SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

EDITORIAL COMMENT

Cannabis and Heart Disease

Forward Into the Great Unknown?*

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The paper by DeFilippis et al. (1) in this issue of the *Journal* is a timely reminder of how little we know about cannabis consumption, cardiovascular disease (CVD), and cannabis' health effects in general. It is also a firm confirmation of the negative effects of any cocaine use, a much better understood risk factor for acute myocardial infarction, stroke, and diminished survival. Cannabis has long been the most widely used "illicit substance" in the United States; recent data (from 2014) for past month marijuana use in persons age ≥12 years was 8.4% (2).

However, the status of cannabis in the United States is increasingly licit. Evolving public opinion (61% of U.S. adults sampled in 2018 think marijuana should be legal) (3), an exhaustion with a "war" on a drug that about one-half of U.S. adults have used at some point in their life, and perhaps the very real appeal of new streams of tax revenue have led to the approval of medical cannabis in 30 states plus the District of Columbia, 9 of which (plus the District of Columbia) legalized recreational use. This includes Massachusetts, the site of the DeFilippis et al. (1) study, which is expected to have tax-stamped recreational cannabis products for sale to any adult age >21 years by July 2018. Federally, cannabis remains illegal and is a schedule-I controlled substance (no accepted medical use, high abuse potential).

What should we tell our adult patients about cannabis, based on DeFilippis et al. (1) and other studies? The data here show that "young myocardial infarctions (MIs)" with marijuana exposure at baseline did worse in terms of long-term survival. The 120 cases who had a first new acute type 1 MI at age ≤50 years and who were "marijuana-positive" had lower all-cause and lower CVD survival during an average follow-up time of 11 years (vs. the 1,866 cases with no detected marijuana or cocaine exposure). Marijuana and cocaine exposure at baseline were each associated with longitudinal hazard ratios for death of about 2. These marijuana results mirror studies of all MIs, including "old MIs" (4). It is reasonable for cardiologists and primary care providers to caution new MI patients of any age to refrain from marijuana use. Although these data did not track continued marijuana use post-MI, the logic is to encourage patients to move from this study's marijuana user to the nonuser bin, and *potentially* improve their odds of survival. Why not, and what would be the harm of such common-sense advice?

Providers could cite the current study, conducted at 2 Boston hospitals from 2000 to 2016, as well as the National Academy of Science's 2017 Report, "The Health Effects of Cannabis and Cannabinoids," an exhaustive survey and synthesis of data, both for good (medicinal use) and for ill (potential harms) (5). This report summarized the evidence as "limited" that acute cannabis smoking is positively associated with an increased risk of acute MI (as a triggering event), and found "no evidence to support or refute" associations between any chronic effects of cannabis use and increased risk of acute MI (5). DeFilippis et al. (1) summarize possible mechanisms for cannabinoid-receptor-mediated pro-MI effects (decreased contractility, free radicals, smooth muscle hypertrophy). Despite potential "pros" for an individual patient's continued use of cannabis, we have enough data to recommend reducing or ceasing their intake of inhaled marijuana smoke.

What then, if the cannabis-using patient pushes back? What if the patient informs you that he or she has converted to cannabis lozenges, says they reduce

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stress (also harmful), opines on the harmless reputation of marijuana versus cocaine or opioids, and references the growing population-wide rates of use? Plus, the patient might ask, "What proven strategies do you recommend I use to quit cannabis?" Here, we as health care providers are kind of stuck, because now we must pause and consider the vast uncertainty of the science regarding cannabis and health, acknowledge key limitations of the data by DeFilippis et al. (1), reflect that we really have no proven effective treatments for cannabis use disorders when we do identify them, and keep in perspective important real-world priorities. After all, this same patient likely now has some other behavior change heavy lifts: quit smoking, increase exercise, lose weight, limit alcohol, and adhere to guideline-based medical therapies.

The data by DeFilippis et al. (1) were striking in that the prevalence of detected marijuana use—about 8% of the 2,097 MIs—was similar to U.S. population estimates for the same years. A case-control ratio of 1:1 for the prevalence of a potential risk factor is not a glaring danger sign. This is in distinct contrast to the cocaine exposure rate of ≥4%, which exceeded national rates of cocaine use by 4 to 10×. Further, more of the marijuana cases were smokers: 65% versus 49% of control subjects. Smoking status is adjusted for in the survival models, but this important baseline difference immediately establishes the importance of key confounders, most of which are unmeasured in this dataset. Regular, problematic marijuana and other drug and alcohol users, who we assume were the most likely to have cannabis use charted or have a urine toxicology obtained, were also (we know from this and other studies) (6) more likely to be smokers, heavy drinkers, and other drug users (including cocaine), and may have had disproportionate rates of comorbid human immunodeficiency virus, hepatitis C virus, or depression. These are all potentially important risk factors for any number of poor health outcomes, and an ability to control for and contrast among these many baseline and ongoing subgroup variables is a crucial strength of observational research. In this study, alcohol and opioid use were ignored (during an increasingly fatal period of opioid-related overdoses in Massachusetts). No other medical or mental health conditions likely contributing to mortality, such as human immunodeficiency virus or major depression, seemed to have been measured. The operational definition of recent baseline marijuana use, which was retrospective chart review of real charts lacking any universal screening or diagnostic interviews concerning marijuana use, or positive urine toxicology tests, which were also not universally performed, severely limits the validity of this study's marijuana-positive label. Presumably, many recent cannabis users were simply missed and instead classified as marijuana-negative. This study, then, likely does not change the balance of the National Academy's conclusion that the evidence of a real cannabis-CVD risk is limited at best. Richer observational data specifically targeting these cannabis-MI questions would be helpful, and interventional trials targeting cannabis reduction and improved heart health may be warranted.

So, although the data for harm is limited, what if you wish to press the issue, as the potential danger from continued marijuana use is possible? How then to advise a patient on reducing or quitting cannabis use or treating a diagnosable cannabis use disorder? SBIRT (Screening, Brief Intervention, and Referral to Treatment), which is intended to decrease the frequency of drug use in general adult medical care settings, including cannabis use, is thus far ineffective in very large randomized trials (7). What if your patient has tried but cannot cut down and is having frank social and health problems related to marijuana use, including their recent MI? These are likely positive criteria for a DSM-5 cannabis use disorder, but, as it turns out, we have very little proven effective treatments to offer. There are no indicated medication treatments, and guidelines generally recommend generic individual and group behavioral counseling interventions (including 12-step involvement, Cognitive Behavioral Therapy, contingency management, or motivational enhancement therapy), none of which have been shown to consistently drive cannabis abstinence long-term (8). We are a bit stuck, in other words, even in the face of a patient who is trying his or her best to cut down on marijuana, is not succeeding, and is asking for our help in facing this potential threat to his or her overall survival. Compassion, encouragement, and referral to specialty addiction treatment are the rule, but these interventions are not expected to have great effects.

Finally, fewer and fewer people are "smoking weed," and the studied risks of cannabis, which are almost entirely based on users of inhaled combustible marijuana smoke, will need to be updated. Returning to the surge of legal cannabis in the United States, the practice of inhaling combusted marijuana plant matter is declining as a proportion of overall regular cannabis use. An extended array of cannabis products, including edibles, transdermal formulations, and electronic cigarette-like cartridges of cannabis oil, mean the typical use of cannabis is no longer just marijuana smoke (9). This may have important implications for marijuana-MI studies, including this one, if more and more adults are no longer repeatedly

inhaling high-temperature, unfiltered smoke. This may also provide some opportunities for harm reduction counseling among persistent marijuana smokers, who may well be better off from a cardiovascular standpoint by consuming cannabis edibles. We simply do not know whether this would help, but parallels with continued nicotine replacement therapy or e-cigarette use by former adult smokers are not out of place.

Our compliments to DeFilippis et al. (1) on their important contribution to the literature on a timely and under-researched question. We encourage increasing collaboration among cardiologists and drug use and addiction experts to further advance our understanding of the potential health consequences of increased cannabis use in the United States.

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KEY WORDS cannabis, cardiovascular risk factor, heart disease