heroin were combined as one category. Ecstasy, LSD, and solvents were excluded from the analyses, due to the low frequencies of these drugs (all <10 %).

The National Patient Registry covers all public hospital contacts in Denmark, including inpatient, day hospital, and emergency units, and gives discharge diagnoses, using the ICD-10 codes. All treatment in Danish public hospitals is free for patients.

The Cause of Death Register covers all deaths in Denmark, and was used to establish the mortality rate, as well as the time and cause of death using the ICD-10 codes.

Additional registers included the National Criminal Justice register, the Psychiatric Demographic Register, and basic demographic registers to assess legal, psychiatric and immigration, and employment status.

Outcome variables

The study focused on two outcome variables (Koch et al. 2011):

1. CVD was defined as an inpatient episode in which the primary ICD-10 diagnosis for the episode was a disease of the circulatory system (I00–I99), or an outpatient, including emergency room, episode in which the patients were given a diagnosis of heart failure (I11.0, I13.0, I13.2, I50.0) or atrial fibrillation

and flutter (I48.0). All cases diagnosed within the 3650 days (10 years) leading up to admission for DUD were coded.

2. New incidence was defined using the same criteria for the period from date of admission until death or at the end of 2011. In addition, patients were considered incident if cause of death was coded as a disease of the circulatory system (I00–I99).

Analyses

Prevalence was estimated in 5-year intervals of age by gender. Odds ratios for each strata and confidence intervals were calculated and pooled for both genders. A χ^2 test was used to test for trends indicating that the difference between individuals differed by age. Incidence was estimated among patients who had never been diagnosed with CVD before their first admission to treatment. Univariate odds ratios are reported for differences between patients with a history of CVD and other variables.

Competing risks regression was used to assess links between patient variables and CVD incidence (Haller et al. 2013). Competing risks regression posits a model for the sub-hazard function of a cause-specific event of primary interest that occurs in a situation when other events can occur that "prevent" the primary event from happening. In this case, if patients die from a cause that is unrelated to CVD, they are no longer at risk for CVD, yet they cannot be considered censored either. In the presence of such competing failure events, a standard Cox proportional hazards regression can produce incidence-rate curves that are misleading, and the effects of covariates on these curves cannot be quantified. Competing risks regression provides an alternative model for producing incidence curves that represent the observed data, and for which describing covariate effects is straightforward.

The maximum likelihood approach to competing risks regression was conducted according to Fine and Gray (1999). The predictors were age, gender, the presence or absence of various types of drugs (licit or illicit methadone, other opioid agonists, cannabis, cocaine, amphetamines, benzodiazepines, alcohol), and injection use. For injection use, codes were (1) never injected, (2) ever injected, and (3) not reported. To control for overall functioning, the following predictor variables were included: working or studying in the calendar year of admission to treatment for DUD, charges with an offense during the 365 days leading up to treatment, and care at a psychiatric facility in the 365 days prior to entering treatment. In a preliminary analysis, we controlled for number of different drugs used, but this variable had to be dropped due to colinearity with the remaining variables. We estimated the variance inflation factor for the predictors, a quantifier of the severity of multicollinearity. Since traditional cut-offs have been shown to be excessively restrictive (O'Brien 2007), a cut-off value of ten or higher was chosen to combine variables. Finally, logistic regression was used to assess associations between significant predictors from the competing risks model and the five most common types of CVD. Analyses were conducted using Stata 13 for Windows. We considered results significant if the p value was <0.05.

Ethics

This research was based on data collected for administrative and monitoring purposes. According to Danish law, such studies are not subject to evaluation by the regional ethics committees. To the knowledge of the authors, no burden or risk was imposed on the patients included in this study as a result of the research conducted (World Medical Association 2013) and no individuals can be identified through the data presented.

The Danish Data Protection Agency has approved all procedures in relation to data collection, and storage of the data. All data were stored at a central server by Statistics Denmark.

Results

Sample description

The mean age at treatment admission for DUD was 30.8 years (SD = 9.6); 13,405 (76.0 %) of the patients were male. Of all patients, 47.6 % reported using opioids, 52.4 % cannabis use, 17.9 % benzodiazepine use, 19.9 % amphetamine use, 20.1 % cocaine use, and 24.3 % alcohol use. Of the sample, 7.3 % reported abstinence at intake. The mean number of drugs per respondent was 2.1 (SD = 1.7).

Of the sample, 36.1 % reported never injecting drugs, 12.2 % injecting, but never sharing injection equipment, 16.4 % sharing injecting equipment, and 35.4 % did not answer the question. For particular drugs, 36.8 % of heroin users reported injecting the drug, as did 0.2 % of those reporting prescription methadone use, 8.9 % of those reporting illicit methadone use, 2.1 % of those reporting other opioid use, 6.0 % of amphetamine users, 15.8 % of cocaine users, and 1.5 % of those reporting benzodiazepine use.

Prevalence

The prevalence of CVD at treatment entry was 4.7 % (822 patients). Descriptive statistics are given in Table 1 by CVD history. Data from the present cohort as well as data

Table 1 Prevalence of cardiovascular disease among patients aged 18–74 Denmark 2001–2007, and in the general population Denmark 2009

Age	Men						Women					
	No CVD (*N*)	CVD (*N*)	Percentage (%)	Population prevalence 2009[a] (%)	OR	95 % CI	No CVD (*N*)	CVD (*N*)	Percentage (%)	Population prevalence 2009[b] (%)	OR	95 % CI
18–24	3909	36	0.9				1319	16	1.2			
25–34	4767	150	3.1				1265	72	5.4			
35–44	2978	190	6.0	1.9	3.29	(2.81–3.84)	921	94	9.3	1.7	5.90	(4.70–7.35)
45–54	1063	165	13.4	7.7	1.86	(1.57–2.20)	403	51	11.2	6.5	1.82	(1.33–2.44)
55–64	105	26	19.9	17.3	1.18	(0.74–1.83)	70	14	16.7	11.9	1.48	(0.77–2.65)
65–74	11	5	31.3	27.9	1.17	(0.32–3.67)	9	3	25.0	18.5	1.47	(0.26–5.88)
Total	12,833	572	4.3		2.27	(2.04–2.53)	3987	250	5.9		2.98	(2.52–3.52)

[a] Koch et al. (2011)

[b] Ibid

Table 2 Descriptive statistics for the cohort (Denmark 2001–2007, $N = 17{,}642$)

	History of cardiovascular disease ($n = 822$)		No history of cardiovascular disease ($n = 16{,}820$)		Odds ratio of cardiovascular disease history	95 % confidence interval	*P* value
	N (%)	Standard deviation	*N* (%)	Standard deviation			
Age at intake (years)	38.66	10.04	30.36	9.39	1.082	(1.075–1.090)	0.000
Drugs used past year at baseline (non-exclusive)							
Methadone, illicit	103 (12.5)		1778 (10.6)		1.212	(0.980–1.499)	0.076
Methadone, prescribed	329 (40.0)		2377 (14.1)		4.055	(3.503–4.693)	0.000
Other opioids	324 (39.4)		6057 (36.0)		1.156	(1.002–1.334)	0.046
Benzodiazepines	168 (20.4)		2981 (17.7)		1.193	(1.002–1.419)	0.047
Cocaine	116 (14.1)		3431 (20.4)		0.641	(0.525–0.783)	0.000
Amphetamine	83 (10.1)		3434 (20.4)		0.438	(0.348–0.551)	0.000
Cannabis	293 (35.6)		8952 (53.2)		0.487	(0.421–0.563)	0.000
Alcohol	155 (18.9)		4130 (24.6)		0.714	(0.597–0.853)	0.000
Infection risk behavior							
Never injected	164 (20.0)		6201 (36.9)		Reference		
Ever injected	278 (33.8)		4762 (28.3)		2.207	(1.813–1.678)	0.000
Not reported	380 (46.2)		5857 (34.8)		2.453	(2.035–2.965)	0.000
No previous treatment[a]	534 (65.0)		6922 (41.2)		0.377	(0.326–0.437)	0.000
Referred for methadone treatment	434 (52.8)		4115 (24.5)		3.453	(1.998–3.978)	0.000
Male gender	572 (69.6)		12,833 (76.3)		0.711	(0.610–0.828)	0.000
Working or studying[b]	127 (15.5)		5587 (33.2)		0.367	(0.303–0.445)	0.000
Immigrant	56 (6.8)		1272 (7.6)		0.893	(0.676–1.178)	0.425
Born to immigrant parents	9 (1.1)		190 (1.1)		0.961	(0.490–1.883)	0.908
Criminal history in past year	510 (62.0)		9349 (55.6)		1.306	(1.131–1.508)	0.000
Any mental health care in past year	161 (19.6)		3020 (18.0)		1.113	(0.933–1.328)	0.325

[a] Reference categories not included

[b] Individuals with missing data not included ($n = 212$, five with CVD, 207 with no CVD)

from a study of a general population sample from Denmark based on 2009 figures are included in Table 2 (Koch et al. 2011).

The pooled odds ratio for CVD among men with DUD was 2.27 (95 % CI: 2.04–2.53), and 2.98 for women (95 % CI: 2.52–3.52). For both men [χ^2 (1) = 36.14, $p < 0.001$] and women [χ^2 (1) = 42.33, $p < 0.001$], there were significant trends indicating that the risk of CVD was relatively higher in lower age brackets compared with older. The most remarkable differences for both genders are in the age bracket from 35 to 44 years of age where the odds ratio for having a history of CVD among DUD patients was 3.29 for men (95 % CI 2.81–3.84), and 5.90 for women (95 % CI 4.70–7.35), compared with the general population.

Differences between patients with and without CVD

The patients with CVD had a more severe history of drug use and social maladjustment, more often reported using prescription methadone [odds ratio (OR) = 4.055, $p < 0.001$], and less often cannabis (OR = 0.487, $p < 0.001$). The patients also injected more often (OR = 2.207, $p < 0.001$), or did not respond to the question about injection (OR = 2.453, $p < 0.001$), were more likely to be referred to methadone treatment (OR = 3.453, $p < 0.001$), and to have a criminal record (OR = 1.306, $p < 0.001$). Also, patients with CVD were older (OR = 1.082 per year, $p < 0.001$), less likely to be men (OR = 0.711, $p < 0.001$) and to be working or studying (OR = 0.367, $p < 0.001$). Patients with no previous treatment episodes were less likely to have a history of CVD (OR = 0.377, $p < 0.001$).

Incidence

Due to the exclusion of a few patients who had been diagnosed with CVD more than 10 years prior to entering drug treatment and whose data on work status were missing, 16,807 patients could be included as patients at risk for incidence calculations (in all 99.9 % of 16,820 patients at risk). The mean follow-up time period per patient was 7.5 years (range 0–11 years).

After admission to DUD treatment, 1535 patients were diagnosed with a CVD, either in a hospital or as the cause of death (9.1 % of all patients at risk; incidence of CVD). The incidence of CVD for the group who entered DUD treatment between 2000 and 2006 was thus 1342 new incidence cases per 100,000 person years. A total of 1584 (9.4 %) of the patient at-risk group died during follow-up, i.e., before 1 December 2011, and of these 86 died of CVD, leaving 1498 patients who died of non-CVD causes. The variance inflation factor for the predictor variables ranged from 1.02 to 1.50, indicating minimal multicollinearity, far below recommended thresholds, indicating that multicollinearity was not a significant problem for the analyses (O'Brien 2007).

Predictors of incidence are summarized in Table 3. Significant predictors included a history of injection use (SHR = 1.41, $p < 0.01$), missing data on injection use (SHR = 1.23, $p = 0.005$), older age at intake (SHR per year = 1.04, $p < 0.001$), use of prescription methadone prior to treatment entry (SHR = 1.32, $p < 0.001$), benzodiazepine use (SHR = 1.21, $p = 0.005$), having been referred for methadone substitution treatment (SHR = 1.15, $p = 0.022$), and criminal history (SHR = 1.14, $p = 0.019$). An additional interaction analysis showed that methadone was more important in women than in men, but failed to achieve statistical significance ($p = 0.08$).

Figure 1 shows the cumulative index function by methadone use (left-hand panel) and by self-reported injection drug use (right-hand panel). As can be seen, both factors are associated with an increased risk of new incidence CVD.

Types of CVD

Table 4 shows the types of incident CVD observed in the cohort covering the entire observation period. The most common types of CVD were diseases of veins, lymphatic vessels, and lymph nodes, followed by cerebrovascular disease, ischemic heart disease, and diseases of arteries, arterioles, and capillaries. Among the causes of death, the most common were ischemic heart disease and cerebrovascular disease.

Discussion

The findings show a high prevalence of CVD at a relatively young age among Danish patients with DUD at entry to drug use disorder treatment compared to published data from the general population. Also, the annual incidence of CVD is relatively high compared to the general population in Denmark (Koch et al. 2011), especially considering the mean age of 38 years in the cohort. During follow-up, the statistically significant risk factors for CVD were having used prescribed methadone or benzodiazepines in the year before entering treatment, being referred for methadone maintenance, reporting lifetime injection drug use, and a criminal record. These risk factors combined reflect that the patients with CVD had a more severe history of drug use and social maladjustment, but also support a more direct association between long-term opioid exposure and CVD. In terms of cannabis and stimulants, this study failed to show any link between use of these substances and risk of CVD.

In terms of the specific mechanisms linking drugs of abuse, routes of administration, and specific conditions,

Table 3 Predictors of new incidence of cardiovascular disease (competing risks regression) Denmark 2001–2007

	Sub-hazard ratio	95 % confidence interval	*P* value
Age at intake in years	1.04	(1.03–1.04)	0.000
Drugs[a]			
Prescribed methadone	1.32	(1.15–1.51)	0.000
Illicit methadone	1.05	(0.90–1.23)	0.520
Other opioids	1.12	(1.00–1.26)	0.060
Benzodiazepines	1.21	(1.06–1.38)	0.005
Cocaine	0.95	(0.82–1.11)	0.504
Amphetamine	0.75	(0.63–0.89)	0.001
Cannabis	0.92	(0.82–1.03)	0.163
Alcohol	0.98	(0.86–1.13)	0.824
Infection risk behavior			
Never injected	Reference		
Injected	1.41	(1.22–1.63)	0.000
Not reported	1.23	(1.06–1.41)	0.005
No previous treatment	0.97	(0.87–1.09)	0.623
Referred for methadone maintenance	1.15	(1.02–1.31)	0.022
Male gender	0.93	(0.83–1.09)	0.266
Working or studying	0.91	(0.80–1.04)	0.173
Immigrant	0.78	(0.64–0.96)	0.019
Born to immigrant parents	0.96	(0.58–1.58)	0.865
Criminal history in past year	1.14	(1.02–1.28)	0.019
Mental health services contact in past year	1.10	(0.96–1.26)	0.152

$N = 16{,}807$, total days at risk: 46,011,461. Incident cases: $n = 1535$, dying of unrelated causes: $n = 1498$, Wald χ^2 (19) = 465.95, $p < 0.0001$

[a] Drugs dummy coded, in all cases reference category is non-use of same drug

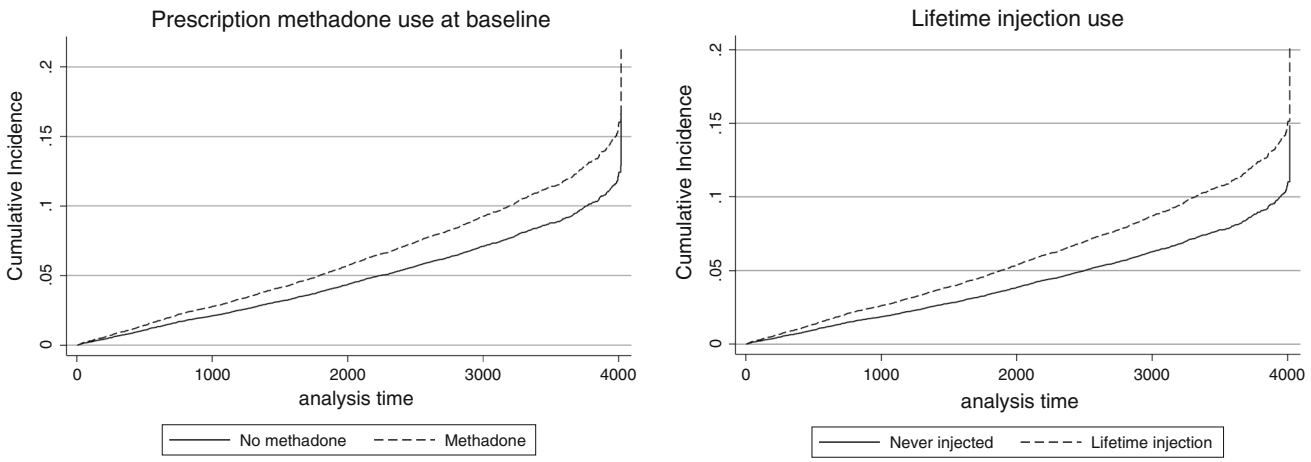

Fig. 1 Estimated cumulative incidence function by prescription methadone use (*left-hand panel*) and injection use (*right-hand panel*), Denmark 2001–2007. Analysis time is days in admission to treatment for substance use disorders, corresponding to up to 11 years

large-scale studies such as this may not provide the detailed information required to understand what causes disease and death in individual cases (Vieweg et al. 2013). However, the many cases of CVD linked to the veins and related organ systems are likely to be the result of intravenous drug use with unclean syringes and substances, causing local infections and inflammation. The observation of elevated rates of CVDs of arteries, coronary heart disease, and cerebrovascular disorders indicates that besides the local venous infections caused by injection practice, drug use, and opioid

Table 4 Types of cardiovascular disease in the cohort during the observation period excluding all patients prevalent at intake (Denmark 2001–2007, $N = 16{,}807$)

	At hospital contact including outpatient and inpatient settings		As underlying cause of death	
	N	Per 10,000	*N*	Per 10,000
Acute rheumatic fever (I00–I02)	0	0	0	0
Chronic Rheumatic disease (I05–I09)	4	2	1	1
Hypertension (I10–I15)	101	60	0	0
Ischemic heart disease (I20–I25)	276	164	30	17
Pulmonary heart disease (I26–I28)	93	55	9	5
Pericarditis (I30–I32)	52	31	0	0
Endocarditis (I33–I39)	160	95	11	6
Cardiomyopathy (I40–I43)	28	17	4	2
Conduction disorders (I45)	26	15	1	1
Cardiac arrest (I46)	112	67	2	1
Heart failure (I50)	74	44	3	2
Complications and ill-defined descriptions (I51)	16	10	11	6
Cerebrovascular disease (I60–I69)	287	171	28	16
Diseases of arteries, arterioles and capillaries (I70–I79)	241	143	6	3
Diseases of veins, lymphatic vessels and lymph nodes (I80–I89)	1425	847	5	3
Other and unspecified disorders of the circulatory system (I95–I99)	103	61	0	0

exposure in particular, may affect the cardiovascular system in a more systemic way, for example, through inflammatory, immunological, or altered hormonal processes.

This study does not provide sufficient evidence to suggest that methadone is associated with CVD, independently of its effects as an opioid agonist. However, the study yields support to the thesis that exposure to methadone contributes significantly to the cumulative risk of CVD resulting from chronic exposure to opioids in general (Reece and Hulse 2013, 2014; Sadeghian et al. 2007, 2010), Thus, it is not necessarily the methadone per se which constitutes the risk factor for CVD, but rather the cumulative exposure to opioids.

The links between benzodiazepine use and risk of CVD should be interpreted with caution, given the small number of studies supporting such a link and the modest effect sizes of these studies, and the potential for confounding of the effects of anxiety and depression on CVD risk with the effects of benzodiazepines (Jaussent et al. 2013; Lapane et al. 1995; Seldenrijk et al. 2015).

The observation that amphetamine use was associated with an lowered risk for both incident CVD compared to non-use of amphetamines was unexpected, as amphetamines have been reported to affect the cardiovascular system negatively (Hawley et al. 2013; Mooney et al. 2009; Westover et al. 2008). We cannot rule out that this was a false negative finding. It may be that amphetamine users are not as likely to seek health care during acute cardiovascular events, or that cardiovascular events among drug users more often are coded by ICD-10 codes relating to the drug use, i.e., "overdose with amphetamine", rather than primary cardiovascular diagnoses. On the other hand, studies have reported that fatal amphetamine overdoses are rare (Degenhardt et al. 2005; Nyhlen et al. 2011).

Age and gender

The most remarkable difference between the general population and the cohort of drug users was that in the young age brackets, CVD was substantially more common among patients seeking treatment for DUD. Among older patients, the prevalence of CVD approached that of the general population. In terms of gender, female patients were more likely to have CVD prior to entering treatment for SUD, but were not at higher risk following admission to treatment. Their odds of having CVD in the youngest age bracket were also significantly higher than that of the men. This is an issue that requires further study, since there is evidence that the long-term effects of opioids on the cardiovascular system are more serious in women than in men (Khademi et al. 2012; Reece and Hulse 2014).

Clinical implications

The observation that patients referred for and undergoing methadone maintenance treatment are at higher risk of CVD should lead treating physicians to pay extra attention to this patient group concerning CVD history and

cardiovascular health in general, since these patients may have difficulty accessing healthcare both in the substance use treatment system and in the general health system (Robbins et al. 2010). Further, there is now increasing evidence to suggest CVD, particularly arterial early onset aging, is a significant long-term side-effect of taking opioids whether in a therapeutic context or recreationally. This risk should be taken into account when prescribing types and doses of medication in opioid maintenance treatment. Patients should be educated about the elevated risk of CVD associated with opioid use and injection behavior, safer substance use and injection practices, the indications of CVD, and the importance of seeking healthcare in the event of symptoms indicating CVD.

Strengths and limitations

The main strengths of our study were the use of a large, national sample of patients, access to complete national registers, and a long period of measurement before and after treatment entry.

Coverage of health and cause of death registers are nearly complete. A small number of private hospitals in Denmark do perform some heart surgery, but the number of patients treated in these hospitals is considered to be so small that it is not of significance for the assessment of the prevalence and incidence of CVD in Denmark (Koch et al. 2011).

Additionally, we were able to control for a range of important indicators of drug use severity and social deprivation. However, the study also had significant limitations. One important limitation is that we do not have quality data on the Danish Drug Abuse Treatment Register in terms of coverage and quality of the data. Specifically, in the register's data collection form, patients were only asked about substance use in the previous year, but not about frequency of use or whether the use caused the patient problems. This means that we were not able to control for the varying drug use patterns of the patients.

We note that only 0.2 % of patients using prescription methadone reported injecting it in the year prior to entering treatment. This low figure may reflect under-reporting of methadone injection or the lack of questions about frequency in the data collection form. Under-reporting may have occurred with a higher frequency for prescription methadone users if patients feared that disclosing such injection would prevent them from getting take-home dosages or result in a higher level of monitoring with urine testing or supervised intake.

Although a high proportion of patients with CVD will end up in treatment, it is possible that patients with CVD and DUD in particular may ignore symptoms of CVD longer than people who do not have DUD, and may instead cope with pain and discomfort by increasing their use of drugs or alcohol, leading to a possible under-representation of CVD in this study. Also, it is possible that cases of CVD may have been misclassified as drug-related problems and behaviors.

Further, in relation to the link between opioid maintenance medication and CVD risk, it is a limitation that other treatment options for substitution treatment such as buprenorphine and diacetylmorphine were not generally available during the period when the patients in this study entered treatment. Thus, the study cannot contribute to comparison of these treatment options in relation to CVD risk.

A more significant limitation is that we have no data on treatment compliance during treatment. We strongly suspect that the monitoring of abstinence during treatment has varied greatly in different areas in Denmark over time, but we do not have access to robust data to test the importance of such monitoring in relation to later incidences of CVD.

Conclusions

Persons seeking treatment for DUD experience a higher prevalence of CVD than the general population, both in terms of CVD history prior to treatment entry and as CVD incident during follow-up. The most common types of CVD were disorders of the venous system. Higher severity of DUD, including injection drug use and methadone use, was associated with a higher incidence of cardiovascular disease during DUD treatment.

Perhaps the most important issue here is whether higher incidence of arterial side cardiovascular disease is the result of opioid exposure.

The presented epidemiologically derived results in combination with previously published findings point toward long-term exposure to opioids as being an independent and significant risk factor for CVD. It is important to bear in mind that even opioid medications as part of opioid maintenance treatment may contribute to this cumulative risk. The possible added risk for CVD should be part of the overall risk assessment and clinical focus when clinicians initiate opioid maintenance treatment for opioid addicted persons. Further research in the role of the long-term effects of opioid exposure on CVD is needed. Existing and new alternatives to the current medications in opioid methadone maintenance treatment should be further evaluated in terms of their influence on the risk of CVD. For patients who are already receiving long-term opioid maintenance treatment with opioids, the adequate provision of somatic health care services, including screening, monitoring, and treatment for CVD, is a significant task for service providers.

It is important to bear in mind that the provision of opioid maintenance treatment is currently the most potent and recommended evidence-based treatment for opioid addiction with the potential of reducing overall mortality by 50 % or more during treatment, largely due to reductions in fatal overdoses (e.g., Gibson et al. 2008). While this evident benefit of opioid maintenance treatment largely outweighs the potential added risk of CVD as shown in this study, improved knowledge about side-effects is an important future priority.

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