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CLINICAL RESEARCH
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Cannabis for chronic pain: cardiovascular safety in a nationwide Danish study

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See the editorial comment for this article 'Cannabis by any name does not smell as sweet: potential cardiovascular events with medical cannabis', by R.L. Page, https://doi.org10.1093/eurheartj/ehad848.

Abstract

Background and Aims A rising number of countries allow physicians to treat chronic pain with medical cannabis. However, recreational cannabis use has been linked with cardiovascular side effects, necessitating investigations concerning the safety of prescribed medical cannabis.

Methods Using nationwide Danish registers, patients with chronic pain initiating first-time treatment with medical cannabis during 2018–21 were identified and matched 1:5 to corresponding control patients on age, sex, chronic pain diagnosis, and concomitant use of other pain medication. The absolute risks of first-time arrhythmia (atrial fibrillation/flutter, conduction disorders, paroxysmal tachycardias, and ventricular arrhythmias) and acute coronary syndrome were reported comparing medical cannabis use with no use.

Results Among 1.88 million patients with chronic pain (46% musculoskeletal, 11% cancer, 13% neurological, and 30% unspecified pain), 5391 patients claimed a prescription of medical cannabis [63.2% women, median age: 59 (inter-quartile range 48–70) years] and were compared with 26 941 control patients of equal sex- and age composition. Arrhythmia was observed in 42 and 107 individuals, respectively, within 180 days. Medical cannabis use was associated with an elevated risk of new-onset arrhythmia {180-day absolute risk: 0.8% [95% confidence interval (CI) 0.6%–1.1%]} compared with no use [180-day absolute risk: 0.4% (95% CI 0.3%–0.5%)]: a risk ratio of 2.07 (95% CI 1.34–2.80) and a 1-year risk ratio of 1.36 (95% CI 1.00–1.73). No significant association was found for acute coronary syndrome [180-day risk ratio: 1.20 (95% CI 0.35–2.04)].

Conclusions In patients with chronic pain, the use of prescribed medical cannabis was associated with an elevated risk of new-onset arrhythmia compared with no use—most pronounced in the 180 days following the initiation of treatment.

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Structured Graphical Abstract

Key Question

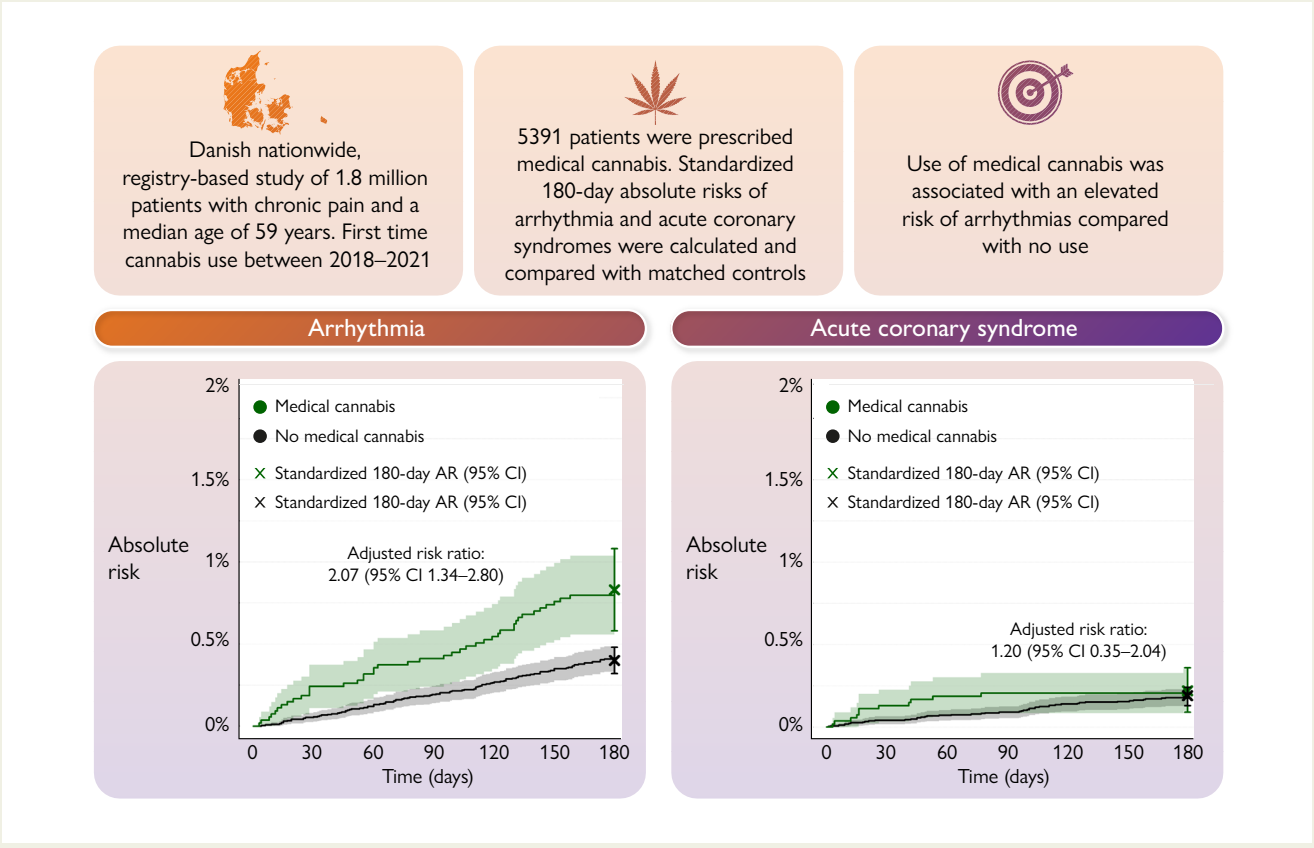
Data regarding cardiovascular side effects following medical cannabis use in chronic pain patients are limited. As recreational cannabis use has been associated with an increased cardiovascular risk, it is important to understand side effects following medical cannabis use.

Key Finding

Use of medical cannabis was associated with an elevated 180-day risk of new-onset arrhythmias compared with no use, while risk of acute coronary syndrome was low and similar in both users and non-users. The largest risk differences were found in patients with cancer or cardiometabolic disease.

Take Home Message

Due to the investigated cohort's low median age and low prevalence of comorbidities, the notable relative risk increase of arrhythmias may be reason for concern, even though the absolute risks in this study population are modest.



Medical cannabis and cardiovascular risk. A graphical representation of the main findings showing the risk of new-onset arrhythmia and acute coronary syndrome in patients with chronic pain according to the use of medical cannabis. AR, absolute risk; CI, confidence interval.

Keywords Drug safety • Medical cannabis • Arrhythmia • Acute coronary syndrome • Stroke • Heart failure • Chronic pain

Introduction

Data regarding cardiovascular side effects in relation to medical cannabis use in patients with chronic pain are very limited.[1–4] Nevertheless, an increasing number of countries are legalizing medical cannabis for treating chronic pain.[5] The active cannabinoid compounds in cannabis, tetrahydrocannabinol (THC) and cannabidiol (CBD), interact with the endocannabinoid system and have been associated with elevated heart rate, hypotension, and increased cardiac oxygen demand—in relation to *recreational cannabis* use.[6–8] Moreover, *recreational cannabis* use has been associated with an increased risk of arrhythmia and, to a lesser extent, acute coronary syndrome.[6,7,9]

The prevalence of chronic pain is high and rising; hence, the interest in new treatments is substantial.[10] This includes medical cannabis, although factors such as precise indications, efficacy, and magnitude of effect are continuously debated.[2–4] Consequently, it seems imperative to

investigate any side effects following the use of medical cannabis, especially cardiovascular side effects already linked to *recreational cannabis* use.[6,7,9]

Using Danish nationwide registers, associations between medical cannabis use and new-onset arrhythmia (atrial fibrillation/flutter, conduction disorders, paroxysmal tachycardias, and ventricular arrhythmias) among patients with chronic pain were investigated. A preliminary project description is available (see Supplementary data online, *Preliminary Project Description*).

Methods

Health registers

All data in this study originate from Danish nationwide health registers. These have been described in other reports and have been used previously by this research group using similar study designs (see Supplementary data online, *Appendix*).[11–16]

Setting

Medical cannabis has not been formally approved for the treatment of chronic pain in Denmark. However, on 1 January 2018, a medical cannabis trial programme was initiated by the Danish health authorities allowing any Danish physician to prescribe medical cannabis for chronic pain.[17] During the study period, medical cannabis products containing the combinations of CBD and THC were available for prescription, while products containing only CBD or only THC could be specifically ordered for manufacturing at certain pharmacies. Medical cannabis was available as inhalers, oromucosal sprays, oral solutions, tablets, and capsules. During the study period, all three types of medical cannabis could be prescribed for the treatment of chronic pain, creating a practical setting for this study.[17]

Population, exposure, and matching

All patients aged 18–100 years old and diagnosed with chronic pain or a disorder often linked to chronic pain (arthritis, back-related pain, disc-related pain, complicated fractures, cancer, neurological disease, headaches, and other unspecified pain diagnoses) during 2013–21 were identified. Diagnoses used were inspired by Gustavsson *et al.*[18] and revised to fit a Danish context (see Supplementary data online, *Table S1*). If a patient was diagnosed with more than one chronic pain diagnosis, the first diagnosis given was used for categorization. The study period was 2018–21; thus, patients diagnosed before 1 January 2018 were included on this date, and patients diagnosed during the study period were included on the date of diagnosis. Patients with a claimed prescription of medical cannabis before inclusion or with a history of arrhythmia were excluded (*Figure 1*). Case patients were identified, and follow-up was initiated on the date of their first claimed prescription of medical cannabis. To be certain that as many patients as possible prescribed medical cannabis for pain were included in the initial cohort, chronic pain was broadly defined on purpose (see Supplementary data online, *Table S1*). However, this loose definition equally elevated the chance that patients being prescribed medical cannabis would differ significantly from the remaining cohort. Thus, a matched cohort of control patients from within the cohort was comprised. Each medical cannabis–exposed case patient was matched on the date of the first claimed prescription to five control patients. Control patients were alive and without prior medical cannabis exposure or an outcome event, and the following matching variables were defined at inclusion into the chronic pain cohort: age, sex, chronic pain diagnosis, and the use of other pain medication [non-steroidal anti-inflammatory drugs (NSAIDs), anti-epileptic drugs, and opioids]. Matching was done using exact risk set sampling with a replacement where each control patient had to be similar to the case patient based on the given categorical variables.[19] See Supplementary data online, *Table S1* for specified International Classification of Diseases 10th revision and Anatomical Therapeutic Chemical codes used.

Outcome and follow-up

The outcome of new-onset arrhythmia was defined as a hospitalization or outpatient visit coded with a primary or secondary diagnosis of atrial fibrillation/flutter, conduction disorders, paroxysmal tachycardias, or ventricular arrhythmias (see Supplementary data online, *Table S1*). Thus, only diagnoses previously related to recreational cannabis use and diagnoses that would normally indicate treatment or further observation and evaluation were included.[6–9] Patients were followed up from the date of their first-time claimed prescription of medical cannabis or the corresponding date among control patients until the event of new-onset arrhythmia, death, 31 December 2021, or the completion of the predefined observation period of 180 days.

Baseline characteristics

Baseline characteristics were described at the time of inclusion for the entire cohort according to grouped chronic pain diagnoses: musculoskeletal, neurological, cancer, or unspecified pain (see Supplementary data online, *Table S1*). Likewise, characteristics at the date of follow-up initiation for exposed case patients and control patients were reported, including stratification by a medical cannabis agent.

The following characteristics were defined as present if any hospital contact was recorded within 5 years of baseline: hypertension, diabetes mellitus, ischaemic heart disease, ischaemic stroke, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, and chronic liver disease. Similarly, patients were defined as being concomitantly treated with the following medication if a prescription was claimed within 180 days before baseline: beta-blockers, renin–angiotensin system inhibitors, loop diuretics, statins, antiplatelet agents, and pain medication (NSAIDs, anti-epileptics, tricyclic anti-depressants, and opioids). In order to capture hypertension and diabetes mellitus diagnosed and treated outside of the hospital system, patients claiming at least two different antihypertensive agents and patients claiming a glucose-lowering drug were correspondingly identified as having hypertension and diabetes mellitus as well (see Supplementary data online, *Table S1*). Educational level was described at baseline and categorized according to the highest level of completed education as elementary or high school, vocational education, and higher education.

Subgroup analyses

The following stratified analyses were predefined to identify groups of particular risk or interest: stratified by (i) sex, (ii) age, (iii) medical cannabis agent, (iv) cancer as underlying pain diagnosis, and (v) history of cardiometabolic disease (hypertension, diabetes mellitus, ischaemic heart disease, heart failure, or ischaemic stroke).

Statistical analysis

Categorical characteristics were presented with total numbers and percentages, and continuous variables were presented as median with an interquartile range.

The Aalen–Johansen estimator was utilized to estimate the crude 180-day absolute risk of new-onset arrhythmia comparing exposed case patients with unexposed control patients in order to show simple descriptive statistics of the outcome.[20] Consecutively, multiple logistic regression and the inverse probability of censoring-weighted estimating equations were used to fit the statistical models and to account for censoring and competing risk of death accordingly.[21–23] We prespecified the adjustments for the following at the date of a claimed medical cannabis prescription or the corresponding date among controls: ischaemic heart disease, hypertension, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, educational level, and numeric age (adjustment variables were omitted for

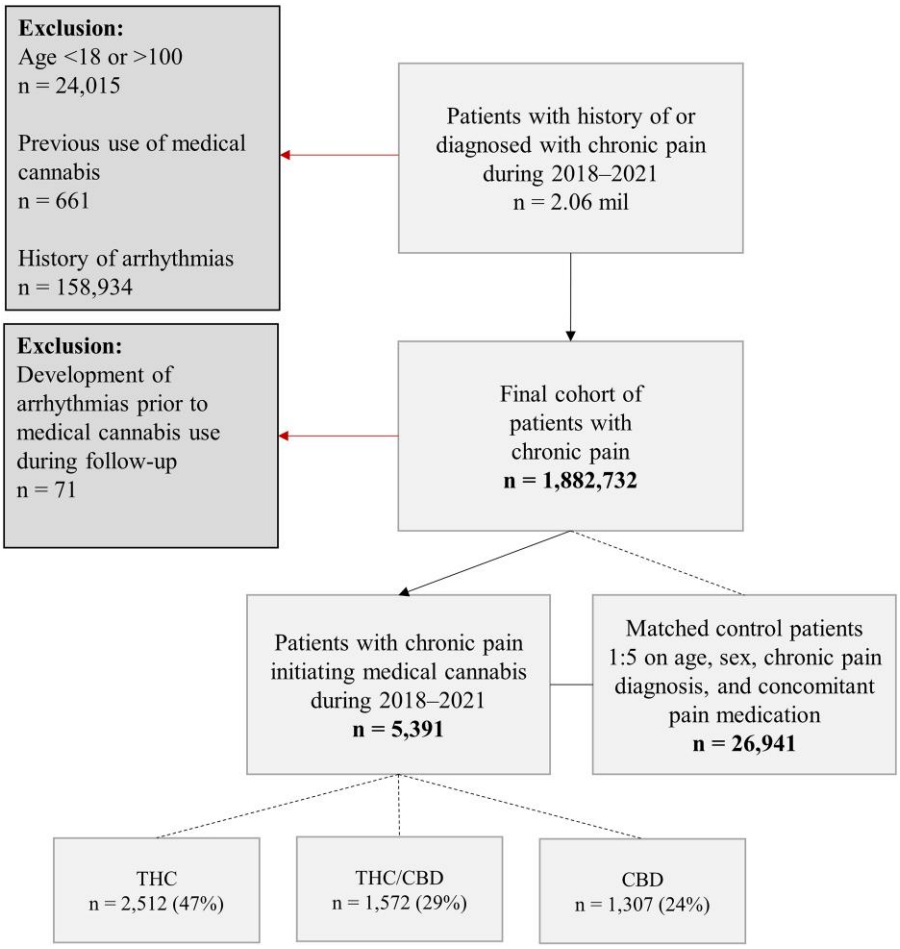


Figure 1 Flowchart of the matched study cohort. Flowchart showing the underlying cohort of patients with a diagnosis of chronic pain along with the matched dataset based on medical cannabis use within this cohort. Tetrahydrocannabinol refers to medical cannabis agents containing a large majority of tetrahydrocannabinol as the active component, tetrahydrocannabinol/cannabidiol refers to agents containing an equal amount of both, and cannabidiol refers to agents containing only cannabidiol. THC, tetrahydrocannabinol; CBD, cannabidiol

subgroups specified by one or more of the mentioned variables). The 95% confidence intervals (CIs) were obtained using bootstrap.[23] The standardized 180-day absolute risks with 95% CI were derived from the models and reported comparing patients exposed to medical cannabis with those who were not.

R (version 4.2.1 for Windows, R Foundation for Statistical Computing) was used for data management, statistical analysis, and illustrations.[24]

The statistical design is described in detail in the Supplementary data online, *Statistical Analysis Plan*.

Supplementary analyses

(1) To assess whether medical cannabis could be associated with an increased risk of acute coronary syndrome, a similar analysis with a primary or secondary diagnosis of acute coronary syndrome linked to an overnight hospitalization as an outcome was conducted as well.
(2) Similar analyses were done using a less-specific arrhythmia outcome definition (including syncope, extra-systoles, etc.) to assess the overall impact on patients' well-being, the hospital system, and public health resources possibly associated with medical cannabis use and arrhythmia (see Supplementary data online, *Table S1*). Analyses restricting the outcome to only include new-onset atrial fibrillation were conducted as well.
(3) To assess whether possible associations between concomitant treatment with opioids, anti-epileptics, and NSAIDs influenced the main comparison, either through previously reported direct effects or as proxy variables for pain severity, additional analyses where concomitant pain treatment at the start of follow-up was included as adjustment variables were conducted.[25–27]
(4) Analyses restricting the exposure definition to at least two consecutive prescription claims of medical cannabis were performed to better describe risk in, presumably, longer term users.
(5) To further test the robustness of the main results, a supplementary statistical approach was used as well. Multiple logistic regression models were fitted using the inverse probability of treatment-weighted equations to account for differences in the probability of receiving treatment between the compared groups.[23] Please see Supplementary data online, *Statistical Analysis Plan* for further details.
(6) To evaluate whether the associations persisted at longer follow-up, the main analyses were repeated with 365 days of follow-up.
(7) For exploratory purposes, additional analyses investigating associations between the use of medical cannabis and the risk of first-time stroke

and heart failure were conducted. The statistical analyses were similar to the main analyses, but the study group was further restricted to not include patients with a known history of stroke or heart failure, respectively, for each analysis.

Results

Characteristics

A total of 1.88 million patients with chronic pain were included in the cohort [median age 55 years (inter-quartile range: 41–69), 54% women], and pain diagnoses were 46% musculoskeletal, 11% cancer, 13% neurological, and 30% unspecified. Patients with cancer were older and had a slightly higher prevalence of comorbidity but were less likely to be concomitantly treated with pain medication compared with patients with musculoskeletal, neurological, or unspecified pain (see Supplementary data online, *Table S2*).

During the study period, 5391 patients [median age 59 (inter-quartile range: 48–70) 63.2% women] initiated medical cannabis treatment (24% CBD, 29% CBD/THC, and 47% THC). Patients initiated on medical cannabis were more likely to be concomitantly treated with other pain medication while comorbidity was similarly prevalent (*Table 1*). Comparing patients initiated on different medical cannabis agents, patients were similar according to age, comorbidity, and concomitant medication (*Table 1*).

New-onset arrhythmia

Within 180 days of follow-up, 42 exposed case patients developed new-onset arrhythmia (76% atrial fibrillation/flutter, 12% paroxysmal tachycardias, and 12% other arrhythmias), and 107 had an event among control patients (79% atrial fibrillation/flutter, 14% conduction disorders, and 7% other arrhythmias; see Supplementary data online, *Table S4*). The use of medical cannabis was associated with a standardized 180-day absolute risk of new-onset arrhythmia of 0.8% (95% CI 0.6%–1.1%) compared with a standardized 180-day absolute risk of 0.4% (95% CI 0.3%–0.5%) among matched control patients yielding a standardized 180-day absolute risk difference of 0.4% (95% CI 0.2%–0.7%) and a risk ratio of 2.07 (95% CI 1.34–2.80; *Figure 2*).

The association between medical cannabis use and the increased 180-day absolute risk of new-onset arrhythmia was consistently similar to the main analyses across prespecified subgroups but did not reach statistical significance in all analyses (*Figure 3*). The highest standardized 180-day absolute risk differences, comparing medical cannabis use with no use, were found among patients with cancer [180-day absolute risk difference of 1.1% (95% CI 0.2%–1.9%)] or cardiometabolic disease [180-day absolute risk difference of 0.8% (95% CI 0.2%–1.4%); *Figure 3*].

Supplementary analyses

(1) No significant association between the use of medical cannabis and the risk of acute coronary syndrome hospitalization was found [180-day absolute risk difference of 0.04% (95% CI −0.1%–0.2%) and an 180-day risk ratio of 1.20 (95% CI 0.35–2.04). The 180-day absolute risk among exposed case patients was 0.2% (95% CI 0.1%–0.3%), and the 180-day absolute risk among unexposed control patients was 0.2% (95% CI 0.1%–0.2%; see Supplementary data online, *Figure S1*).

(2) When redefining the outcome of arrhythmia to also include less-specific and less-severe diagnoses, similar results were obtained [risk ratio of 1.90 (95% CI 1.42–2.37)]. Different types of arrhythmia events observed using this definition are shown in Supplementary data online, *Table S4*. Assessing exclusively new-onset atrial fibrillation/flutter as an outcome yielded similar results as well with a risk ratio of 2.04 (95% CI 1.19–2.89) comparing medical cannabis use with no use (see Supplementary data online, *Figure S2*).

(3) Including concomitant treatment with opioids, anti-epileptics, and NSAIDs as adjustment variables yielded similar results compared with the main analyses. Comparing exposed case patients with unexposed control patients, risk ratios of 1.97 (95% CI 1.27–2.66) and 1.14 (95% CI 0.34–1.95) were found, correspondingly for new-onset arrhythmia and acute coronary syndromes.

(4) Restricting the exposure to only count patients as exposed following a second claimed prescription of medical cannabis, non-significant tendencies with the risk of new-onset arrhythmia were found with a risk ratio of 1.40 (95% CI 0.67–2.13) and a 180-day absolute risk difference of 0.2% (95% CI −0.1%–0.5%) comparing exposed case patients with unexposed control patients.

(5) Using the inverse probability of treatment weighting, associations were similar [risk ratio: 2.07 (95% CI 1.30–2.83)] to the main analyses with a 180-day absolute risk of new-onset arrhythmia of 0.8% (95% CI 0.6%–1.1%) vs. 0.4% (95% CI 0.3%–0.5%), correspondingly for use and no use of medical cannabis. Results obtained in the predefined subgroups were equal to the main analyses as well (data not shown).

(6) The standardized 1-year absolute risk of arrhythmia was elevated among patients exposed to medical cannabis (events, $n = 63$) compared with control patients (events, $n = 242$) with a risk ratio of 1.36 (95% CI 1.00–1.73; see Supplementary data online, *Figure S3*). No significant association was found for the outcome of acute coronary syndrome [risk ratio: 1.35 (95% CI 0.64–2.05); see Supplementary data online, *Figure S3*].

(7) Among patients exposed to medical cannabis ($n = 5207$ and $n = 5309$, correspondingly for stroke and heart failure analyses), 22 and 13 first-time events of stroke and heart failure, respectively, were observed within 180 days. Similarly, among control patients ($n = 26\,024$ and $n = 26\,531$), 117 and 119 first-time events were observed. Comparing patients exposed to medical cannabis with control patients, no significant associations with an elevated 180-day risk of first-time stroke or heart failure were found [risk ratios of 0.99 (95% CI 0.55–1.43) and 0.63 (95% CI 0.26–0.99), respectively] (see Supplementary data online, *Figure S4*).

Discussion

In a nationwide cohort of patients with chronic pain and a median age of 59 years, the use of medical cannabis was associated with an elevated 180-day risk of new-onset arrhythmia compared with no use. The 180-day absolute risk in both groups was <1%. The largest risk differences were found in patients with cancer or cardiometabolic disease. No associations were found between medical cannabis use and the risk of acute coronary syndrome (*Structured Graphical Abstract*).

Cardiovascular side effects following *recreational* cannabis use have been described previously, with THC and CBD identified as the main active compounds.[6,7,9] Activating the endocannabinoid system through receptors CB1 and CB2, THC and CBD have been related to arrhythmia through induction of the sympathetic nervous system, inhibition of the parasympathetic nervous system, and interaction with ion channels involved in the cardiac conduction system.[6]

Table 1 Characteristics at the beginning of follow-up among exposed case patients and the corresponding control patients, according to the medical cannabis agent

Characteristics	All		THC		THC/CBD		CBD	
	Control patients (*N* = 26 941)	Exposed case patients (*N* = 5391)	Control patients (*N* = 12 559)	Exposed case patients (*N* = 2512)	Control patients (*N* = 7856)	Exposed case patients (*N* = 1572)	Control patients (*N* = 6526)	Exposed case patients (*N* = 1307)
Age, median (IQR)	59 (48–71)	59 (48–70)	58 (46–69)	58 (46–69)	60 (49–70)	60 (49–70)	61 (49–73)	61 (49–73)
Women, *n* (%)	17 031 (63.2)	3407 (63.2)	7399 (58.9)	1480 (58.9)	5082 (64.7)	1017 (64.7)	4550 (69.7)	910 (69.6)
Pain diagnosis, *n* (%)								
Musculoskeletal	10 459 (38.8)	2092 (38.8)	4999 (39.8)	1000 (39.8)	2790 (35.5)	558 (35.5)	2670 (40.9)	534 (40.9)
Cancer	4507 (16.7)	903 (16.8)	1865 (14.8)	373 (14.8)	1670 (21.3)	334 (21.2)	972 (14.9)	196 (15.0)
Neurological	3595 (13.3)	720 (13.4)	1650 (13.1)	330 (13.1)	1031 (13.1)	207 (13.2)	914 (14.0)	183 (14.0)
Unspecified	8380 (31.1)	1676 (31.1)	4045 (32.2)	809 (32.2)	2365 (30.1)	473 (30.1)	1970 (30.2)	394 (30.1)
Comorbidity, *n* (%)								
Hypertension	5735 (21.3)	968 (18.0)	2597 (20.7)	409 (16.3)	1709 (21.8)	311 (19.8)	1429 (21.9)	248 (19.0)
Diabetes mellitus	2750 (10.2)	549 (10.2)	1267 (10.1)	232 (9.2)	836 (10.6)	195 (12.4)	647 (9.9)	122 (9.3)
Ischaemic heart disease	1315 (4.9)	296 (5.5)	612 (4.9)	135 (5.4)	385 (4.9)	96 (6.1)	288 (4.9)	65 (5.0)
Ischaemic stroke	891 (3.3)	195 (3.6)	403 (3.2)	73 (2.9)	254 (3.2)	77 (4.9)	234 (3.6)	45 (3.4)
Chronic obstructive pulmonary disease	1122 (4.2)	270 (5.0)	480 (3.8)	124 (4.9)	345 (4.4)	95 (6.0)	297 (4.6)	51 (3.9)
Chronic kidney disease	548 (2.0)	137 (2.5)	245 (2.0)	68 (2.7)	174 (2.2)	45 (2.9)	129 (2.0)	24 (1.8)
Heart failure	395 (1.5)	89 (1.7)	180 (1.4)	35 (1.4)	124 (1.6)	33 (2.1)	91 (1.4)	21 (1.6)
Liver disease	489 (1.8)	146 (2.7)	217 (1.7)	71 (2.8)	170 (2.2)	50 (3.2)	102 (1.6)	25 (1.9)
Medication, *n* (%)								
Pain medication								
NSAID	5056 (18.8)	1276 (23.7)	2327 (18.5)	555 (22.1)	1524 (19.4)	375 (23.9)	1205 (18.5)	346 (26.5)
Opioids	7962 (29.6)	2643 (49.0)	3511 (28.0)	1194 (47.5)	2618 (33.3)	888 (56.5)	1833 (28.1)	561 (42.9)
Anti-epileptics	6310 (23.4)	1880 (34.9)	2797 (22.3)	837 (33.3)	2128 (27.1)	628 (39.9)	1385 (21.2)	415 (31.8)
Tricyclic anti-depressants	1057 (3.9)	592 (11.0)	471 (3.8)	279 (11.1)	358 (4.6)	188 (12.0)	228 (3.5)	125 (9.6)
Other indications								
Beta-blockers	2814 (10.4)	516 (9.6)	1285 (10.2)	214 (8.5)	861 (11.0)	168 (10.7)	668 (10.2)	1349 (10.3)
RASi	6403 (23.8)	1095 (20.3)	2901 (23.1)	477 (19.0)	1876 (23.9)	352 (22.4)	1626 (24.9)	266 (20.4)

Continued

Table 1 *Continued*

Characteristics	All		THC		THC/CBD		CBD	
	Control patients (*N* = 26 941)	Exposed case patients (*N* = 5391)	Control patients (*N* = 12 559)	Exposed case patients (*N* = 2512)	Control patients (*N* = 7856)	Exposed case patients (*N* = 1572)	Control patients (*N* = 6526)	Exposed case patients (*N* = 1307)
Thiazides	2115 (7.9)	407 (7.5)	959 (7.6)	165 (6.6)	623 (7.9)	124 (7.9)	533 (8.2)	118 (9.0)
Loop diuretics	1676 (6.2)	385 (7.1)	744 (5.9)	153 (6.1)	522 (6.6)	132 (8.4)	410 (6.3)	100 (7.7)
Statins	5953 (22.1)	901 (16.7)	2707 (21.6)	397 (15.8)	1832 (23.3)	289 (18.4)	1414 (21.7)	215 (16.4)
Anti-platelets	3983 (14.8)	724 (13.4)	1776 (14.1)	330 (13.1)	1236 (15.7)	230 (14.6)	971 (14.9)	164 (12.5)
Educational level, *n* (%)								
Elementary or high school	8759 (32.5)	1551 (28.8)	4030 (32.1)	753 (30.0)	2563 (32.6)	422 (26.8)	2166 (33.2)	376 (28.8)
Vocational education	11 469 (42.6)	2221 (41.2)	5351 (42.6)	1014 (40.4)	3378 (43.0)	667 (42.4)	2740 (42.0)	540 (41.3)
Higher education	6713 (24.9)	1619 (30.0)	3178 (25.3)	745 (29.7)	1915 (24.4)	483 (30.7)	1620 (24.8)	391 (29.9)

Characteristics at the initiation of follow-up comparing case patients exposed to medical cannabis and the corresponding control patients. Characteristics stratified by cannabis agent are shown as well. Tetrahydrocannabinol refers to medical cannabis agents containing a large majority of THC as the active component, THC/CBD refers to agents containing an equal amount of both, and CBD refers to agents containing only CBD.
IQR, inter-quartile range; RASi, renin–angiotensin-system inhibitor; NSAID, non-steroidal anti-inflammatory drug; THC, tetrahydrocannabinol; CBD, cannabidiol.

Specifically, the expression of CB1 and CB2 was confirmed in cardiac tissue in mice, and interestingly, they were shown to have opposite effects with the activation of CB1 likely contributing to atrial cardiomyopathy and possibly supraventricular arrhythmias.[28,29] Previous clinical reports base their findings and conclusions on the use of *recreational* cannabis, but investigations concerning prescribed medical cannabis are lacking.[2]

To our knowledge, this is the first and only study investigating these associations with contemporary data. It is based on nationwide data through 4 years with an established cannabis pilot programme where any Danish physician was allowed to prescribe medical cannabis for chronic pain.[17] Previous reports seem to find stronger associations between THC exposure and cardiovascular side effects compared with CBD.[2,3,6,7] However, in this study, the results stratified by medical cannabis agents were similar, questioning whether CBD and THC could play similar roles in the proposed association with arrhythmia. Patients with known cardiometabolic disease and patients with cancer were the subgroups associated with the highest absolute risk differences, which could reflect an elevated susceptibility to the proposed side effects of medical cannabis use.[7] Although this finding was not surprising, quantifying the possible risk increase in patient groups suspected to be more susceptible and fragile could help inform on any possible need for mitigation and monitoring strategies. Moreover, significant associations between the risk of new-onset arrhythmia and medical cannabis use were also found in subgroups without cancer or cardiometabolic disease, which may further underline the validity of the overall association. The apparent lack of association between medical cannabis use and the risk of acute coronary syndrome, stroke, and heart failure could indicate that the short-term effect of medical cannabis use is mostly associated with alterations to the cardiac conduction system or atrial cardiomyopathy.[28,29] However, these findings should be explored further as larger sample sizes or longer follow-ups could yield different results—especially since the most common arrhythmia observed, atrial fibrillation, is closely linked to the risk of acute coronary syndrome, stroke, and heart failure.[30]

Not all patients continued the treatment beyond their first claimed prescription. This may be explained by the lack of effect or perhaps by early side effects leading to discontinuation of treatment. Restricting exposure to require two consecutively claimed medical cannabis prescriptions yielded insignificant results which might propose the association to be immediate and perhaps transient. Speculatively, this finding could also indicate that if patients tolerate the initial use of medical cannabis, the risk of continuing treatment might be very small. This is also suggested by the risk differences decreasing when patients were followed for longer than 180 days. This finding, however, could also be a result of patients categorized as on medical cannabis discontinuing treatment during follow-up for various, unknown reasons. The age of patients being prescribed medical cannabis was surprisingly low, which perhaps emphasizes the urgent demand for effective chronic pain treatment.[2,10] Likewise, commonly used pain treatments, such as NSAIDs, anti-epileptics, and opioids, have also been linked to elevated risk of arrhythmia.[25–27] As such, alternatives to medical cannabis pain treatment might equally well increase the risk of arrhythmias, which is important to bear in mind when considering the use of medical cannabis. However, adjusting for concomitant pain medication did not seem to alter the associations found between medical cannabis and the risk of arrhythmia in this cohort. This may imply a balanced comparison, or it could equally well be explained by patients already on concomitant pain medication might be more likely to have tolerated the medication without side effects. With the investigated

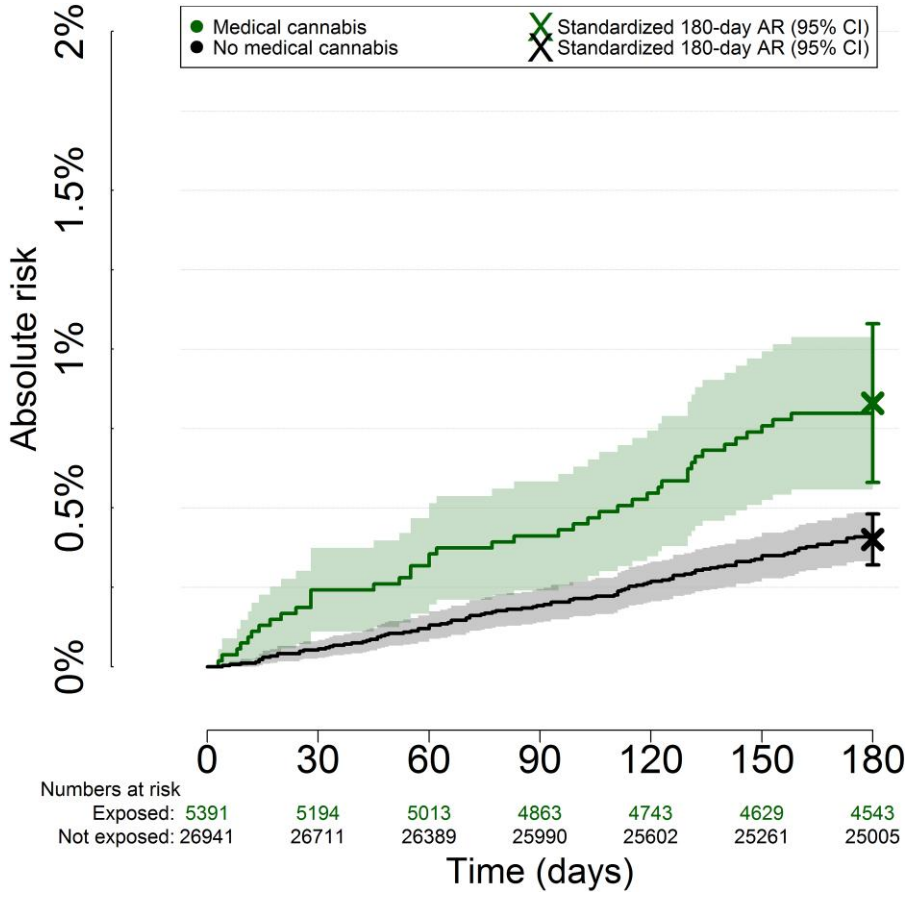


Figure 2 Crude and standardized 180-day absolute risk of new-onset arrhythmia comparing patients exposed and not exposed to medical cannabis. Curves are unadjusted absolute risks with 95% confidence intervals of new-onset arrhythmia for exposed and non-exposed. *X* indicates the standardized 180-day absolute risk with 95% confidence intervals derived from logistic regression models weighted by the inverse probability of censoring; adjusted for numeric age, educational level, known history of hypertension, ischaemic heart disease, diabetes mellitus, heart failure, and chronic obstructive pulmonary disease; and fitted in relation to the competing risk of death. AR, absolute risk; CI, confidence interval

cohort's low age and low prevalence of comorbidity in mind, the notable relative risk increase of new-onset arrhythmia, mainly driven by atrial fibrillation/flutter, could be a reason for concern, albeit the absolute risks in this study population were modest. Especially, if growing acceptance and availability of medical cannabis treatment will lead to increased use among patient groups with inherently greater risk of arrhythmia. If corroborated in future, randomized studies, previously unknown associations between the risk of new-onset arrhythmia and medical cannabis use should motivate improved vigilance regarding medical cannabis use—particularly with medical cannabis as pain treatment still being debated.[2,3]

Clinical perspective

Despite reviews questioning the value of medical cannabis use in patients with chronic pain,[2–4] the number of countries legalizing medical cannabis use is rising.[5] Meanwhile, data on the cardiovascular side effects following prescribed medical cannabis use are sparse—if existent at all.[2] Despite the observational nature of these findings, any knowledge on cardiovascular risk following medical cannabis use is vital for any physician prescribing medical cannabis, a position more and more physicians will likely find themselves in.

Strengths and limitations

Inclusion from nationwide health databases should minimize selection and inclusion bias, which is an important strength of this study. The broad definition of chronic pain increased heterogeneity in the cohort. However, exposed case patients and control patients were similar in terms of most characteristics, and the finding of similar results compared with the main findings in subgroups and supplementary analyses redefining outcome, exposure, and statistical method should strengthen perceived generalizability. Not all patients in the exposure group claimed a second prescription of medical cannabis, which could indicate that all exposed patients did not necessarily continue treatment. Speculatively, this could for example be due to side effects or the lack of effect. However, non-adherence in the exposure group would bias the results towards no association. Previous reviews suggest that route of administration could affect the treatment potency; thus, it is a limitation that we could not discriminate between administration routes.[2,3] It is a limitation that the registers do not contain information on disease severity, clinical measures, blood tests, and lifestyle factors, although including educational level in the statistical analyses should help reduce potential bias in relation to lifestyle factors in particular.[31,32] Baseline characteristics in relation to comorbidity and

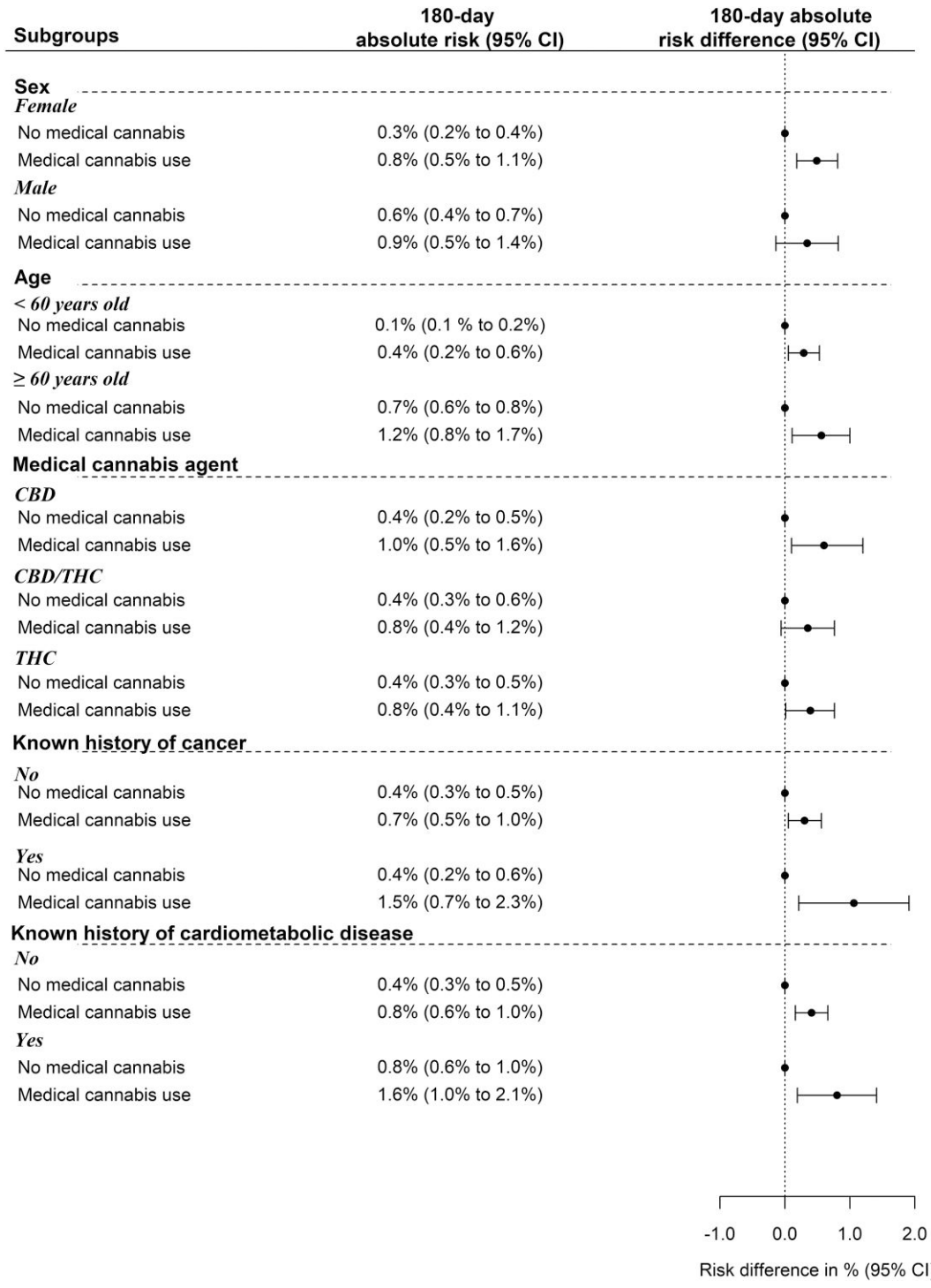


Figure 3 Standardized 180-day absolute risk and risk differences of new-onset arrhythmia comparing patients exposed and not exposed to medical cannabis, according to subgroups. Tetrahydrocannabinol refers to medical cannabis agents containing a large majority of tetrahydrocannabinol as the active component, tetrahydrocannabinol/cannabidiol refers to agents containing an equal amount of both, and cannabidiol refers to agents containing only cannabidiol. The forest plot depicts standardized 180-day absolute risk differences comparing medical cannabis use with no use. The statistical method is described in *Figure 2*. CI, confidence interval; THC, tetrahydrocannabinol; CBD, cannabidiol

concomitant medication were for the most part clinically similar between exposed patients and control patients, but the presence of residual confounding cannot be ruled out with certainty. Reassuringly, considerable unmeasured confounding should also bias the outcome of acute coronary syndrome towards a positive association, which was not the case.

Conclusions

In a nationwide cohort of patients with chronic pain, the use of medical cannabis was associated with an elevated risk of new-onset arrhythmia compared with no use. Despite a low absolute risk difference, this is vital knowledge for any prescribing physician due to the rising demand for medical cannabis as pain treatment.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

C.T.-P. reports research grants from Novo and Bayer. M.L. reports research grants from Karen Elise Jensen Fonden, Danish Heart Foundation, Bayer, and BMS; speaker fees from BMS/Pfizer, Bayer, Astra Zeneca, MSD, and Merck; and advisory board positions with BMS/Pfizer, Bayer, and Mundipharma. M.S. reports speaker fees from Novartis, Bohringer Ingelheim, Bayer, Novo, and Astra Zeneca. All other authors report no conflict of interest.

Data Availability

It is not allowed by Danish law to share the data used for this study.

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Ethical Approval

Observational studies using administrative health registers are exempt from ethical approval in Denmark. The study was approved by the Data Protection organization of the Capital Region of Denmark (approval no. P-2019-191).

Pre-registered Clinical Trial Number

Not applicable.

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