Clinical Considerations for Cannabis Use and Cardiovascular Health

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**Key Points**

- The American Heart Association (AHA) released a scientific statement critically reviewing the evidence available on cannabis safety and efficacy profile related to cardiovascular health and provided a guide for clinicians regarding the current legal status, health implications, therapeutic possibilities, and clinical interventions among patients who use cannabis.
- The cardiovascular effects of cannabis can vary based on the dose and timing of exposure, potency, and formulations of products, route of administration, and concurrent use of other drugs. Clinical assessment of patients who use cannabis should include a comprehensive evaluation of cannabis use or exposure and determination of the risk for adverse cardiovascular effects and potential drug-drug interactions, especially among patients with underlying cardiovascular comorbidities.
- Clinical interventions among patients with a higher risk of cannabis-related cardiovascular adverse events include, but are not limited to, patient counseling to modify cannabis use patterns when heavy use or cannabis use disorder is identified, patient education about dose titration to reduce severe side effects, eliminating or reducing THC-containing products among patients with underlying cardiovascular diseases who may have a higher risk of adverse cardiovascular events, and assessing the risk of drug-drug interactions.
- The complexity and variability of cannabis products, the presence of other cannabinoids and chemicals, intraindividual and interindividual use pattern variations, and lack of sufficient information disclosed by patients due to legal and social concerns can stand as barriers to clinical interventions to reduce the potential for drug-drug interactions, even when guidelines are available.

**Keywords**

Marijuana · Cannabis · Cannabinoids · Cardiovascular effects · Major adverse cardiovascular events · Drug-drug interactions

**Introduction**

As the recreational and medicinal use of cannabis evolves [1–3], concerns regarding its unknown effects [4–6], especially those pertaining to cardiovascular health [7], are growing among clinicians. Cannabis is a complex plant with over a hundred cannabinoids [8], each capable of potentially interacting with the autonomic nervous
system resulting in a range of acute and chronic cardiovascular effects [9–13]. Cannabinoids can also pose risks for adverse drug events and drug-drug interactions, including interactions with cardiovascular medications [14]. The direct and indirect effects of cannabis on the cardiovascular system require clinical attention during patient assessment and management, especially given their potential relationship with adverse cardiovascular events [7] and drug-drug interactions. The increasing prevalence of cannabis use calls for clinicians to understand the cardiovascular implications affecting patient safety, treatment plans, and long-term risks and benefits.

The American Heart Association (AHA) released a scientific statement reviewing the cardiovascular safety and efficacy profile of medical and recreational cannabis use [7]. The statement provided an updated summary of the literature on several related topics, including pharmacology, administration, dosing, potential and known benefits of cannabis, and cardiovascular safety considerations. The statement also examined the current evidence on the association between cannabis use and major adverse cardiovascular events (MACE) and emphasized the knowledge gaps that force clinicians to deal with unknown risks. The AHA’s scientific statement provided invaluable insights and proposed guidance in clinical interventions for potential drug-drug interactions, clinical considerations in special populations, future public and clinical education directions, research considerations, and policy adaptation.

In this commentary, we underline some of the proposed guidelines in the AHA scientific statement that could help clinicians assess, manage, and anticipate/reduce cardiovascular risks among patients who use cannabis. We also highlight three areas related to clinical assessment that require further discussion: cannabis use assessment, cannabis-related cardiovascular risk, and cannabis-drugs interactions.

**Cannabis Use Assessment**

The absence of a comprehensive assessment of cannabis use in clinical settings is evident [15]. This absence has been attributed to several factors on the patient (e.g., fear of stigma, confidentiality concerns, significant variations in cannabis use patterns, inconsistent cannabis product labeling), provider (e.g., lack of knowledge or training), and system levels (e.g., additional burden, lack of resources, limited treatment options, lack of standardized assessment models) [15–18]. The absence of such assessment leads to missing important information regarding cannabis exposure that could help determine physiological responses to cannabis, including the frequency, quantity, duration, recency, age of initiation, routes of and methods of administration, motives for use, tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations and ratios, potency, and source of cannabis products. Yet, assessing use characteristics is crucial for anticipating potential cardiovascular risks and planning treatment options for patients who use cannabis since the onset and course of the anticipated cardiovascular effects can vary based on the time, dose, and potency of exposure, as well as the route of administration, formulations, and concurrent drug use [9–14, 19–25]. Moreover, substantial interindividual and intraindividual variations in use patterns and exposure make it difficult to anticipate or generalize effects based on a mere positive or negative use status.

Cannabis-induced cardiovascular effects are mainly mediated by cannabionoid type 1 receptor activation and controlled by sympathetic nervous system activation and parasympathetic nervous system inhibition and can be categorized as acute and chronic effects [9, 26]. The AHA statement focused on the early phase of the acute effects of cannabis on the cardiovascular system, mainly resulting from THC-induced sympathetic nervous system activation and parasympathetic inhibition through cannabinoid type 1 receptor activation [27–29]. However, the cardiovascular response to cannabis exposure happens in a “biphasic manner” [13], and their onset can vary based on the time and dose of exposure [9–13]. For example, new (naïve) cannabis users experience dose-response increases in heart rate and blood pressure immediately after smoking cannabis [9, 10]. The resulting chronotropic and hypertensive effects lead to increased heart rates, increased cardiac oxygen demand, and elevated blood pressure in the early acute phase [9, 13]. Increases in systolic blood pressure can be 20–100% of baseline systolic blood pressure at the peak plasma concentration of THC and can persist up to 60 min after smoking discontinuation [9, 10]. Chronic or heavy users may experience increases in heart rate, left ventricular contractility, and cardiac output after heavy daily cannabis consumption (estimated as THC ≥10 mg/day) [30]. While lower doses of cannabis can cause sympathetic stimulation and catecholamine release, higher doses have been shown to cause parasympathetic stimulation [31, 32].

Delayed cardiovascular effects of cannabis are also important mechanisms to consider when determining cardiovascular risk, especially related to MACE. Peripheral vasodilation and baroreflex deregulation can induce a
strong parasympathetic response resulting in supine and postural arterial hypotension and bradycardia [33], leading to decreased cerebral blood velocity and potentially increasing the risk of ischemic strokes [34]. Atherosclerosis and cerebral vasospasm have also been identified as etiologic factors for cannabis-related cardiovascular disease [35].

Understanding these delayed cardiovascular responses is especially critical in patients with underlying cardiovascular comorbidities and those who have a higher risk of stroke. Chronic cannabis use has been associated with oxidative endothelial injury, atherosclerotic changes, dysrhythmias, coronary vasospasm, and cerebral hypoperfusion [36–41]. All these described effects can potentially be pathophysiological mechanisms for MACE linked to cannabis use (Fig. 1). Notably, the cardiovascular benefits of cannabis have not been established [4, 6, 19, 42].

Fig. 1. Biphasic acute and chronic cardiovascular effects of THC, mediated by CB1R activation, and their potential association with major adverse cardiovascular effects. CB1R, cannabinoid type 1 receptor; MACE, major adverse cardiovascular events; THC, tetrahydrocannabinol.
Additionally, while casual or infrequent use is likely to have minimal effects on heart transplant outcomes, the presence of cannabis use disorder (CUD) has been linked with noncompliance with immunosuppressant therapy, infection, graft failure, and death among heart transplant recipients [43]. In 2020, the Canadian Cardiovascular Society/Canadian Cardiac Transplant Network recommended receiving treatment for CUD in addition to abstinence from cannabis smoking, vaping, or inhaling other burned or heated cannabis products for at least 6 months before being listed as a candidate for heart transplantation [44]. Clinicians should assess for the presence of CUD among patients using cannabis, especially those who are planning to receive a transplant. Tools such as the Cannabis Use Disorders Identification Test-Revised (CUDIT-R) [45, 46] are available and may be practical for...
clinicians to identify patients requiring counseling or treatment for CUD. Differentiating between different types of cannabis exposure, such as casual versus chronic use, light versus heavy use, high versus low THC exposure, the timing of exposure, and the presence of CUD, is important for assessing potential cardiovascular risks and may also help explain the underlying pathological mechanisms by which cannabis poses an increased cardiovascular risk (Fig. 2).

**Cannabis-Related Cardiovascular Risk Assessment**

While cannabis has been shown to induce cardiovascular effects in different age-groups and patient populations, certain vulnerable populations may be at an increased risk of experiencing adverse cardiovascular events, such as patients with underlying cardiovascular conditions, including pre-existing ischemic heart disease and a history of previous myocardial infarction [47, 48]. Careful assessment of patients’ underlying cardiovascular health is essential to determine the risk level of experiencing cannabis-related cardiovascular adverse effects and planning clinical interventions. Assessment should include thorough history taking (e.g., history of arrhythmias, hypertension, atherosclerosis, ischemic heart disease, previous myocardial infarction, previous stroke or transient ischemic attacks, smoking, and other substance use), physical examination (e.g., checking for blood pressure abnormalities, tachycardia, arrhythmias, etc.), and assessment of cardiovascular side effects related to cannabis consumption, such as tachycardia, and orthostatic hypotension, or specific routes of administration, such as severe side effects associated with oral consumption. Recent data suggest that cannabis use may be a risk factor for developing or accelerating atherosclerotic cardiovascular disease (ASCVD), including in younger and female patients [49, 50]. Given the increasing prevalence of cannabis use among younger people [51], its role in early-onset ASCVD will be an ever-evolving issue, prioritizing ASCVD risk assessment, especially among younger patients.

Clinically, THC should be used sparingly and cautiously in patients with cardiovascular diseases. THC-containing prescription products are contraindicated in people with cardiovascular disease, including hypertension, heart failure, coronary artery disease, and a history of stroke [25, 52]. Synthetic THC-based prescription products, mainly dronabinol (Marinol® and Syndros™ in the USA and REDUVO™ in Canada) and nabilone (Cesamet™ in the USA), are approved and available for patients in the USA and Canada [53, 54]. Caution is recommended in patients using synthetic cannabinoids, given the existing synergistic effects and increased potency that may further exacerbate cardiovascular adverse effects [55]. Patients who experience severe cardiovascular and other side effects related to oral THC administration are candidates for education about dose titration [19]. CBD-only use, however, has not been associated with clinically significant adverse side effects, except in cases with extremely high doses or in studies involving mixtures of other cannabinoids (mainly THC) [14, 56]. Yet, the potential for drug-drug interactions between CBD and cardiovascular medications is evident through modulation by the cytochrome P450 and UDP glucuronosyltransferase family 1 member A9 metabolism pathways [56] and should be considered during clinical assessment. Moreover, polypharmacy in patients with underlying cardiovascular comorbidities (and other comorbidities) requires additional assessment to determine their risk of drug-drug interactions with cannabis, especially within older age-groups [27]. Figure 2 illustrates the steps involved in assessing the risk of adverse cardiovascular effects related to cannabis use and suggests possible clinical interventions and considerations.

**Drug-Drug Interactions Risk Assessment**

The AHA statement provided a comprehensive discussion of potential drug-drug interactions specific to cannabis of clinical importance. Of note, several case reports have associated increased international normalized ratio values and bleeding complications with cannabis in patients using warfarin [57–59]. The interaction between cannabis and warfarin has been explained by the inhibition of CYP2C9, leading to decreased warfarin metabolism [59]. While the evidence associating bleeding risk and complications remains undetermined, close monitoring of patients receiving anticoagulants who report using cannabis is recommended, and adjustments in warfarin or cannabis doses may be warranted.

In addition to the drug-drug interactions modulated by the cytochrome P450 and uridine 5’-diphospho-glucuronosyltransferase metabolism pathways discussed in the AHA statement, other interaction pathways are also important to consider [14]. For example, THC, CBD, and cannabinol inhibit carboxylesterases, which have key roles in the bioactivation and bioinactivation of several medications, including multiple cardiovascular medica-
tions such as clopidogrel, warfarin, dabigatran, and angiotensin-converting enzyme inhibitors [60]. While the focus has been directed toward pharmacokinetic interactions, additive pharmacodynamics interactions between cannabis and other coadministered drugs with akin physiological effects are more clinically relevant, especially if they can induce the same undesirable side effects, such as increased tachycardia with the coadministration of cannabis and sympathomimetics or tricyclic antidepressants [61].

The AHA statement has proposed clinical interventions to help clinicians and patients when drug interactions are suspected. Cardiovascular medications with potential interactions with cannabis and the corresponding possible clinical interventions are summarized in Figure 2. However, it should be noted that the proposed interventions are most helpful when physicians can easily modulate their patient’s cannabis intake. For example, medical cannabis patients who use consistently labeled cannabis products may adjust doses easily. Nonetheless, previous studies have shown that most cannabis users, including medical, prefer smoking flower products [52, 53]. Cannabinoid composition, concentrations, and ratios may substantially vary in these products and between and within users, not to mention that most cannabis users have access to products from outside dispensaries that may not be labeled or could possibly contain contaminants, pesticides, or heavy metals [18]. Moreover, for medical cannabis users, cardiologists are unlikely to be the authorizing physician [62, 63]. Thus, dose adjustments rely on disclosing medical cannabis use in patient counseling.

In addition, while most described potential interactions were related only to THC and CBD in the AHA statement, a vast number of other cannabinoids (e.g., cannabinol) may also cause potentially serious interactions [22]. Cannabis is a complex plant with more than 100 cannabinoids, all of which could theoretically have interactions with other drugs [14]. Decreasing or modulating cannabis doses may be far more complex and challenging when accounting for other cannabinoids.

**Conclusion**

While there is evidence that cannabis may have therapeutic benefits in certain diseases (e.g., epilepsy, pain), many potential risks of cannabis use are related to its cardiovascular effects. Clinicians need to be aware of these cardiovascular effects and potential risks to provide adequate patient assessment, determine risk, and plan appropriate interventions. The AHA scientific statement on medical marijuana, recreational cannabis, and cardiovascular health is a valuable source of information that reviews different relevant areas of importance for clinicians, researchers, and other stakeholders.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Ruba Sajdeya, Sebastian Jugl, Joshua D. Brown, and Amie J. Goodin conceptualized and drafted the work. Robert L. Cook, Joshua D. Brown, and Amie J. Goodin drafted and revised. All authors approved the final version.

**Editor’s Note**

Evidence in Context is part of the outreach effort of the Consortium for Medical Marijuana Clinical Outcomes Research to examine and discuss implications of research into cannabis and cannabinoids for clinical practice, thus providing a translational approach to these studies to make clear, concise, and actionable evidence available for clinicians and patients.

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