JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 16, 2021

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Marijuana Use

A New Risk Factor for Periprocedural Bleeding?*

Mamas A. Mamas, DPHIL,[a] Pablo Lamelas, MD[b,c]

The use of marijuana is expanding in the United States as more states are legalizing its use for both recreational and medicinal purposes. Marijuana is the most widely used illicit substance in the United States and Europe, with more than 39 million individuals reporting the use of marijuana in the National Survey on Drug Use and Health in 2016 and 2017 (1). Marijuana is derived from the dried leaves, flowers, stems, and seeds of the *Cannabis sativa* or *Cannabis indica* plant, in which tetrahydrocannabinol is the main psychoactive component of the plant, which includes at least 65 other cannabinoids including cannabidiol.

The effects of marijuana are mediated through cannabinoid receptors, which belong to the superfamily of 7-transmembrane, G protein–coupled receptors that are important in the regulation of physiological processes involved in cardiovascular regulation, central nervous system regulation and plasticity, immune function, inflammation, metabolism, and pain (2). Cannabinoid receptors are expressed in tissues throughout the body, including the central and peripheral nervous system, the myocardium, vascular tissue, and platelets.

There is growing interest around the impact of cannabis in patients with cardiovascular diseases (1), particularly given the ubiquitous expression of cannabinoid receptors throughout the cardiovascular system and their direct and indirect effects on pathways involved in the coagulation cascade. Cannabis may interfere with many of the metabolic pathways of antithrombotic agents used in patients to treat cardiovascular diseases. Cannabis is metabolized by the same cytochrome P450 enzymes as warfarin, including CYP3A4, CYP2C9, and CYP2C19, and has been shown to increase the international normalized ratio in patients treated with warfarin, with subsequent bleeding events (3). Cannabinoids also bind to membrane transporters, including P-gp, which are known to be important for the transport of direct oral anticoagulant agents including rivaroxaban, apixaban, and dabigatran, which are commonly used in therapeutic anticoagulation in patients with nonvalvular atrial fibrillation and acute coronary syndrome, leading to increased serum levels of these medications. The product labels for apixaban and rivaroxaban both warn against their use with strong CYP3A and P-gp inhibitors, as this could lead to increased exposure and increased risk for bleeding complications. Cannabidiol is also known to inhibit CYP enzymes (CYP2C8, CYP2C9, and CYP2C19) at clinically relevant concentrations, which is particularly important in patients with cardiovascular disease treated with clopidogrel. Clopidogrel is an inactive prodrug that is metabolized by CYP2C19, along with pathways through CYP3A, CYP2C9, CYP1A2, and CYP2B6, into its active thiol metabolite. Cannabis use may result in decreased metabolism of clopidogrel into its active metabolite and, therefore, diminish its antiplatelet efficacy. Finally, cannabis is known to have anticoagulant effects through inhibition of thrombin-induced clot formation (4) and is known to inhibited both adrenaline- and adenosine diphosphate–induced platelet aggregation in a dose-dependent manner (5).

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the [a]Keele Cardiovascular Research Group, Centre for Prognosis Research, Keele University, Keele, United Kingdom; [b]Interventional Cardiology, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina; and the [c]Department of Health Research Methods Evidence and Impact, McMaster University, Hamilton, Ontario, Canada.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2021.07.002

Antithrombotic therapy is the cornerstone of pharmacologic treatment aimed at preventing ischemic events following percutaneous coronary intervention (PCI), in which balancing the risk for ischemic and bleeding complications at the individual patient level is central. Given that it is estimated that more than 2 million adults with cardiovascular disease in the United States have used marijuana (1), and cannabinoids affect the anticoagulation cascade, platelet function and reactivity, and the efficacy of many of the drugs used in PCI, it is surprising that the effects of marijuana use on PCI outcomes have not received more widespread attention.

SEE PAGE 1757

In this issue of *JACC: Cardiovascular Interventions*, Yoo et al (6) report their study of marijuana use and in-hospital outcomes among 113,477 patients who underwent PCI at 48 nonfederal hospitals in Michigan between 2013 and 2016 (6). The investigators report that 3.5% of their population used marijuana in the month preceding their procedures and that marijuana users were more than a decade younger (mean age 54 vs 66 years), more likely to be black (26% vs 11%) and current or recent smokers (73% vs 27%), and less likely to be insured than patients who did not use marijuana. Similarly, patients using marijuana had a lower prevalence of traditional cardiovascular risk factors such as diabetes, dyslipidemia, hypertension, and peripheral vascular disease and were less likely to have histories of coronary revascularization. Despite this more favorable risk factor profile, marijuana users were twice as likely to undergo PCI for ST-segment elevation myocardial infarction. The investigators report that the use of marijuana was associated with significantly higher risks for in-hospital major bleeding (odds ratio [OR]: 1.54; 95% confidence interval [CI]: 1.20-1.97; $P < 0.001$) and cerebrovascular accidents (OR: 11.01; 95% CI: 1.32-91.67; $P = 0.026$) but no significant differences in mortality (OR: 0.94; 95% CI; 0.54-1.62; $P = 1.00$) or stent thrombosis (OR: 1.02; 95% CI: 0.40-2.58; $P = 0.97$) between the groups.

The present study overcomes the limitations associated with the use of administrative databases of previous work (7), with more granular procedural and pharmacologic data.

Nevertheless, there are several limitations to the present analysis, including case ascertainment, in which marijuana use was determined from the patient's medical record at the time of PCI and was defined as the use of marijuana at any time within 1 month prior to index PCI. Importantly, physicians and data entry clerks were not specifically instructed to ask patients about marijuana use. This is likely to have resulted in underestimation of marijuana use in this cohort, particularly given that the study period was prior to the legalization of marijuana for recreational use in Michigan (which occurred in 2018). Second, there are no data on the frequency of marijuana use or its temporal relationship to the index admission or PCI procedure. The impact on the coagulation cascade and drug pharmacokinetics is likely to be more significant the more temporally related it is to the index procedure. Finally, the investigators were unable to capture major bleeding or ischemic events postdischarge. The latter point is particularly important; marijuana use is independently associated with treatment nonadherence in a wide range of medical conditions and would be particularly relevant to the longer term outcomes following PCI, for which adherence to antiplatelet regimes is important to avoid ischemic complications. Marijuana use is also more commonly encountered in those with poor socioeconomic status, homelessness, and other important social determinants of health that may contribute to poor longer term outcomes post-PCI. Finally, a particular limitation of observational studies of marijuana use and cardiovascular disease is the presence of collider bias (8). If marijuana use increases the risk for coronary artery disease, as suggested by this analysis with increased ST-segment elevation myocardial infarction presentation, then multiple unmeasured confounders would likely favor a null association between marijuana use and adverse clinical events. Indeed, the 10-year difference in mean age is probably a hint of substantial collider bias. Therefore, on top of other limitations, we should be cautious before concluding "no impact" on mortality or other major events in such analyses.

So how should the data of Yoo et al (6) influence our practice when faced with patients undergoing PCI who use marijuana? Although studies such as that of Yoo et al (6) may provide insight into periprocedural in-hospital outcomes associated with marijuana, there are few data to guide practitioners regarding post-discharge outcomes. Given the potential effects on the coagulation cascade, platelet biology, and drug metabolism, physicians should record the history of marijuana use as they would smoking history and advise patients regarding potential risks, particularly in the context of treatment with antithrombotic regimens. As highlighted previously, marijuana use may increase the propensity toward bleeding complications but may

also make antiplatelet agents such as clopidogrel less effective, thereby potentially increasing the risk for ischemic events. Bleeding avoidance strategies such as the radial-first approach should be adopted, and antithrombotic regimes (both type and duration) should be personalized at the individual patient level taking into consideration their overall balance of ischemic and bleeding risk and whether patients are likely to adhere to therapies. As Donald Rumsfeld noted, "There are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns—the ones we don't know we don't know." Currently, there are many unknown unknowns about marijuana use and longer term PCI outcomes.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Mamas A. Mamas, Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, Stoke on Trent ST5 5BG, United Kingdom. E-mail: mamasmamas1@yahoo.co.uk.

REFERENCES

1. DeFilippis EM, Bajaj NS, Singh A, et al. Marijuana use in patients with cardiovascular disease: *JACC* review topic of the week. *J Am Coll Cardiol*. 2020;75:320–332.

2. Richards JR. Mechanisms for the risk of acute coronary syndrome and arrhythmia associated with phytogenic and synthetic cannabinoid use. *J Cardiovasc Pharmacol Ther*. 2020;25:508–522.

3. Greger J, Bates V, Mechtler L, Gengo F. A review of cannabis and interactions with anticoagulant and antiplatelet agents. *J Clin Pharmacol*. 2020;60:432–438.

4. Coetzee C, Levendal RA, van de Venter M, Frost CL. Anticoagulant effects of a cannabis extract in an obese rat model. *Phytomedicine*. 2007;14:333–337.

5. Formukong EA, Evans AT, Evans FJ. The inhibitory effects of cannabinoids, the active constituents of *Cannabis sativa L*. on human and rabbit platelet aggregation. *J Pharm Pharmacol*. 1989;41:705–709.

6. Yoo SGK, Seth M, Vaduganathan M, et al, on behalf of the Blue Cross Blue Shield of Michigan Cardiovascular Consortium Investigators. Marijuana use and in-hospital outcomes after percutaneous coronary intervention in Michigan, United States. *J Am Coll Cardiol Intv*. 2021;14:1757–1767.

7. Kwok CS, Alraies MC, Mohamed M, et al. Rates, predictors and the impact of cannabis misuse on in-hospital outcomes among patients undergoing percutaneous coronary intervention (from the National Inpatient Sample). *Int J Clin Pract*. 2020;74:e13477.

8. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology*. 2003;14:300–306.

KEY WORDS major bleeding, marijuana, outcomes, percutaneous coronary intervention