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JACC REVIEW TOPIC OF THE WEEK

Marijuana Use in Patients With Cardiovascular Disease

JACC Review Topic of the Week

Ersilia M. DeFilippis, MD,[a] Navkaranbir S. Bajaj, MD, MPH,[b] Amitoj Singh, MD,[c] Rhynn Malloy, PharmD,[d] Michael M. Givertz, MD,[d] Ron Blankstein, MD,[d] Deepak L. Bhatt, MD, MPH,[d] Muthiah Vaduganathan, MD, MPH[d]

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) select patients who would benefit from screening for marijuana use including the use of urine toxicology to supplement the social history; 2) compare the differences in inhaled toxin profile between tobacco smoking and marijuana smoking; 3) discuss the medication classes that have potential pharmacologic interactions with marijuana and its derivatives; and 4) identify the barriers to rigorous controlled clinical trials on marijuana and its cardiovascular effects.

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From the [a]Columbia University Irving Medical Center, New York, New York; [b]University of Alabama at Birmingham, Birmingham, Alabama; [c]Sarver Heart Center, University of Arizona, Tucson, Arizona; and the [d]Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, Massachusetts. Dr. Blankstein has received research support from Amgen and Astellas. Dr. Bhatt has served on the Advisory Board of Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, and Regado Biosciences; has served on the Board of Directors of Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; has served as Chair of the American Heart Association Quality Oversight Committee, NCDR-ACTION Registry Steering Committee, and VA CART Research and Publications Committee; has served on Data Monitoring Committees for Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi-Sankyo), and the Population Health Research Institute; has received honoraria from the American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), and WebMD (CME steering committees); has served as Deputy Editor of *Clinical Cardiology*; has received research funding from Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, PLx Pharma, Pfizer, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; has received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as Site Co-Investigator for Biotronik, Boston Scientific, St. Jude Medical (now Abbott), and Svelte; is a Trustee of the American College of Cardiology; and has performed unfunded research for FlowCo, Merck, Novo Nordisk, and Takeda. Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (National Institutes of Health/National Center for Advancing Translational Sciences Award UL 1TR002541); has served on Advisory Boards for Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, and Relypsa; and has participated on clinical endpoint committees for studies sponsored by Novartis and the National Institutes of Health. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Marijuana Use in Patients With Cardiovascular Disease

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Ersilia M. DeFilippis, MD,[a] Navkaranbir S. Bajaj, MD, MPH,[b] Amitoj Singh, MD,[c] Rhynn Malloy, PharmD,[d] Michael M. Givertz, MD,[d] Ron Blankstein, MD,[d] Deepak L. Bhatt, MD, MPH,[d] Muthiah Vaduganathan, MD, MPH[d]

ABSTRACT

Marijuana use is increasing as more states are legalizing cannabis for both medicinal and recreational purposes. National survey data estimate that >2 million Americans with established cardiovascular diseases currently use or have used marijuana in its variety of forms, including inhalation and vaping. Cannabinoid receptors are distributed in multiple tissue beds and cells, including platelets, adipose tissue, and myocytes. Observational data suggest associations between marijuana and a broad range of adverse cardiovascular risks. Marijuana is becoming increasingly potent, and smoking marijuana carries many of the same cardiovascular health hazards as smoking tobacco. Synthetic cannabinoids have been linked to more sustained and deleterious pharmacodynamic effects. Marijuana is classified as a Schedule I substance, thus limiting its rigorous study for cardiovascular health effects. This review summarizes cardiovascular considerations related to marijuana use, pharmacological interactions, and future steps to provide clearer guidance regarding its cardiovascular safety. Screening for marijuana use is encouraged, especially in young patients presenting with cardiovascular disease.
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The use of marijuana and its derivatives is increasing as more states are legalizing these products for both medicinal and recreational purposes (1,2). This accompanies an increasing prominence of vaping and new tobacco products, such as electronic cigarettes and water pipe (hookah) smoking, both of which have prompted statements by the American Heart Association (3,4). Furthermore, vaping-related health hazards are on the rise, with increasing reports of pulmonary illnesses and respiratory failure (5). With growing use, patients are increasingly inquiring about the cardiovascular safety of marijuana, especially when used alongside other commonly prescribed cardiovascular therapies. Yet, the cardiovascular effects of marijuana are still not fully understood, and comprehensive scientific studies and recommendations are lacking to guide the cardiovascular community (6). Limited observations have implicated delta-9-tetrahydrocannabinol (THC), the active ingredient in marijuana, in contributing to a broad range of cardiovascular events (7–9); however, the level of evidence has not been robust. In addition, cannabinoids may have drug interactions with a variety of cardiovascular medications. In this review, we discuss relevant mechanisms of potential cardiovascular risks related to marijuana, discuss pharmacological interactions with common cardiovascular therapies, and synthesize a practical approach to approaching marijuana use in cardiovascular clinical care settings.

CURRENT USE OF MARIJUANA IN THE UNITED STATES

CHEMICAL PROPERTIES AND COMMON USES. Marijuana is a greenish-gray mixture of the dried leaves, flowers, stems, and seeds of the *Cannabis sativa* or *Cannabis indica* plant. The plant also contains >500 other chemicals, including >100 compounds that are chemically related to THC, called cannabinoids. Specifically, common compounds include cannabinol (CBN), cannabidiol, and THC, which is the most psychoactive chemical in marijuana (10). Cannabinoids are available in oral, sublingual, and topical formulations.

The effects of marijuana are mediated through the endocannabinoid system (11,12). Cannabinoid (CB) receptors are distributed in multiple tissue beds and cell types (**Figure 1**). CB-1 receptors are present in high concentrations in the central and peripheral nervous systems, but also exist on platelets, adipose tissue, myocytes, liver, pancreas, and skeletal muscle (11). Therefore, exogeneous cannabinoids can exert effects on multiple systems (**Table 1**) (12). In settings of tissue injury, endocannabinoids are generated in excess with enhanced CB-1 receptor signaling. CB-2

HIGHLIGHTS

- We estimate that >2 million U.S. adults who have reported ever using marijuana have cardiovascular disease.
- Observational studies have suggested an association between marijuana use and a range of cardiovascular risks.
- Marijuana is becoming increasingly potent, and smoking marijuana carries many of the same cardiovascular health hazards as smoking tobacco.
- Few randomized clinical trials have been conducted or are planned to explore the effects of marijuana on cardiovascular risk.
- Screening and testing for use of marijuana are encouraged in clinical settings, especially in the care of young patients presenting with cardiovascular disease.

receptors are present on immune cells, osteoclasts, and osteoblasts.

In addition to naturally derived cannabinoids, various related formulations have been synthesized. The U.S. Food and Drug Administration has approved 3 cannabinoids for medical use: 1) cannabidiol, an oral solution for the treatment of seizures in rare forms of epilepsy; 2) dronabinol (synthetic THC) to treat refractory chemotherapy-associated nausea/vomiting and human immunodeficiency virus-related anorexia/weight loss; and 3) nabilone (synthetic chemical structure similar to THC) for refractory chemotherapy-associated nausea/vomiting.

The potency of marijuana has been steadily increasing over time (13). Synthetic cannabinoids (SCB), including "Spice" and "K2," have existed for more than a decade, during which they may have undergone potentially dangerous pharmacological alteration. These SCBs are not under specific federal regulation (14). SCBs may be up to 100-fold more potent than THC and have been linked to more sustained and deleterious downstream pharmacodynamic effects (15,16). Similarly, hydroponic methods of cultivation used in small-scale recreational production may include potentially harmful plant growth regulators and produce more potent marijuana.

BURDEN OF DISEASE. Marijuana is the most commonly used drug of abuse according to the 2015 National Survey on Drug Use and Health. It is currently classified as a Schedule I drug by the U.S. Drug Enforcement Administration, meaning that it is a drug with "no currently accepted medical use and a high potential for abuse." However, it is worthwhile recognizing this is a policy distinction, and there is existing evidence for medical use for noncardiovascular conditions.

Data from the National Survey on Drug Use and Health, an annual survey of the U.S. civilian, noninstitutionalized population, demonstrated that in 2016 and 2017, >39 million respondents reported use of marijuana in the last year (**Figure 2**). Its use is more prevalent among men than women—a gender gap that widened in the years 2007 to 2014. A recent analysis of the Behavioral Risk Factor Surveillance System found that adults with medical conditions were significantly more likely to report current marijuana use (17). Most (77.5%) of marijuana users reported smoking as their method of administration (17).

We conducted a dedicated query of the NHANES (National Health and Nutrition Examination Survey) from 2005 to 2016 to estimate marijuana use in patients with cardiovascular diseases. In NHANES, marijuana use was defined as those responding "yes" to ever using hashish or marijuana. Cardiovascular disease was defined broadly as those responding "yes" to ever being told by a health care provider they had congestive heart failure, coronary heart disease, or a heart attack. In 2015 to 2016, the response rates to both sets of questions were 49.4%. By applying sampling weights to available respondent data, we estimated that 2 million (2.3%) of the 89.6 million adults who reported marijuana use had cardiovascular disease in the United States in 2015 to 2016 (**Figure 3**). However, given the substantial nonresponse, these data are subject to response bias.

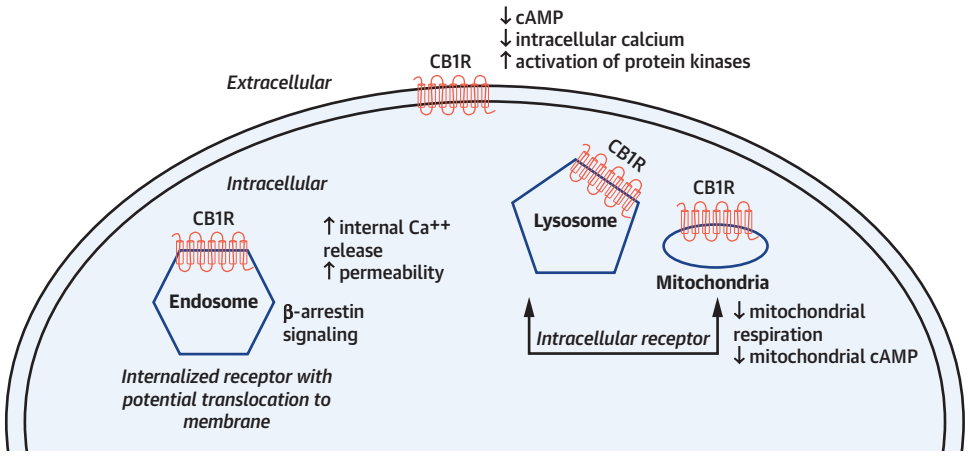
An analysis of the NIS (National Inpatient Sample) from 2010 to 2014 identified 465,959 hospitalizations (representing 2.3 million weighted hospitalizations in the U.S. population) of people with history of marijuana use, using administrative coding. The most common nonpsychiatric primary discharge diagnoses included diabetes mellitus, acute myocardial infarction, and nonspecific chest pain, among others (18). Importantly, patients with coronary atherosclerosis and peripheral vascular disorders independently faced the highest risks of in-hospital mortality (18).

LEGALIZATION. In recent years, there has been increasing legalization at the state level both with regard to medical use and recreational use. Recreational marijuana is currently legal in 11 states and the District of Columbia; other states are currently

ABBREVIATIONS AND ACRONYMS

CB = cannabinoid
CBN = cannabinol
CYP = cytochrome P
SCB = synthetic cannabinoids
THC = delta-9-tetrahydrocannabinol

FIGURE 1 Cellular Mechanisms of Marijuana Effects



Cannabinoid receptor 1 (CB1R) is typically located on the cell surface and generally inhibits cyclic adenosine monophosphate (cAMP) formation that, in turn, decreases calcium influx. It can be internalized as a ligand-induced receptor mediating signaling pathway via β-arrestin. In contrast, intracellular CB1Rs do not translocate and can increase intracellular calcium through release of internal lysosomal calcium stores via increased membrane permeability. Additionally, CB1Rs located in mitochondria will decrease mitochondrial respiration and cAMP formation, thus regulating cellular energy metabolism.

contemplating similar legalization policies. Medical marijuana was legal in 33 states as of July 2019.

MECHANISMS OF CARDIOVASCULAR RISKS ASSOCIATED WITH MARIJUANA

With increasing patterns of use and potency of marijuana, recent increases in cannabis-related adverse health effects have been reported (19). However, these associations have been largely based on case reports, case series, or observational studies (20). When reported, marijuana use has often been self-reported, and few have collected "doses" or blood levels. Many epidemiological studies may be confounded by factors related to health care access and other adverse health behaviors (concurrent tobacco use and other drugs of abuse). Acknowledging the limited scope of data, few mechanisms of cardiovascular risk have emerged (7) (**Figure 4**).

TABLE 1 Distribution and Potential Effects of CB1R Signaling (12)

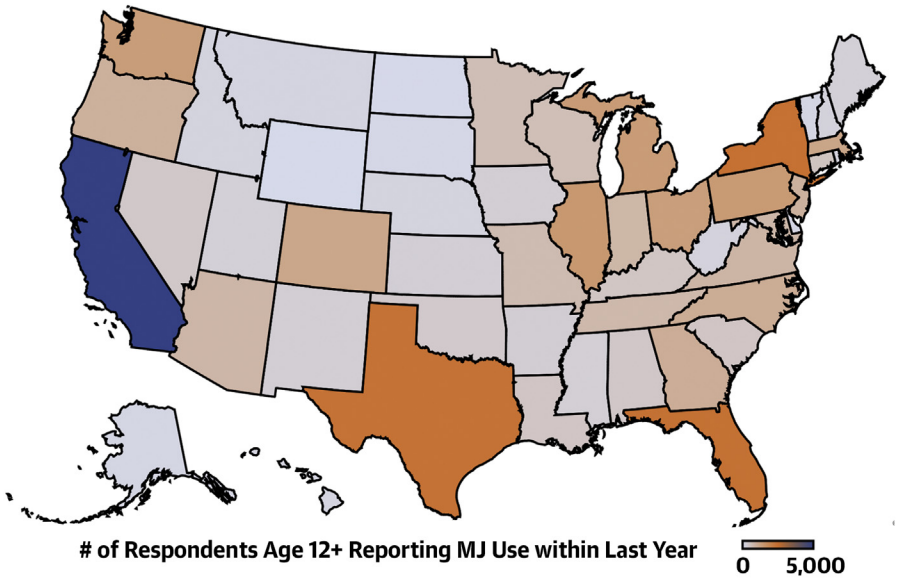
Brain
• Inhibition of pathological excitotoxicity associated with seizures/epilepsy via inhibition of glutamate release • Neuroprotective in patients with Alzheimer's, Huntington's, and Parkinson's disease • Appetite activation via the hypothalamus
Endocrine
• Communication with leptin, orexin, ghrelin to improve appetite stimulation
Gastrointestinal
• Gastrointestinal motility and absorption regulation via the enteric nervous system and intestinal mucosa that may aid in the management of nausea/vomiting and in inflammatory bowel processes • Up-regulation of CB1R in hepatic cells may lead to hepatic insulin resistance, fibrosis, and lipogenesis
Cardiovascular
• CB1R activation in cardiomyocytes, vascular endothelial cells, and smooth muscle cells may lead to oxidative stress, inflammation, fibrosis, vasodilation, and negative inotropy

Due to lack of evidence surrounding human expression of the cannabinoid receptor 2, limited data are available related to downstream effects of its receptor signaling.
CB1R = cannabinoid receptor 1.

SMOKING-RELATED CARDIOTOXICITY. Although the dominant psychogenic substance differs in tobacco (nicotine) and marijuana (THC), when smoked, many cardiotoxic chemicals are similarly produced (**Table 2**). When the combustion products of both substances are profiled, both contain a similar array of chemicals (21). Although marijuana is smoked with fewer puffs, larger puff volumes and longer breath holds may yield greater delivery of inhaled elements (22).

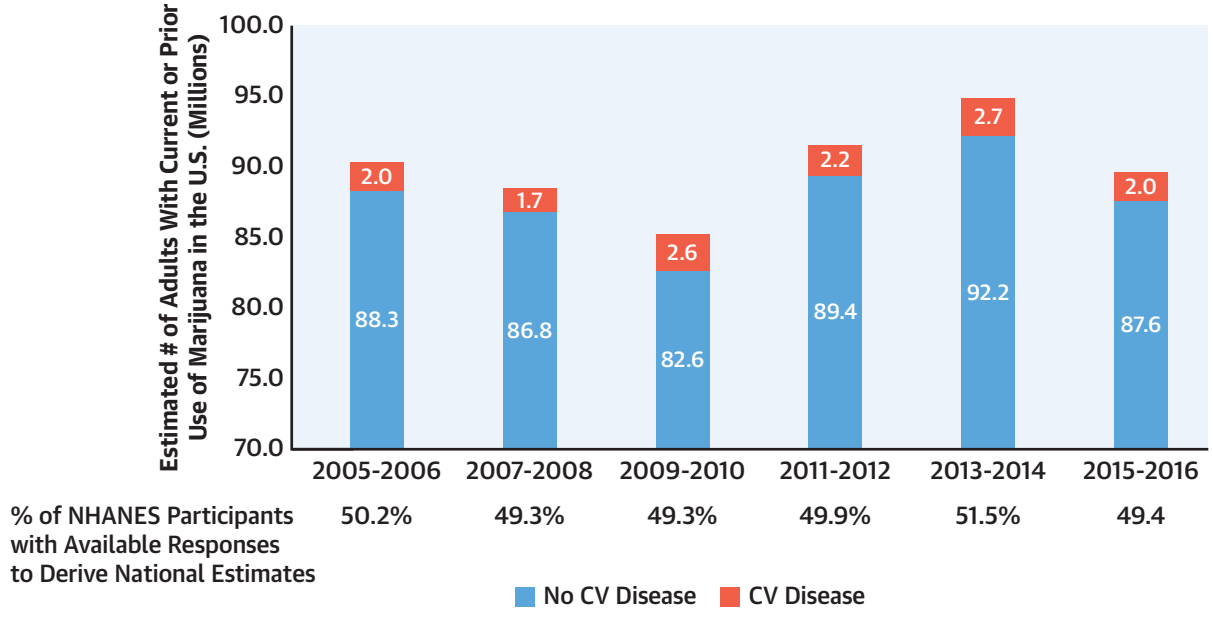
CORONARY ARTERY DISEASE. Mechanistically, marijuana use may pose potential cardiovascular risk in patients with atherosclerotic cardiovascular disease, especially early after acute coronary syndromes (23,24). In the acute setting, cannabis smoking can

FIGURE 2 Reported Use (in Thousands) of Marijuana in the Last Year, From 2016 to 2017 National Survey on Drug Use and Health



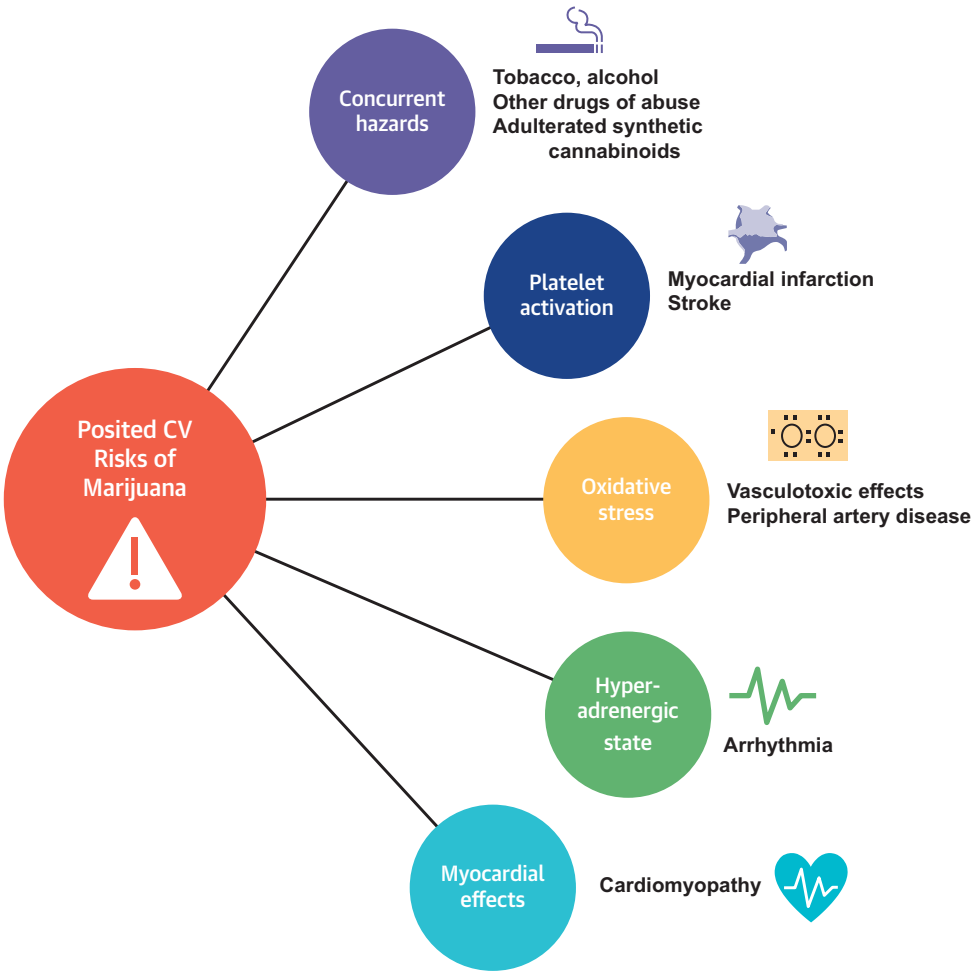
Data were extracted from the National Survey on Drug Use and Health, an annual survey of the U.S. civilian, noninstitutionalized population, from 2016 to 2017. Across the United States, >39 million respondents reported use of marijuana (MJ) in the last year. Mapping software was powered by Bing.

FIGURE 3 Estimated 1.7 to 2.7 Million Adults Reporting Prior or Current Marijuana Use Who Have Cardiovascular Disease, 2005 to 2016, From NHANES



Marijuana use was defined as those responding "yes" to ever using hashish or marijuana. Cardiovascular (CV) disease was defined broadly as those responding "yes" to ever being told by a health care provider they had congestive heart failure, coronary heart disease, or a heart attack. Response rates to both questions ranged from 49.3% to 51.5% throughout the study timeframe. NHANES = National Health and Nutrition Examination Survey.

FIGURE 4 Potential Mechanisms of CV Risk With Exposure to Marijuana



The quality of evidence supporting these posited mechanistic relationships is modest. CV = cardiovascular.

lead to increases in heart rate and blood pressure, secondary to sympathetic nervous system activation (25), augmenting myocardial oxygen demands (8). Aronow and Cassidy (26) determined that exercise time until angina onset was reduced after smoking a single marijuana cigarette compared with placebo in a small experiment of 10 patients with coronary artery disease. Chronic use promotes tolerance and may be associated with less pronounced physiological effects (27). Other postulated mechanisms include production of oxidant gases resulting in cellular stress, platelet activation, increased oxidized low-density lipoprotein cholesterol formation, and induction of an inflammatory response.

Epidemiological studies have identified a potential temporal link between marijuana use and myocardial infarction. In a meta-analysis of 36 studies, the top 3 triggers of myocardial infarction included use of cocaine, eating a heavy meal, and smoking marijuana (28). Furthermore, in a systematic analysis of 33 studies, 28 found an increased risk of acute coronary syndromes with marijuana use (25). This observed risk association appears temporally related to recency of use. For instance, among 3,882 patients with myocardial infarction in the Determinants of Myocardial Infarction Onset Study (29,30), 3% smoked marijuana in the prior year; 37 of whom had smoked within 24 h and 9 within 1 h of myocardial infarction (29). Marijuana users were more likely to be men, obese, and current cigarette smokers. In addition, marijuana use, which is more prevalent in younger adults, is not infrequently detected among

patients presenting with early-onset myocardial infarction. In the Partners YOUNG-MI registry of patients who presented with first myocardial infarction under the age of 50 years, marijuana use was reported or tested positive in >6% (31). Marijuana use was associated with twice the hazard of death among these patients even after adjusting for tobacco use (31). Another mechanism of coronary pathology is coronary vasospasm in the absence of coronary artery disease.

ARRHYTHMIAS. A broad range of cardiac electrical effects, including atrial fibrillation/flutter, atrioventricular block/asystole, sick sinus syndrome, ventricular tachycardia, and Brugada pattern, have been described with marijuana use (32–34). Increased catecholamines and β-adrenergic stimulation with THC may theoretically increase arrhythmogenicity (35). In an NIS study from 2010 to 2014, Desai et al. (32) found that 66,179 of 2,459,856 (3%) of those with reported marijuana use experienced arrhythmias (mostly atrial fibrillation).

CEREBROVASCULAR DISEASE. Cerebrovascular events have also been reported in association with marijuana use (36–39), including with SCBs (40). Mechanisms related to potential cerebrovascular risks include direct vasculotoxic effects, alterations in hemodynamics, or incident atrial fibrillation/flutter (36,41). Furthermore, even transient exposure to marijuana smoke can induce endothelial dysfunction (42). One population survey found that individuals who had smoked marijuana in the past year experienced a 3.3× higher rate of cerebrovascular events (37). A case series described 14 patients with ischemic stroke who had exposure to cannabis during or before symptoms began, with 5 experiencing recurrent stroke with re-exposure (38). Among 334 patients who experienced acute ischemic stroke under the age of 45 years over a 9-year period, 17% were cannabis users. These patients were typically younger and were more likely to be men (43).

PERIPHERAL ARTERY DISEASE. Thrombosis and ischemia of other vascular beds have also been reported (44). Delta-8 and delta-9-tetrahydrocannabinols can induce peripheral vasoconstriction (45). Cannabis arteritis has been reported in young men who developed distal ischemia leading to necrosis of fingers or toes (45–47), commonly with concurrent use of tobacco (47). Arteriographic evaluation reveals anomalies resembling Buerger's disease (45). Exposure to secondhand smoke from marijuana for 1 min impaired femoral artery flow-mediated dilatation, a measure of endothelial dysfunction, for at least 90 min, which was longer than impairment by tobacco secondhand smoke (42).

CARDIOMYOPATHY. Cannabis use has been associated with myocardial dysfunction, independent of coronary artery disease. Rabbits who have received a selective CB2 agonist demonstrate concentration-dependent decreases in cardiac contractility (48).

TABLE 2 Comparison of Use Patterns, Regulation, and CV Effects of Marijuana and Tobacco Smoking

	Marijuana Smoking	Tobacco Smoking
Estimated current use	>39 million*	34.3 million†
Recent trends in use	Rising	Declining
Psychoactive substance	Tetrahydrocannabinol	Nicotine
Composition	Similar particular matter and chemical toxin profile	Similar particular matter and chemical toxin profile
Typical use pattern	Larger puff and inhaled volume, longer breath-hold	More frequent puffs
FDA-approved products for medicinal use	Cannabidiol (seizures); dronabinol and nabilone (nausea, anorexia, weight loss)	None
DEA controlled substance	Yes (Schedule I)	No
Current level of epidemiological evidence of CV toxicity	+	+++
Safe dose/level	?	None

*People reporting use in the past year according to the 2016 to 2017 National Survey on Drug Use and Health. †Based on the U.S. Department of Health and Human Services, current smokers defined as people who reported smoking at least 100 cigarettes during their lifetime and who, at the time they participated in a survey about this topic, reported smoking every day or some days.

CV = cardiovascular; DEA = Drug Enforcement Administration; FDA = U.S. Food and Drug Administration.

TABLE 3 Pharmacokinetic Characteristics of Cannabinoids (10,14,76)

		Affected Metabolism Pathways	
Cannabinoid Compound	Substrate Pathway	Inhibitor	Inducer
Cannabidiol	CYP3A4 CYP2C19	CYP3A4 CYP2D6 CYP2C8/9/19 CYP1A1/2 CYP1B1 CYP2B6	
Tetrahydrocannabinol	CYP2C9 CYP3A4	CYP3A CYP2D6 CYP2C9 CYP2B6	CYP1A1/2
Cannabinol	CYP2C9 CYP3A4	CYP3A CYP2D6 CYP2C9 CYP2B6	
Synthetic cannabinoids	CYP2C9 CYP1A2 CYP2D6	CYP1A CYP2C8/9/19 CYP3A	

TABLE 4 Medications Affected by Cannabinoids (10,14,63,77)

Mechanism	Cannabinoid Involved	Key Therapy Affected	Anticipated Change in Drug Level
CYP3A4 inhibition	CBD, THC, CBN, SCB	Antiarrhythmic (amiodarone, quinidine, lidocaine)	↑
		Calcium-channel blockers (dihydropyridine + nondihydropyridine)	↑
		Isosorbide dinitrate/mononitrate	↑
		Statins (atorvastatin, lovastatin, simvastatin)	↑
CYP2C9 inhibition	CBD, THC, CBN, SCB	Warfarin	↑
		Statins (rosuvastatin, fluvastatin)	↑
		Nonsteroidal anti-inflammatory drugs (celecoxib, ibuprofen, naproxen)	↑
CYP2D6 inhibition	CBD, THC, CBN	Beta-blockers (carvedilol, metoprolol)	↑
		Antiarrhythmic (flecainide, mexiletine, propafenone)	↑
CYP1A inhibition/induction	CBD, CBN, SCB	Theophylline, caffeine	Inhibition: ↑ Induction: ↓

↑ = increase; ↓ = decrease; CBD = cannabidiol; CBN = cannabinol; SCB = synthetic cannabinoids; THC = delta-9-tetrahydrocannabinol.

Case reports have suggested associations of cannabis with stress cardiomyopathy (49) and myocarditis/myopericarditis, an entity referred to as "toxic myocarditis" (50,51).

METABOLIC ALTERATIONS. Early studies had shown that cannabinoids contribute to weight gain in patients with human immunodeficiency virus, leading to the rationale for use of dronabinol as an appetite stimulant (52,53). Furthermore, a trial of rimonabant, an endocannabinoid receptor antagonist, demonstrated weight loss and improved metabolic abnormalities (54). However, multiple recent epidemiological studies have suggested that cannabis may be protective against weight gain and related alterations in metabolism (55–57). In 1 study, cannabis users had lower low-density lipoprotein cholesterol; when cannabis was discontinued, a subset had an increase in weight greater than nonusers (55). In 2016, a small randomized double-blind trial showed that in patients with diabetes mellitus, tetrahydrocannabivarin (compared with placebo) significantly decreased fasting plasma glucose levels and improved pancreatic β-cell function (58).

POTENTIAL PHARMACOLOGICAL INTERACTIONS WITH CARDIOVASCULAR MEDICATIONS

Cannabinoids can interfere with the action of multiple classes of cardiovascular therapies by inhibiting the cytochrome P (CYP) 450 family (10,59,60). Additional pharmacokinetic interactions may occur at the level of membrane transporters. Glycoprotein P (P-gp) expression is affected by the duration of exposure to cannabinoids (61). With chronic exposure, the expression of P-gp is down-regulated, but with short exposure it is up-regulated. Cannabinoids inhibit breast cancer–resistant protein and increase accumulation of its substrates (62). Additionally, a withdrawal phenomenon has been reported after abrupt discontinuation due to the high affinity of THC to cannabinoid binding receptors (14).

CANNABIDIOL. Cannabidiol is a substrate of CYP3A4 and CYP2C19 and is a more potent inhibitor of CYP3A and CYP2D6 compared with other cannabinoids (**Table 3**) (10). It also influences uridine 5'-diphospho (UDP)-glucuronosyltransferases.

CANNABINOL AND DELTA-9-TETRAHYDROCANNABINOL. THC and CBN are substrates of CYP2C9 and CYP3A4, and both similarly inhibit a variety of CYP450 enzymes (10). CBN additionally inhibits UDP-glucuronosyltransferase enzymes, and THC has been shown to induce the CYP1A enzyme.

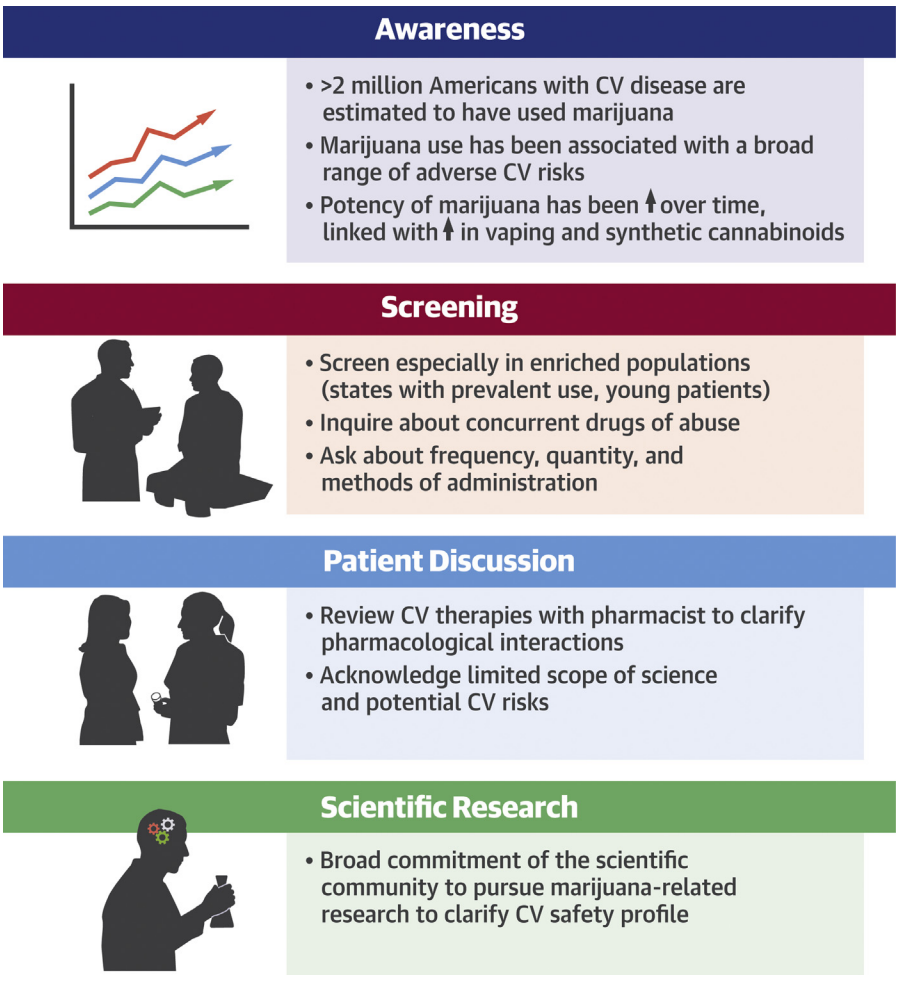
SYNTHETIC CANNABINOIDS. There is very little evidence surrounding the pharmacokinetic and pharmacodynamic effects of SCBs. In vitro studies have shown that SCBs are potential substrates of CYP2C9, CYP1A2, CYP2D6, and other CYP450 enzymes (depending on the specific formulation of SCB) (**Table 3**) (10,14).

AFFECTED MEDICATION CLASSES. Cannabinoids affect key classes of cardiovascular medications including antiarrhythmics, calcium-channel blockers, statins, β-blockers, and warfarin (**Table 4**) (10,14,63–65). The anticipated changes in drug levels are described, but limited clinical data are available guiding the need for dose or therapeutic changes.

CARDIOVASCULAR CLINICAL CARE APPLICATIONS

WHEN TO SCREEN AND TEST. In light of accumulating data suggesting prevalent use of marijuana,

CENTRAL ILLUSTRATION **Practical Approach to Screening for Marijuana Use Among Patients With Cardiovascular Disease**



DeFilippis, E.M. et al. J Am Coll Cardiol. 2020;75(3):320-32.

In light of the accumulating data regarding marijuana use and cardiovascular (CV) effects, it is increasingly important for clinicians to screen patients for use, educate about its potential effects, and contribute to ongoing research in the field.

including among patients with established cardiovascular disease, it is important to integrate screening, counseling, and testing when appropriate into clinical care (**Central Illustration**). Cardiovascular specialists should be aware of local regulations and state-specific legalization status of marijuana products. We would advocate for routine screening for marijuana use. There are a variety of tools available for assessing for marijuana use, although most were validated in adolescents and young adults and no 1 tool has been universally accepted (66,67). Whenever possible, questions should encompass frequency, quantity, and methods of administration (i.e., joints, hand pipes, vaporizers, edibles, oils) (66). Based on epidemiological predilection, screening may be particularly high-yield in states with reported high marijuana use density and among young patients presenting with cardiovascular disease. It may be reasonable to also perform urine toxicology in the setting of myocardial infarction and new-onset heart failure. Marijuana testing is required prior to an evaluation for heart transplantation. Use of nonprescription SCBs should be avoided given higher potential for pharmacological

manipulation and increased potency. Patients should be reminded that marijuana (when smoked) yields an inhaled chemical profile comparable to tobacco smoking. Patients should be screened for and counseled regarding the hazards of concurrent use of other illicit drugs, especially those with known adverse cardiovascular effects (e.g., cocaine, methamphetamines).

CLINICAL IMPLICATIONS. Among patients with cardiovascular disease and known marijuana use, multidisciplinary assessment with a pharmacist is encouraged to determine whether anticipatory dose changes are required for therapies with known interactions. Heightened awareness is needed among cardiovascular specialists of the broad range of potential health consequences of marijuana and its derivatives. Cardiovascular specialists should have open discussions with patients acknowledging the limited scientific data, but potential cardiovascular hazards of marijuana use, especially when used via smoking/inhalation routes. Given the increasing popularity of "vaping" in the United States, marijuana is also being delivered in vaporized forms, especially among young adults. Clinicians should counsel patients about the variable concentrations of psychoactive THC delivered via different methods of use; importantly, vaporized cannabis may yield high concentrations with greater pharmacodynamic effects than smoked cannabis (68). Shared decision-making is encouraged if marijuana is used for symptom management or palliative purposes, incorporating estimates of life expectancy and cardiovascular risks.

HEART TRANSPLANTATION. Heart transplant candidacy may be affected by marijuana use (69). Current International Society for Heart and Lung Transplantation guidelines allow each center to develop its own criteria for candidacy regarding marijuana use. Potential concerns include medication adherence due to the psychotropic effects of THC, infectious complications in the setting of immunosuppression, as well as interactions with tacrolimus due to inhibition of CYP3A4 (69).

GAPS IN KNOWLEDGE AND NEXT STEPS

Currently, there are no guidelines surrounding marijuana and cardiovascular disease. In 2017, the National Academies of Sciences, Engineering, and Medicine released a report on the health effects of marijuana. For cardiometabolic risk, they concluded that the evidence was unclear regarding the association between cannabis use and myocardial infarction, stroke, and diabetes mellitus (70).

LACK OF REGULATION. With growing use and potential multisystem health effects, it is critical to regulate marijuana (71). On May 31, 2019, at a U.S. Food and Drug Administration public hearing, continued efforts to develop new drugs from cannabis were encouraged, while evaluating questions related to safety through development of an internal working group (72).

NEED FOR RESEARCH. Significant barriers exist to cannabis research (73,74) that include, but are not limited to, the heterogeneity of the drug (i.e., various forms and routes of administration) and variability in state laws and their implementation (75). Real-world observational studies have inconsistently reported use, dose, and formulation. For instance, cannabis is the source of >60 compounds with varying pharmacological activity (75). The scientific community and federal government should remain committed to marijuana-related research so that safe and effective products can be developed. States where marijuana legalization is impending may allow for randomized, stepped roll out as an opportunity to study potential population-level effects.

Due to its Schedule I status, it is illegal to conduct rigorous controlled trials of marijuana products in the United States. A search of ClinicalTrials.gov for the terms "marijuana," "cannabidiol," and "THC" yielded studies mostly outside of the United States in a broad range of conditions, including neurodegenerative diseases, inflammatory bowel disease, cancer, pain syndromes, addiction, and pediatric epilepsy. Few trials were evaluating cardiovascular risk markers, none of which were actively enrolling as of July 2019 or were large enough to assess cardiovascular outcomes.

CONCLUSIONS

Marijuana use continues to increase nationally in light of changing policies around legalization. We estimate that >2 million patients with cardiovascular disease report current or prior use of marijuana. Observational studies have suggested a potential association between marijuana and a range of cardiovascular risks, although the level of evidence has not been robust. Few randomized clinical trials have been conducted or are planned to examine effects of marijuana on cardiovascular risk, due in part to its Schedule I federal designation as a controlled substance. Acknowledging the modest strength of current evidence, screening and testing for use of

marijuana in select cardiovascular settings is encouraged. Furthermore, patients who are at high-risk of cardiovascular events should be counseled to avoid or at least minimize marijuana use. It is imperative to conduct rigorous scientific research evaluating marijuana to inform recommendations for patient care and to provide a framework for the cardiovascular community.

ADDRESS FOR CORRESPONDENCE: Dr. Muthiah Vaduganathan, Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115. E-mail: mvaduganathan@bwh.harvard.edu. Twitter: @ersied727, @bajaj_nav, @RonBlankstein, @DLBHATTMD, @mvaduganathan.

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