Clinical Policy: Critical Issues Related to Harms of Cannabis Exposure in Adult Patients Presenting to the Emergency Department, Cardiovascular Considerations

DRAFT

From the American College of Emergency Physicians Clinical Policies Subcommittee on Cannabis Consumption.

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ABSTRACT

This clinical policy from the American College of Emergency Physicians is a novel document. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical question: 1) Are people who have recently or chronically consumed marijuana at increased risk of cardiovascular effects requiring a visit to the emergency department compared with the overall population of ED visits? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Cannabis use is increasing in North America. Between 2008 and 2022, per capita past-year cannabis use in the U.S. increased 120% and daily or near-daily use (at least 21 days per month) increased 15-fold. (Caulkins 2024) Increasing use of cannabis has followed changes in its legal status, first by state-led legalization of medical marijuana and later by state legalization of recreational cannabis. Liberalization of cannabis' legal status has led to increased access to cannabis as well as decreasing perceptions of harm.

Increasing cannabis availability has revealed some safety concerns. Cannabis-related emergency department (ED) visits have increased. (Roehler 2021). Recent studies have raised concerns regarding an association between cannabis use and CV events (Jouanjus 2017, Moussouttas 2004, Jeffers 2024). Cannabinoid (CB) receptors are expressed in CV tissue and on platelets, presenting a plausible pathophysiologic pathway. Underlying mechanisms responsible for this correlation may be due to decreased perfusion or procoagulant effects of cannabis. Most strokes related to cannabis consumption are ischemic in nature (versus hemorrhagic), and neuroimaging suggests that reversible cerebral angiopathy is associated with at least some of these presentations. (Wolff 2013) The multifocal intracranial stenosis observed in these cases is thought to be a variant of reversible cerebral vasoconstriction syndrome (RCVS), which cannabis has been shown to cause. In addition to cerebral

vasospasm, transient coronary vasospasm has been associated with cannabis exposure. (Goyal 2017) In animal studies, endothelial function is impaired after exposure to cannabis smoke (Wang 2016). Thrombotic causes of CV events may be explained by a cannabis-related increase in procoagulant proteins leading to platelet activation. (Deusch 2004) Cannabis use has been associated with dysrhythmias, including atrial fibrillation, ventricular tachycardia, and ventricular fibrillation, perhaps due to either ischemia or direct interaction with the cardiac conduction system (Richards 2020, Goyal 2017). Although multiple plausible pathophysiologic pathways have been proposed, there is no solid theoretical underpinning for the observed association. Additionally, the numerous proposed interactions between cannabis and the cardiovascular system suggest that these CV events may be multifactorial.

In February 2022, the Board of Directors tasked the Clinical Policies Committee with the first resolved of Resolution 50(21), Complications of Marijuana Use, which states: "RESOLVED, That ACEP develop practice guidelines on the treatment of complications of marijuana use as seen in emergency department presentations[.]"

After an initial scoping search did not reveal substantive literature to address a critical question on this topic, the Clinical Policies Committee received permission to adjust the aim of the clinical policy to address considerations of potential harm related to increasing marijuana availability. The Clinical Policies Committee is developing a series of clinical policies examining the relationship between cannabis use and ED relevant conditions. This policy examining adverse cardiovascular events as the outcome is the first in this series.

METHODOLOGY

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of PubMed, Science Direct, Scopus, and Embase were performed. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the

bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP clinical policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the recommendation (ie, Consensus recommendation). Internal and external review comments were received from _____. Comments were received during a 60-day open comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site. The responses were used to further refine and enhance this clinical policy; however, responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this clinical policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the

background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances in which consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as consistency of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient (Appendix C).

This policy is not intended to be a complete manual on the evaluation and management of adult patients with blunt trauma but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to answer the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline is intended for patients age 16 and older presenting to the ED for cardiovascular events (including acute coronary syndrome and stroke).

Exclusion Criteria. This guideline is not intended for patients age 15 and under, pregnant patients, patients with accidental cannabis exposure, or patients using non-cannabis substances such as synthetic cannabinoids.

CRITICAL QUESTIONS

Are people who have recently or chronically consumed marijuana at increased risk of cardiovascular effects requiring a visit to the emergency department compared with the overall population of ED visits?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Physicians may consider medical cannabis use a risk factor for cardiovascular events, including ACS and stroke.

Consensus Recommendations

Potential Benefit of Implementing the Recommendations:

Recognition of medical cannabis use as a risk factor for CV events can aid a physician in risk-stratifying a patient presenting to the ED with signs and symptoms suggesting a CV event.

Integrating knowledge of medical cannabis use as a risk factor for adverse cardiovascular events into ED substance abuse intervention efforts.

Informing policy discussions related to medical cannabis

Potential Harm of Implementing the Recommendations:

Discouraging medical cannabis patients from utilizing cannabis for whom the benefits may outweigh the risks

Key words/phrases for literature searches: Marijuana, Cannabis, THC, Tetrahydrocannabinol, Cannabinol, Emergency Medicine, Emergency Department, Emergency Room, Cardiovascular effects, Myocardial Infarction, Cardiomyopathy, Dysrhythmia, Arrhythmia, Stroke, Cardiac Arrest, Atrial Fibrillation, Long QT, Tachycardia, Ventricular Premature Complexes, Ventricle extrasystole, Atrial Premature Complexes, Atherosclerosis

Study Selection: Two hundred and fifty-seven articles were identified in the searches. Seventeen were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, 0 Class I studies, 0 Class II studies, and 1 Class III study were included for this critical question (Appendix E4, available at http://www.annemergmed.com). Appendix E6 lists the 16 articles graded for methodological rigor but were ultimately found to not meet methodological criteria for inclusion for this question.

Although numerous studies have examined the association between cannabis exposure and cardiovascular outcomes, few have specifically focused on ED populations or utilized ED relevant outcomes.

In a 2021 class III longitudinal retrospective cohort study, Zongo et al examined the association between medical cannabis use and ED presentations for CV events. This study matched adult patients authorized to use cannabis (n = 18,653) with up to three controls selected from the general population of Ontario (n = 51,243) with matching

based on age, geographic location, income, and history of health conditions. The primary outcome was an ED visit or hospitalization for ACS or stroke and secondary outcome was for any CV event. Patients authorized to use medical cannabis had an increased incidence of ACS or stroke [adjusted hazard ratio (aHR) 1.44 (95% CI 1.08 - 1.93)] over a median follow-up of 242 days. When stratified for sex, the association was only statistically significant among males: aHR 1.77 (1.23–2.56). For the secondary outcome (any CV event), the aHR was 1.47 (1.26–1.72), with no difference between males and females. Of note, no dose-response analysis was performed. Additionally, the generalizability of this study to the general ED population and recreational users of marijuana is unclear. It is possible that the medical marijuana authorized population carries distinct risks for cardiovascular events, that marijuana interacts uniquely with underlying medical conditions to increase cardiovascular risks, or that unmeasured confounders are at least partly responsible for the observed association. This study provides weak but direct evidence to support the consideration of medical cannabis use as a risk factor adverse cardiovascular events in an ED population.

Future Research

While early reports suggest an association between cannabis exposure and CV outcomes requiring ED visits, this relationship is still poorly understood. Future research should study this effect in other populations, such as recreational cannabis users. Preclinical research should continue to search for pathophysiological mechanisms underlying these adverse outcomes. Although challenging due to the variability in available cannabis products, quantifying the types and levels of exposure that confer risk of adverse CV outcomes will assist physicians in counseling patients about safe cannabis use. Such quantification would also assist physicians in evaluating the risk level of an individual patient given their history of cannabis exposure.

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Appendix A. Literature classification schema.*

Design/ Class	**Therapy**†	**Diagnosis**‡	**Prognosis**§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

Downgrading	Design/Class 1	2	3
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

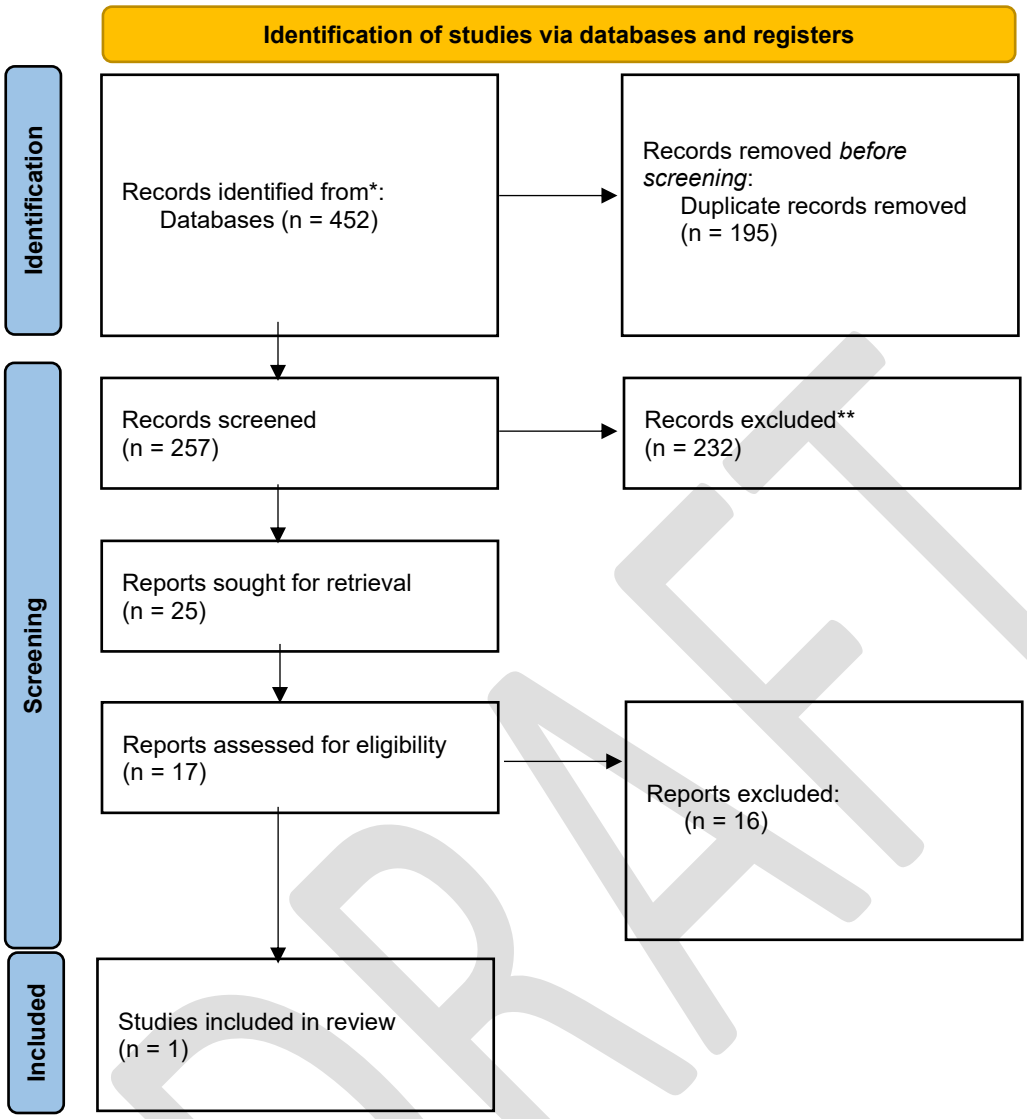
Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.

*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix E4. PRISMA flow diagram (Page 2021)



Evidentiary Table. (please use track changes for any edits made in this)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Zongo (2021)	**III**	Longitudinal cohort study in Ontario, Canada (2014–2017)	18,653 patients authorized for medical cannabis matched to 51,243 controls (population-based). Primary outcome: ED visit/hospitalization for acute coronary syndrome (ACS) or stroke. Secondary outcome: any cardiovascular (CV) event. Conditional Cox proportional hazards regression used for analysis.	- Incidence of ACS/stroke: 7.19/1000 person-years (cannabis group) vs. 5.67/1000 person-years (controls). Adjusted Hazard Ratio (aHR) = 1.44 (95% CI 1.08–1.93). - Incidence of any CV event: 28.34/1000 person-years (cannabis group) vs. 19.00/1000 person-years (controls). aHR = 1.47 (95% CI 1.26–1.72). - Risk was statistically significant among males (ACS/stroke aHR = 1.77, 95% CI 1.23–2.56) and in patients over 40 years (aHR = 1.42, 95% CI 1.05–1.92).	Possible residual confounding (e.g., lifestyle factors, smoking, BMI). No data on cannabis dosage, route of administration, or chemical composition. Potential misclassification bias if controls used cannabis recreationally.

Appendix E6. Articles graded for methodological rigor but ultimately found to be fatally flawed.

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