Acute Ischemic Heart Disease

An exploratory prospective study of marijuana use and mortality following acute myocardial infarction

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Background  The relationship of marijuana use with coronary heart disease, including prognosis among patients with coronary heart disease, is uncertain.

Methods  We conducted an inception cohort study of 1913 adults hospitalized with myocardial infarction at 45 US hospitals between 1989 and 1994, with a median follow-up of 3.8 years. We ascertained total mortality according to self-reported marijuana use in the preceding year.

Results  A total of 52 patients reported marijuana use during the prior year, and 317 patients died during follow-up. Compared with nonuse, marijuana use less than weekly was associated with a hazard ratio of 2.5 (95% CI, 0.9-7.3). The corresponding hazard ratio for weekly use or more was 4.2 (95% CI, 1.2-14.3). The age- and sex-adjusted hazard ratios associated with any use were 1.9 (95% CI, 0.6-6.3) for cardiovascular mortality and 4.9 (95% CI, 1.6-14.7) for noncardiovascular mortality. In a comparison of 42 marijuana users and 42 other patients matched on propensity scores, there were 6 deaths among marijuana users and one among non-users (log-rank \( P = .06 \)).

Conclusions  These preliminary results suggest possible hazards of marijuana for patients who survive acute myocardial infarction. Although marijuana use has not been associated with mortality in other populations, it may pose particular risk for susceptible individuals with coronary heart disease. (Am Heart J 2008;155:465-70.)

Marijuana use is not uncommon in the United States. A 2001-2002 national survey found that 4.1% of the adult population of the United States had used marijuana within the last year.1 Although younger adults were most likely to report marijuana use, such use among adults aged 45 to 64 years was almost 3-fold higher than it had been a decade earlier.

Few studies have documented the long-term outcomes of marijuana users. In one previous study of marijuana use and mortality in the general population,2 Sidney et al2 found no increased risk of mortality associated with marijuana use among Kaiser Permanente enrollees <50 years old, very similar to earlier findings among

Swedish conscripts.3 However, marijuana use has cardiovascular effects that could pose particular risk for older adults and those with coronary heart disease, including a sizable increase in resting heart rate.4 Moreover, in a previous analysis of the Onset Study, the risk of triggering a myocardial infarction (MI) was elevated almost 5-fold within 1 hour after smoking marijuana, compared with periods of nonuse,5 consistent with case reports describing this phenomenon.6-10 However, Steffens et al11 recently found that orally administered tetrahydrocannabinol, a cannabinoid derivative, inhibits atherosclerosis progression in a mouse model, apparently through effects on lymphoid and myeloid cells. Marijuana use also has a wide variety of noncardiovascular effects, including potentially adverse respiratory, neurologic, and immunologic effects.12-14 The net balance of these apparently disparate effects of marijuana use on the most clinically vulnerable patients, such as those with established coronary heart disease, has not been studied.

An impediment to understanding the clinical consequences of marijuana use has been the stark dearth of studies that have collected information on exposure.2,3,15 To address this paucity of information, we explored the association of marijuana use assessed at the time of acute MI (AMI) with subsequent mortality among participants of the Onset Study. This multicenter, prospective cohort study included chart reviews and in-depth personal interviews with hospitalized patients with confirmed AMI.16,17
Methods
Onset Study enrollment and data collection

The Onset Study was conducted in 45 community and tertiary care medical centers. Between August 1989 and September 1994, 1955 patients (601 women and 1354 men) were interviewed a median of 4 days after sustaining a MI. Trained research interviewers identified eligible patients by reviewing coronary care unit admission logs and patient charts. Eligible patients were divided into two groups: those who reported a creatine kinase level above the upper limit of normal for each center, and those who did not. Positive MB isoenzymes were diagnostic of an identifiable onset of symptoms of infarction, and the ability to complete a structured interview. For these analyses, we excluded patients with missing information about marijuana use (n = 22), leaving us 1913 eligible patients for analysis. The institutional review board of each center approved this protocol, and each participant gave informed consent; the Beth Israel Deaconess Medical Center Committee on Clinical Investigations gave subsequent approval for linkage to publicly available mortality records.

Trained interviewers used a structured data abstraction and questionnaire form that queried about a range of possible triggers of MI, including caffeine, alcohol, smoking, exertion, and anger. As part of the interview, participants were asked, “Have you used marijuana, cocaine or amphetamines in the past year,” “how often do you use it,” and “when did you last use it?”

Other information collected from each interview and chart review included patient age, sex, marital status, educational attainment, medical history, and medication use (both prescription and nonprescription). During the chart review, interviewers recorded complications of congestive heart failure or ventricular arrhythmias based upon clinical diagnoses documented in the medical record. Interviewers also collected initial blood pressure on admission and all creatine kinase values available at the time of chart review (median = 4).

We defined initial hypotension as a presenting systolic blood pressure of <90 mmHg. We defined current aspirin use as the reported use of any aspirin or aspirin-containing product in the preceding year. We used屏障90 US Census data to derive median household income from US Postal Service zip codes. We derived body mass index from self-reported height and weight. We defined noncardiac comorbidity as any diagnosis of cancer, respiratory disease, renal failure, or stroke recorded in the medical record. Alcohol consumption was assessed with quantity/frequency items for beer, wine, and liquor, which were summed to yield average intake. Tea and coffee intake were assessed similarly. Binge drinking was assessed as intake of ≥3 drinks in a 2-hour period within the last year. Physical activity was assessed with a validated inventory derived for this study.

We searched the National Death Index for deaths of Onset Study participants through January 1, 1996, and requested death certificates from state offices of vital records for all probable matches, using a previously validated algorithm that included name, date of birth, sex, race, marital status, and state. Three physicians independently verified the determination of each death. Two physicians categorized the cause of each death as due to cardiovascular disease or noncardiovascular disease. Disagreements among raters were resolved by discussion. All-cause mortality was the primary outcome in all analyses, with cardiovascular and noncardiovascular mortality as secondary outcomes.

Statistical analysis

We used Cox proportional hazards models to examine the relationship of marijuana use to mortality after adjustment. We first adjusted for age, sex, and their interaction. In subsequent models, we further controlled for race, body mass index (as linear and quadratic terms), marital status (married versus other), current smoking, previous smoking, usual frequency of exertion (in 3 categories), intake of tea (in 3 categories), usual intake of alcohol (in 3 categories), binge drinking, household income (in quartiles), educational attainment (in 3 categories), previous MI, previous congestive heart failure, diabetes mellitus, hypertension, noncardiac comorbidity, previous medication use (aspirin, β-adrenergic antagonists, calcium-channel blockers, digoxin, diuretics, hypolipidemic agents, and angiotensin-converting-enzyme inhibitors individually), and receipt of thrombolytic therapy. We assigned indicator variables for patients with missing information on educational attainment (n = 58), household income (n = 60), tea intake (n = 33), and smoking (n = 20) and set body mass index to the mean for 21 patients with missing information. Models that excluded individuals with any missing covariate information yielded similar results and are not shown here.

As a sensitivity analysis, we matched marijuana users with an equal number of other patients using propensity scores. Each patient’s score is that individual’s probability that he or she would report marijuana use, based upon demographic, behavioral, and clinical characteristics. To create propensity scores, we used a multivariable logistic regression model, in which the dependent variable was marijuana use, and the independent variables were all covariates used in the Cox models noted above except receipt of thrombolytic therapy, and with the addition of linear and quadratic terms for age and alcohol use and interaction terms of sex with age and race. The area under the receiver operating characteristic curve was 0.96, indicating outstanding discrimination for the logistic model. We then individually matched marijuana users to unique nonusers using the nearest available pair matching method. We were successfully able to match 42 marijuana users to 42 unique patients who did not report such use; the remainder had disjoint ranges of propensity scores. We compared Kaplan-Meier estimates of survival among these 84 patients using the log-rank test.

We tested the proportionality of hazards using time-varying covariates and found no significant violations. We used the SAS System for Windows, release 8.01 (SAS Institute, Inc, Cary, NC) for all analyses. The funding sources for this work had no role in the analysis, presentation, or publication of results.

Results
Patient characteristics

Table I shows the characteristics of the Onset Study participants according to marijuana use. A total of 52 patients (2.7%) reported marijuana use in the preceding year. As expected, marijuana users tended to be younger than other patients; had heavier usual alcohol consumption; and were more likely to be male, current
smokers, and divorced or separated. Among marijuana users, the reported median frequency of use was once every 2 weeks.

Marijuana use and mortality

A total of 317 patients died during a median of 3.8 years of follow-up. Table II shows hazard ratios for mortality, comparing marijuana users to other participants. Marijuana use was associated with 3-fold higher total mortality, both in age- and sex-adjusted and in more fully adjusted models.

To determine whether marijuana use was associated with a gradient in risk of death, we separated marijuana users into those reporting use less than weekly versus weekly or more. Compared with nonusers, use less than weekly was associated with a hazard ratio of 2.5 (95% CI, 1.4-7.0). Additional adjustment for concurrent use of cocaine and 2.8 (95% CI, 1.2-6.7) when we additionally controlled for initial hypotension, complications of congestive heart failure or ventricular arrhythmias during hospitalization, and peak creatine kinase levels as measures of infarct severity. The hazard ratio from a stepwise model (with entry and stay criteria of P = .20) was 3.1 (95% CI, 1.4-7.0). Additional adjustment for coffee intake and intensity of current smoking (in 4 categories) also did not alter our results (hazard ratio 3.1; 95% CI, 1.3-7.5).

Matched-pair analysis

We also determined the survival of 42 marijuana users and 42 other patients matched on propensity score (which is the probability of reporting marijuana use given other baseline characteristics). These groups were generally well matched, including similar mean ages (44.1 years in both groups) and proportions of white participants (69% vs 71%) and current smokers (71% vs 74%).

Although we did not have sufficient numbers of cases to evaluate cardiovascular and non-cardiovascular mortality with precision, 4 of 7 deaths among marijuana users were non-cardiovascular, compared with 75 of 310 among non-users (p exact 0.07). The age- and sex-adjusted hazard ratios associated with any marijuana use were 1.9 (95% CI, 0.6-6.3) for cardiovascular mortality and 4.9 (95% CI, 1.6-14.7) for non-cardiovascular mortality.

Given that approximately 3 quarters of marijuana smokers were also cigarette smokers, we repeated our analyses, restricted to current smokers (who accounted for 62 deaths). The age- and sex-adjusted hazard ratio associated with marijuana use was 4.1 (95% CI, 1.6-10.4). The corresponding hazard ratio when restricted to current consumers of alcohol was 3.7 (95% CI, 1.5-9.1).

We also performed additional analyses in an attempt to ensure our models were robust. The hazard ratio associated with marijuana use was 2.9 (95% CI, 1.2-6.7) when we controlled for concurrent use of cocaine and 2.8 (95% CI, 1.2-6.5) when we additionally controlled for initial hypotension, complications of congestive heart failure or ventricular arrhythmias during hospitalization, and peak creatine kinase levels as measures of infarct severity. The hazard ratio from a stepwise model (with entry and stay criteria of P = .20) was 3.1 (95% CI, 1.4-7.0). Additional adjustment for coffee intake and intensity of current smoking (in 4 categories) also did not alter our results (hazard ratio 3.1; 95% CI, 1.3-7.5).

### Table I. Characteristics of 1913 Onset Study participants according to self-reported marijuana use

<table>
<thead>
<tr>
<th>Marijuana use</th>
<th>Yes (n = 52)</th>
<th>No (n = 1861)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.6 ± 8.8</td>
<td>62.0 ± 12.3</td>
</tr>
<tr>
<td>Female</td>
<td>3 (6)</td>
<td>587 (32)</td>
</tr>
<tr>
<td>White</td>
<td>36 (69)</td>
<td>1681 (90)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8 ± 5.3</td>
<td>27.3 ± 5.2</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>40 (77)</td>
<td>596 (32)</td>
</tr>
<tr>
<td>Former cigarette smoker</td>
<td>9 (17)</td>
<td>781 (42)</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>13 (25)</td>
<td>157 (9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (23)</td>
<td>830 (45)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (8)</td>
<td>389 (21)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>11 (21)</td>
<td>525 (28)</td>
</tr>
<tr>
<td>Angina</td>
<td>5 (10)</td>
<td>478 (26)</td>
</tr>
<tr>
<td>Previous congestive heart failure</td>
<td>1 (2)</td>
<td>81 (4)</td>
</tr>
<tr>
<td>Noncardiac comorbidity</td>
<td>2 (4)</td>
<td>280 (15)</td>
</tr>
<tr>
<td>Regular use of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>2 (4)</td>
<td>220 (12)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>20 (38)</td>
<td>626 (34)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>4 (8)</td>
<td>383 (21)</td>
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<tr>
<td>Calcium-channel blockers</td>
<td>8 (15)</td>
<td>458 (25)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1 (2)</td>
<td>142 (8)</td>
</tr>
<tr>
<td>Hypolipidemics</td>
<td>3 (6)</td>
<td>139 (7)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2 (4)</td>
<td>377 (20)</td>
</tr>
<tr>
<td>Thrombotic use</td>
<td>21 (40)</td>
<td>664 (36)</td>
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<td>Complications of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (6)</td>
<td>276 (15)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>11 (21)</td>
<td>227 (12)</td>
</tr>
<tr>
<td>Q-wave infarction</td>
<td>18 (62)</td>
<td>568 (56)</td>
</tr>
<tr>
<td>Education (years of schooling)</td>
<td>12.4 ± 4.0</td>
<td>12.7 ± 3.0</td>
</tr>
<tr>
<td>Income ($)</td>
<td>32873 ± 13576</td>
<td>38523 ± 13086</td>
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<tr>
<td>Weekly tea intake (cups)</td>
<td>3.7 ± 8.0</td>
<td>4.2 ± 9.5</td>
</tr>
<tr>
<td>Weekly coffee intake (cups)</td>
<td>23.8 ± 31.7</td>
<td>16.5 ± 24.5</td>
</tr>
<tr>
<td>Weekly alcohol intake (servings)</td>
<td>15.0 ± 25.4</td>
<td>4.0 ± 11.1</td>
</tr>
</tbody>
</table>

### Table II. Hazard ratios and 95% CIs for all-cause, cardiovascular, and noncardiovascular mortality after AMI according to marijuana use among Onset Study participants

<table>
<thead>
<tr>
<th>Marijuana use</th>
<th>No</th>
<th>Yes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1861</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>310</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>1.0</td>
<td>3.0</td>
<td>.006</td>
</tr>
<tr>
<td>Adjusted model*</td>
<td>1.0</td>
<td>3.0</td>
<td>.009</td>
</tr>
</tbody>
</table>

*The adjusted model included age, sex, body mass index, marital status, race, income, education, physical activity, current smoking, former smoking, tea intake, usual and binge alcohol intake, medical history (previous AMI, congestive heart failure, diabetes, hypertension, and non-cardiovascular comorbidity), receipt of thrombolytic therapy, and medication use (aspirin, β-blockers, calcium-channel antagonists, ACE inhibitors, digoxin, diuretics, and hypolipidemic agents).
versus 74%). Clinical characteristics of the index infarction, though not part of the matching algorithm, were also comparable, with identical proportions sustaining Q-wave infarctions (60%) and congestive heart failure (7%) and similar peak creatine kinase levels (2035 vs 1979 IU/L). Among these 84 matched patients, 6 marijuana users died, compared with only 1 nonuser (log-rank $P = .06$).

**Causes of death among marijuana users**

We performed a post hoc examination of the death certificates of the 7 patients who reported marijuana use and who died during follow-up. Of the 3 patients who died of cardiovascular causes, 2 died of progressive coronary heart disease and 1 from sudden cardiac death related to ventricular fibrillation. Of the 4 who died of noncardiovascular causes, 1 died in a motor vehicle accident, 1 from AIDS, 1 from carcinoma of the lung, and 1 from both lung cancer and AIDS.

**Discussion**

In this preliminary prospective cohort study of early survivors of AMI, marijuana use, as measured at the time of hospitalization, was associated with 3-fold higher mortality after infarction. There was a gradient in risk, with the highest risk of death among individuals who used marijuana most frequently, and the risk was entirely unchanged by multivariate adjustment.

Marijuana use has important cardiovascular effects that could pose risk for patients with coronary heart disease. Among the best-defined of these is an increase in resting heart rate that can be selectively blocked by pretreatment with a cannabinoid receptor antagonist. This effect may be related to the prolonged catecholamine release that marijuana can induce.27

Marijuana use can also increase supine blood pressure, although it leads to orthostatic hypotension, postural dizziness, and even syncope in some cases.28,29

At the same time that marijuana increases heart rate and, therefore, myocardial oxygen demand, it may also limit oxygen uptake. Marijuana smoking leads to a dose-dependent increase in carbon monoxide exposure50 and even higher blood levels of carboxyhemoglobin than does cigarette smoking.12 These effects have a demonstrably detrimental impact on patients with known coronary heart disease, in whom marijuana use decreases exercise time to the onset of angina by 50%, twice as great an effect as use of a standard cigarette.51

Marijuana use could also lead to higher risk of death among patients by interfering with adherence to standard therapies. Although the relationship of marijuana use and adherence to therapy among patients with coronary heart disease has not been evaluated, it may interfere with adherence to other life-saving medication, such as antiretroviral therapy for human immunodeficiency virus infection.52 The effects of marijuana use on cognitive function could conceivably exacerbate this further.53

Over half of deaths among Onset Study participants who reported marijuana use were noncardiovascular, a substantially higher proportion than in nonusers. Despite the lack of specificity inherent in use of death certificates to assign accurate causes of death,54 our results suggest that patients with coronary heart disease who use marijuana may be at particular for risk for all causes of death, and not recurrent cardiovascular disease alone. In this regard, the possible effects of marijuana use on unintentional injury and upper airway malignancy may be particularly important.55,56 Marijuana use also directly increases risk-taking behavior in some settings,37,38 but our findings were not altered by adjustment for other markers of risky behavior that were available, including binge drinking and cocaine use, perhaps because marijuana use was less strongly related to risk-taking in this relatively older aged cohort.

Similar to our findings, Sidney et al2 also found that marijuana use was associated with AIDS-related death in men. It seems likely that this, at least in part, reflects confounding by indication, in which marijuana is used for nausea or appetite stimulation. However, cannabinoids may also have direct immunosuppressive effects that could accelerate disease progression among susceptible individuals.14 Further studies to understand the degree to which marijuana use could influence postinfarct mortality via direct cardiovascular effects, cognitive changes that reduce adherence, noncardiovascular effects of marijuana, or simply other confounding factors related to marijuana use are clearly needed.

The Onset Study has both strengths and limitations. An important and perhaps unique strength is its assessment of marijuana use in a population of early survivors of MI; to our knowledge, no comparable cohort studies exist. All participants were interviewed in a standardized manner during hospitalization for enzymatically confirmed infarcts, and a relatively large body of information on clinical and sociodemographic variables was obtained.

On the other hand, these results should be viewed as hypothesis-generating only. The number of marijuana smokers was relatively small, follow-up was limited to approximately 4 years, and the confidence limits around our estimates—even when they exclude the null—were relatively wide. The cohort was assembled in the early 1990s, and the association of marijuana use with prognosis, while collected prospectively, was not a primary aim. Although further follow-up of this cohort is not possible and could be of limited value without updated assessments of marijuana, our results do point to the urgent need for larger and longer studies of marijuana use in comparable populations.

As with any observational study, we cannot prove cause-and-effect relationships, although it is unclear how a randomized trial to test our findings could be
performed. Our results were also consistently unchanged by adjustment for a wide variety of clinical characteristics, including alcohol intake and smoking. Nonetheless, there are apt to be unmeasured confounding clinical or lifestyle factors that may be responsible for our findings.

We asked participants to report their usual marijuana use over the year prior to the infarction that resulted in their hospitalization and did not have information on post-MI use, which is likely to have differed from that measured here. Assuming that some marijuana users cease use after hospitalization, we may have underestimated the true effect of postinfarction marijuana use on survival. On the other hand, by assessing marijuana exposure before infarction and before follow-up, we minimized the potential bias that could affect assessment of postinfarction marijuana use alone if sicker patients give up marijuana use more often than healthier patients after hospitalization. Future studies should also include repeated assessments of marijuana use to address this possibility.

In conclusion, marijuana use was associated with 3-fold greater mortality after AMI in this exploratory study, with a graded increase in risk with more frequent use. Because marijuana use appears to be increasing among middle-aged and older adults, this finding may have growing importance in the future. Although marijuana use does not appear to be associated with mortality among the general population, our results suggest that it may carry particular risks for vulnerable populations with established cardiovascular disease.

References


37. Lane SD, Yechiam E, Busemeyer JR. Application of a computational decision model to examine acute drug effects on human risk taking. Exp Clin Psychopharmacol 2006;14:254-64.