# Acute Coronary Syndrome and Khat Herbal Amphetamine Use

## An Observational Report

Waleed M. Ali, MD; K.F. Al Habib, MD; Ahmed Al-Motarreb, MD; Rajvir Singh, PhD; Ahmad Hersi, MD; Hussam Al Faleh, MD; Nidal Asaad, MBBS; Shukri Al Saif, MD; Wael Almahmeed, MD; Kadhim Sulaiman, MD; Haitham Amin, MD; Jawad Al-Lawati, MD; Nizar Al Bustani, MD; Norah Q. Al-Sagheer, MD; Awad Al-Qahtani, MBChB; Jassim Al Suwaidi, MBChB

***Background***—The khat plant is a stimulant similar to amphetamine and is thought to induce coronary artery spasm. Khat is widely chewed by individuals originating from the Horn of Africa and the Arabian Peninsula. The aim of this study was to evaluate the clinical characteristics and outcome of khat chewers presenting with acute coronary syndrome.

***Methods and Results***—From October 1, 2008, through June, 30, 2009, 7399 consecutive patients with acute coronary syndrome were enrolled in the Second Gulf Registry of Acute Coronary Events (Gulf RACE-2). Nineteen percent of patients were khat chewers; 81% were not. Khat chewers were older, more often male, and less likely to have cardiovascular risk factors. Khat chewers were less likely to have a history of coronary artery disease and more likely to present late and to have higher heart rate and advanced Killip class on admission. Khat chewers were more likely to present with ST-segment–elevation myocardial infarction. Overall, khat chewers had higher risk of death, recurrent myocardial ischemia, cardiogenic shock, ventricular arrhythmia, and stroke compared with non–khat chewers. After adjustment for baseline variability, khat chewing was found to be an independent risk factor of death and for recurrent ischemia, heart failure, and stroke.

***Conclusions***—Our data confirm earlier observations of worse in-hospital outcome among acute coronary syndrome patients who chew khat. This worse outcome persists up to 1 year from the index event. This observational report underscores the importance of improving education concerning the cardiovascular risks of khat chewing. **(*Circulation*. 2011;124:2681-2689.)**

**Key Words:** acute coronary syndrome ■ adrenergic beta-antagonists ■ cathinone ■ ethnicity ■ thrombolysis

Chewing the leaves of the plant *Catha edulis* (referred to as khat, mirra, qat, chat, and quaadka) likely dates to times of antiquity and may predate the use of coffee.[1] Twenty million people worldwide are believed to be using khat, which previously was confined to East Africa and the Arabian Peninsula.[2] Unlike other abuse substances, khat is highly perishable. The leaves are freshly stripped from the trees at dawn and rapidly distributed by airplanes and regional organized delivery systems. Khat initially was thought to be of limited concern to Western populations because of its complicated cultivation and distribution systems. However, overnight delivery systems and immigration of khat chewers contributed to its globalized distribution. In England, 7 metric tons of khat is estimated to travel through Heathrow Airport each week, originating from Yemen, Ethiopia, and Kenya.[1] Moreover, to make distribution of khat easier and to preserve its efficacy for a longer period of time, several synthetic forms were developed, including hagigat, rakefet, mephedrone, NB mephedrone (known as *meow meow*), and graba. Hagigat (Hebrew for Gat/khat party), which is capsules of 200 mg of cathinone, appeared in Israel at the end of 2003 and was labeled a natural stimulant.[3] Recently, in the United States, numerous seizures of graba, or dried khat, have been made.[4] Moreover, fresh khat is believed to have been confiscated throughout the United States. According to the National Drug Intelligence Center, East African and Yemeni independent dealers are distributing khat in the United States.[5]

**Clinical Perspective on p 2689**

Cathinone, cathine, and norephedrine are the main components of khat.[6,7] Cathinone is structurally similar to amphet-

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From the Departments of Cardiology (W.M.A., N.A., A.A.-Q.) and Research (R.S.), Hamad Medical Corp, Qatar; King Fahad Cardiac Center, King Khalid University Hospital, College of Medicine, Riyadh, Saudi Arabia (K.F.A.H., A.H.); Security Forces Hospital, Riyadh, Saudi Arabia (H.A.F.); Saud AlBabtain Cardiac Center, Dammam, Saudi Arabia (S.A.S.); Faculty of Medicine, Sana's University, Sana'a, Yemen (A.A.-M.); Department of Cardiology, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates (W.A., N.A.B.); Department of Cardiology, Royal Hospital, Muscat, Oman (K.S.); Mohammed Bin Khalifa Cardiac Center, Bahrain (H.A.); Department of Non-Communicable Diseases Surveillance and Control, Ministry of Health, Muscat, Oman (J.A.-L.); and Cardiac Center, Al-Thawra Hospital, Sana'a, Yemen (N.Q.A.-S.).

Correspondence to Jassim Al Suwaidi, MBChB, FACC, FSCAI, FESC, Department of Cardiology and Cardiovascular Surgery, Hamad General Hospital, PO Box 3050, Doha, Qatar. E-mail jalsuwaidi@hotmail.com or jha01@hmc.org.qa



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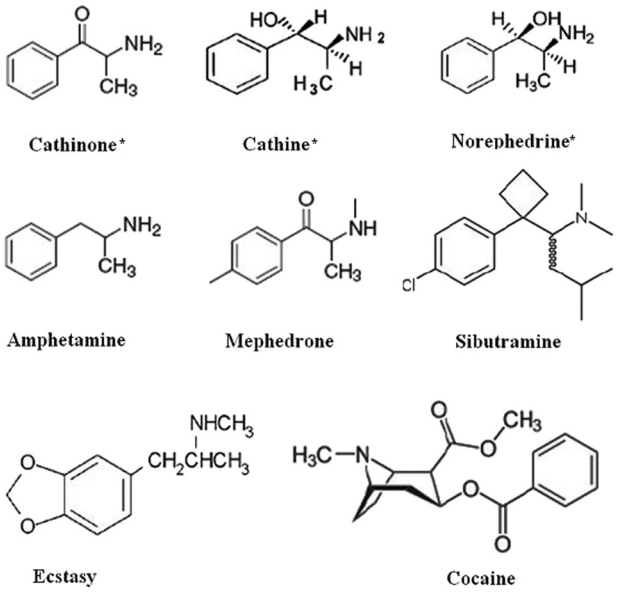


**Figure 1.** Chemical structure of the primary alkaloid constituents of khat (cathinone, cathine, and norephedrine) compared with drugs that are similar to khat constituents structurally and/or functionally.

amine[8] and functionally similar to amphetamine, cocaine, and sibutramine, the diet medication recently withdrawn from the market (Figure 1). Like ecstasy and amphetamine, cathinone exerts pronounced behavioral effects of euphoria, hyperactivity, and restlessness.[9] Cathinone is also thought to be behind the anorexigenic effect of khat, which contributes to the decreased appetite and body weight observed in khat chewers.[10] The First Gulf Registry of Acute Coronary Events (Gulf RACE-1) has recently shown that khat chewing (confined mainly to patients in Yemen) was associated with increased in-hospital risk of stroke and death in patients with acute coronary syndrome (ACS) compared with non–khat chewers who were mainly from different Gulf populations.[11] Mateen and Casino[1] in an accompanying editorial suggested that this increased risk of complications may be attributed in part to variations in income and access to health care between the different Gulf populations studied. Here, we review the clinical characteristics and 1-year outcome of khat chewers presenting with ACS and compare them with non–khat chewers using Gulf RACE-2 registry data.

## Methods

The data were collected from a 9-month prospective, multicenter study of the Gulf RACE-2 that recruited 7399 consecutive ACS patients from 6 adjacent Middle Eastern Gulf countries (Bahrain, Kingdom of Saudi Arabia, Qatar, Oman, United Arab Emirates, and Yemen). Patients diagnosed with ACS, including unstable angina, ST-elevation myocardial infarction (STEMI), and non-STEMI, were recruited from 65 hospitals. An on-site cardiac catheterization laboratory was available in 43% of the hospitals. The majorities of hospitals (71%) were tertiary care ones and had a coronary care unit on site. There were no exclusion criteria; thus, all prospective patients with ACS were enrolled. The study received ethics approval from the institutional ethics bodies in all participating countries. Diagnosis of the different types of ACS and definitions of data variables were based on the American College of Cardiology clinical data standards.[12] History of khat chewing was obtained and recorded at the time of presentation.

A case report form for each patient with suspected ACS was filled out on hospital admission by assigned physicians and/or research assistants in each hospital using standard definitions and was completed throughout the patient's hospital stay. All case report forms were verified by a cardiologist and then sent online to the principal coordinating center,[13] where the forms were further checked for mistakes before submission for final analysis. To avoid double counting of multiple admissions to the registry, the patients' national identification numbers and assigned registry numbers were used. Patients were divided into khat chewers and non–khat chewers.

The aim of the study was to describe the clinical characteristics, therapy, and in-hospital and 1-year outcomes of khat chewers and compare them with those of non–khat-chewing ACS patients.

### Statistical Analysis

Patient characteristics are presented as proportions or mean±SD as appropriate. Whenever possible, rates were used to describe patient populations. The frequencies of categorical variables in the 2 populations (khat chewers and non–khat chewers) were compared by use of the $\chi^2$ test. Continuous variables were compared by use of the 2-tailed Student $t$ test. Variables influencing in-hospital mortality, cardiogenic shock, and stroke were assessed with multiple logistic regression after adjustment for all important confounders (ie, age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking, thrombolytic therapy, and khat use). Odds ratios (ORs), 95% confidence intervals (CIs), and $P$ values were reported for significant predictors. A value of $P<0.05$ was considered statistically significant. All $P$ values were the results of 2-tailed tests. All data analyses were carried out with the SPSS version 18.0.

## Results

A total of 1408 of the patients studied (19%) were khat chewers, mainly of Yemeni origin (75.5%). Khat chewers were more likely to present with STEMI followed by unstable angina and non-STEMI. Baseline characteristics of khat-chewing patients are given in Table 1. Khat chewers were older and more likely to be male. Khat chewers were also less likely to have a history of diabetes mellitus, hyperlipidemia, hypertension, obesity, and renal impairment. Cigarette smoking was more prevalent among khat chewers. Khat chewers were less likely to have a history of coronary artery, coronary revascularization, or heart failure compared with non–khat chewers.

On presentation, khat chewers had higher heart rates and advanced Killip class but lower systolic blood pressure. Laboratory analysis at admission showed lower fasting serum glucose and higher serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides in khat chewers compared with non–khat chewers, whereas low-density lipoprotein cholesterol was comparable.

### Treatment

#### *In-Hospital Treatment*

The majority of khat chewers presented late, with 60.8% of khat chewers presenting >12 hours from the onset of symptoms compared with only 14.3% of non–khat chewers; hence, they were less likely to receive thrombolytic therapy (29.7%) or primary percutaneous coronary interventions (4.6%). Khat chewers were more likely to receive clopidogrel, unfractionated heparin, and angiotensin-converting enzyme inhibitors, as well as angiotensin receptor blockers, whereas low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and β-blockers were prescribed more frequently to non–khat chewers (Table 2).

**Table 1. Clinical Characteristics of Patients With and Without Khat Chewing Presenting With Acute Coronary Syndrome**

| | Khat | No Khat | *P* |
|---|---|---|---|
| n (%) | 1408 (19) | 5991 (81) | |
| Age, mean±SD, y | 57±12.5 | 56.5±12.6 | 0.02 |
| Female, % | 14 | 22 | <0.001 |
| Arabic ethnicity, % | 98.7 | 64.7 | <0.001 |
| Country, % | | | 0.001 |
| Saudi Arabia | 1.8 | 34.1 | |
| Bahrain | 0.1 | 7.3 | |
| Yemen | 96.2 | 6.4 | |
| Qatar | 0.1 | 11.5 | |
| United Arab Emirates | 0.4 | 9.5 | |
| Oman | 1.3 | 31.2 | |
| Diabetes mellitus, % | 23.5 | 42.9 | <0.001 |
| Hypertension, % | 34 | 50 | <0.001 |
| Dyslipidemia, % | 16.6 | 40.8 | <0.001 |
| Smoking, % | 31 | 14 | <0.001 |
| Prior aspirin use, % | 31 | 42.8 | <0.001 |
| Prior statin use, % | 13.6 | 34.7 | <0.001 |
| Family history of CAD, % | 7.2 | 10.7 | <0.001 |
| Prior CAD, % | 32.2 | 42.7 | <0.001 |
| Prior revascularization, % | 6.4 | 13.5 | <0.001 |
| Renal impairment, %* | 0.6 | 4.8 | <0.001 |
| Prior history of CHF, % | 4 | 7 | <0.001 |
| Presentation >12 h (for ST-elevation+LBBB), % | 60.8 | 14.3 | <0.001 |
| At presentation | | | |
| Heart rate, mean±SD, bpm | 89±21 | 83.6±20 | <0.001 |
| Systolic blood pressure, mean±SD, mm Hg | 129±31 | 136.6±28 | <0.001 |
| Diastolic blood pressure, mean±SD, mm Hg | 80.8±19.9 | 81±17 | 0.4 |
| Body mass index, mean±SD, kg/m$^2$ | 25.5±4.6 | 27±5.8 | <0.001 |
| Killip class >1, % | 28.9 | 21.6 | <0.001 |
| GRACE score, %† | | | 0.02 |
| Low | 66 | 69 | |
| Intermediate | 25 | 23.7 | |
| High | 8.7 | 7 | |
| Laboratory result, mean±SD | | | |
| Total cholesterol, mmol/L | 5.3±1.7 | 4.7±1.5 | <0.001 |
| Serum triglycerides, mmol/L | 2.1±1 | 1.7±1 | <0.001 |
| Serum LDL, mmol/L | 3.1±1.1 | 3.1±1.3 | 0.2 |
| Serum HDL, mmol/L | 1.08±0.45 | 1.03±0.51 | 0.005 |
| First blood sugar, mmol/L | 10±5 | 10±5.6 | 0.09 |
| Fasting blood sugar, mmol/L | 6.9±3.6 | 7.4±3 | <0.001 |
| Atypical presentation (%) | 17.7 | 15.5 | <0.001 |
| Final diagnosis, % | | | |
| STEMI-LBBB | 69.8 | 40.9 | <0.001 |
| NSTEMI | 13.6 | 33.5 | <0.001 |
| Unstable angina | 16.6 | 25.5 | <0.001 |
| Coronary angiogram, % | 12 | 36.8 | <0.001 |
| Normal or nonsignificant CAD, % | 18.6 | 13.6 | 0.03 |
| 3-Vessel disease, % | 11.0 | 31.6 | <0.001 |
| 2-Vessel disease, % | 26.7 | 24.2 | 0.4 |
| Single-vessel disease, % | 34.9 | 28.8 | <0.001 |
| LV dysfunction, % | 76.4 | 73.5 | 0.04 |

CAD indicates coronary artery disease; CHF, congestive heart failure; LBBB, left bundle-branch block; GRACE, Global Registry of Acute Coronary Events; LDL, low-density lipoprotein; HDL, high-density lipoprotein; STEMI, ST-segment–elevation myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; and LV, left ventricular.

*Dialysis required.

†For STEMI, low/moderate risk score is 49 to 154 and high risk score is 155–319. For NSTEMI, low/moderate risk score is 1 to 140 and high risk score is 141–372.

### *At Discharge*

At discharge, khat chewers were more likely to be prescribed clopidogrel, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, whereas non–khat chewers were more frequently prescribed β-blockers, calcium channel blockers, and statins.

## In-Hospital Outcome

Khat chewers were more likely to die compared with non–khat chewers (7.5% versus 3.8%; $P<0.001$). Their mortality rate was also higher at the 1-month (15.5% versus 6.4%; $P<0.001$) and 1-year (18.8% versus 10.8%; $P<0.001$) follow-up (Figure 2). Khat chewing was also associated with other adverse events, including heart failure, recurrent myocardial ischemia or MI, ventricular arrhythmia, cardiogenic

**Table 2. Therapy at Admission and on Discharge**

| | Khat, % | No Khat, % | *P* |
|---|---|---|---|
| In-hospital therapy | | | |
| Thrombolytic therapy | 29.7 | 59.4 | 0.001 |
| Primary PCI | 4.6 | 16.4 | 0.001 |
| Aspirin | 98.5 | 98.4 | 0.8 |
| Clopidogrel | 91.7 | 73 | <0.001 |
| Unfractionated heparin | 82.0 | 32.7 | <0.001 |
| Low-molecular-weight heparin | 11.9 | 44.4 | <0.001 |
| Glycoprotein IIb/IIIa inhibitors | 5.8 | 8.3 | 0.001 |
| Angiotensin-converting enzyme inhibitor | 77.6 | 68.7 | <0.001 |
| Angiotensin receptor blocker | 2.4 | 5.4 | <0.001 |
| β-blockers | 65.8 | 75.8 | <0.001 |
| Inotropes | 13 | 6.8 | <0.001 |
| Therapy at discharge | | | |
| Aspirin | 90.4 | 96.8 | <0.001 |
| Clopidogrel | 85.0 | 64.8 | <0.001 |
| Angiotensin-converting enzyme inhibitors | 76.8 | 69.9 | <0.001 |
| Angiotensin receptor blocker | 8 | 6.4 | 0.02 |
| β-blockers | 70.2 | 81.4 | <0.001 |
| Calcium channel blockers | 1.2 | 9 | <0.001 |
| Statins | 89 | 91.9 | 0.001 |

PCI indicates percutaneous coronary intervention.

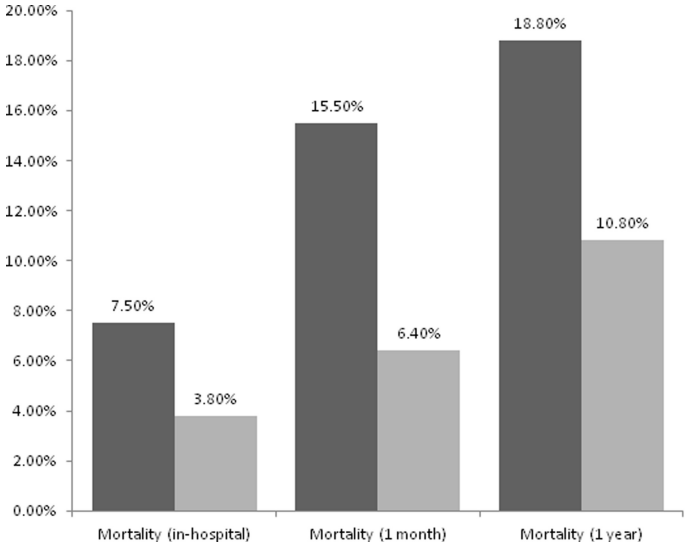


**Figure 2.** In-hospital, 1-month, and 1-year mortality rates according to khat chewing.

shock, and stroke. Of 17 stroke complications in khat-chewing patients, only 1 complication was associated with thrombolytic use. Bleeding complications were comparable between the 2 groups (Table 3).

Thrombolytic therapy was the primary reperfusion strategy in our registry. Although STEMI was the predominant presentation of khat chewers, a significant proportion of khat chewers did not receive reperfusion therapy. However, even after adjustment for reperfusion therapy, including thrombolytic therapy, mortality rates were higher in khat chewers compared with non–khat chewers. This increased mortality rate among khat chewers was also observed in non–ST-segment–elevation ACS patients (Figure 3). Khat chewers who did not receive β-blockers on admission were more likely to have in-hospital mortality, cardiogenic shock, stroke, recurrent myocardial ischemia, ventricular arrhythmia, and heart failure.

Figure 4 demonstrates in-hospital mortality rates according to khat chewing and age. The mortality rates were consistently higher among khat chewers up to 79 years of age. Khat chewers also had higher mortality regardless of sex. Heart failure, recurrent myocardial ischemia, and cardiogenic shock were also higher in female khat-chewing patients compared with female non–khat chewers. Male khat chewers were more likely to develop stroke than male non–khat chewers; among women, this increased risk was not statistically significant compared with their counterparts (Table 4).

**Table 3. Outcome of Patients According to Khat Use**

| | Khat | No Khat | *P* |
|---|---|---|---|
| In-hospital death, % | 7.5 | 3.8 | <0.001 |
| 1-mo Death, % | 15.5 | 6.4 | <0.001 |
| 1-y Death, % | 18.8 | 10.8 | <0.001 |
| Heart failure, % | 18.5 | 11.8 | <0.001 |
| Recurrent ischemia, % | 27.7 | 12.7 | <0.001 |
| Reinfarction, % | 3.8 | 1.7 | <0.001 |
| Cardiogenic shock, % | 11.6 | 4.4 | <0.001 |
| Major bleeding, % | 0.8 | 0.5 | 0.3 |
| Stroke, % | 1.2 | 0.6 | 0.007 |
| Hemorrhagic, n | 13 | 4 | |
| Thrombotic, n | 2 | 23 | |
| Unknown, n | 2 | 6 | |
| Ventilation, % | 6.2 | 4.2 | 0.001 |
| VF/VT, % | 5.6 | 2.3 | <0.001 |

VF/VT indicates ventricular fibrillation/ventricular tachycardia.

## Multivariate Analysis

The association of khat chewing with 1-month and 1-year mortality persisted after adjustment for age, sex, body mass index, diabetes mellitus, hypertension, smoking, diagnosis of STEMI, Killip class >1, β-blocker, prior aspirin use, prior statin use, and renal failure, as well as thrombolytic therapy (1 month: OR=1.69, 95% CI=1.24–2.30, $P$=0.001; 1 year: OR=1.46, 95% CI=1.10–1.94, $P$=0.008; Table 5). This analysis also demonstrated age, female sex, renal impairment, STEMI, and advanced Killip class to be independent predictors of increased risk of death and thrombolytic therapy and β-blocker use to be associated with improved outcome. Independent risk factors for recurrent myocardial ischemia included female sex, diabetes mellitus, and khat use (OR=2.8; 95% CI=2.4–3.3; $P$<0.001). Independent risk factors for heart failure included khat use (OR=1.98; 95% CI=1.6–2.3; $P$<0.001), age, female sex, diabetes mellitus, and hypertension. Finally, independent risk factors for stroke include age, hypertension, and khat use (OR=2.1; 95% CI=1.1–4.2; $P$=0.02).

Among khat chewers, β-blocker use at admission was associated with a 60% reduction in in-hospital mortality (OR=0.398; 95% CI=0.23–0.67; $P$<0.001) after adjustment for the potential confounders of age, sex, medical history of diabetes mellitus and hypertension, smoking, and angiotensin-converting enzyme inhibitor and thrombolytic use. Thrombolytic therapy use in STEMI patients was not associated with lower in-hospital mortality. Among non–khat chewers, when the same analysis was performed, β-blocker use was associated with reduced in-hospital (OR=0.32; 95% CI=0.21–0.48; $P$<0.001), 1-month (OR=0.439; 95% CI=0.303–0.636; $P$<0.001), and 1-year (OR=0.567; 95% CI=0.403–0.798; $P$<0.001) mortality. In STEMI pa-

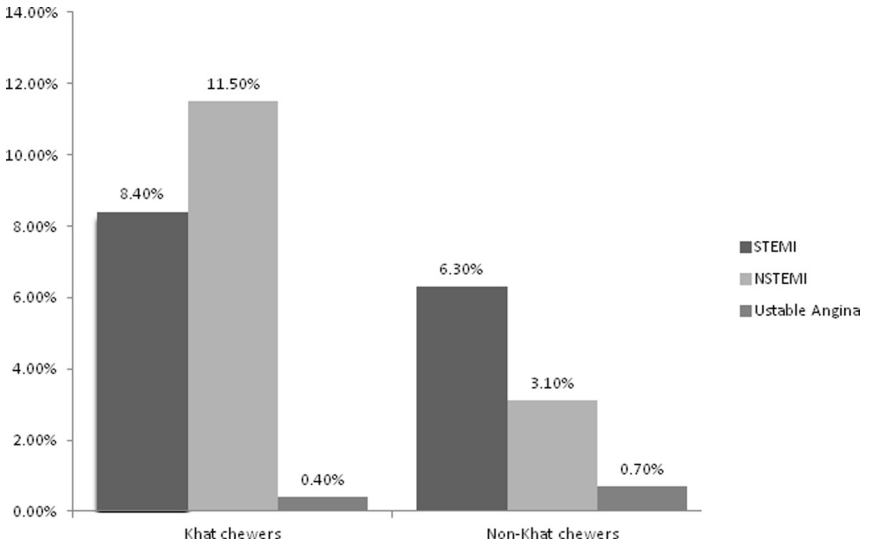


**Figure 3.** In-hospital mortality rates according to khat chewing and acute coronary syndrome type. STEMI indicates ST-segment–elevation myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction.

tients, thrombolytic use was associated with lower in-hospital (OR=0.59; 95% CI=0.39–0.89; $P<0.01$), 1-month (OR=0.54; 95% CI=0.37–0.79; $P=0.002$), and 1-year (OR=0.53; 95% CI=0.377–0.759; $P<0.001$) mortality.

## Discussion

The present study confirms our earlier findings of worse in-hospital outcome among khat chewers presenting with ACS and suggests that the increased risk of death persists up to 1 year after the index event. We also report that the increased stroke risk in khat patients was primarily hemorrhagic in nature and not associated with thrombolytic therapy use. This increased risk of hemorrhagic stroke is consistent with a case report of hemorrhagic stroke with hagigat use.[3] The present study also reports the safety and probable efficacy of $\beta$-blocker use among a large cohort of patients with khat-associated ACS. This is consistent with the recent safety findings of $\beta$-blocker use among drug-associated ACS, including cocaine and amphetamine.[14,15] Moreover, the present study suggests the safety of thrombolytic therapy in these patients.

### Pathogenesis of Khat-Induced Cardiovascular Complications

Our basic findings are consistent with the pharmacodynamic and pathophysiological mechanisms of khat on the cardiovascular system. Cathinone, the most active khat alkaloid, has been shown to increase heart rate and blood pressure in animal and human studies, and this increase seems to coincide with elevated plasma levels of cathinone.[16–19] Hassan et al[17] postulated that this effect was mediated by $\beta_1$-adrenergic receptors. Toennes et al[20] found that blood pressure remains elevated for about 3 hours after 1 hour of chewing about one quarter of a traditional khat-session dose. These effects might increase myocardial oxygen demand and precipitate ACS in susceptible patients and worsen the outcome.

Khat is also believed to induce coronary artery spam. Al-Motarreb et al[21] reported marked vasoconstriction of the coronary vasculature of isolated guinea pig hearts with cathinone infusion. There was also pronounced negative inotropy, possibly related to impaired coronary perfusion. Interestingly, the vasoconstriction of porcine arteries was not blocked by the $\alpha$1-adrenoceptor antagonist prazocin or by the

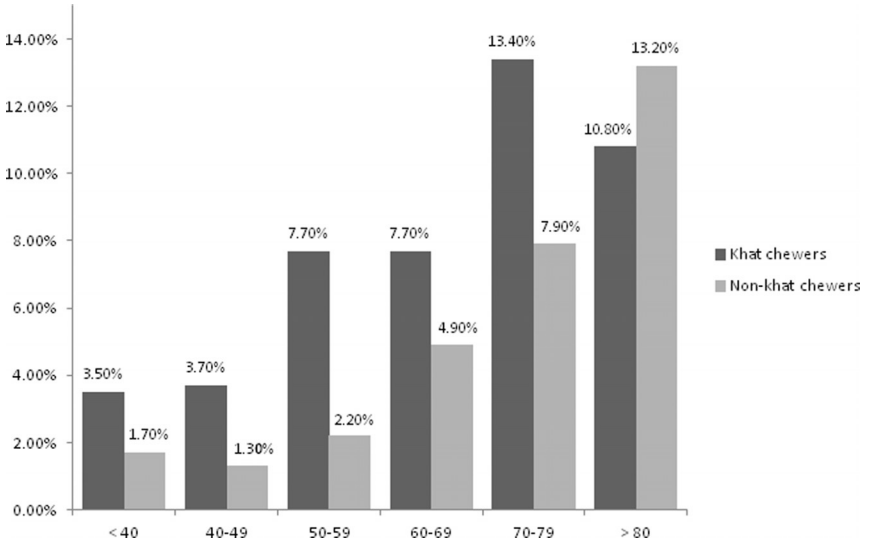


**Figure 4.** In-hospital mortality in khat-chewing and non–khat-chewing patients with acute coronary syndrome stratified by age groups.

**Table 4. In-Hospital Clinical Outcomes in Patients With Acute Coronary Syndrome Stratified by Sex**

| | Male, % | | | Female, % | | |
|---|---|---|---|---|---|---|
| | Khat (n=1210) | No Khat (n=4656) | *P* | Khat (n=198) | No Khat (n=1335) | *P* |
| In-hospital death | 7.1 | 3.1 | <0.001 | 10.1 | 6.2 | 0.04 |
| Heart failure | 17.7 | 10.2 | <0.001 | 23.2 | 17.5 | 0.04 |
| Recurrent ischemia | 25.9 | 11.7 | <0.001 | 38.9 | 16.3 | <0.001 |
| Reinfarction | 3.7 | 1.5 | <0.001 | 4.5 | 2.1 | 0.03 |
| Cardiogenic shock | 11.2 | 3.8 | <0.001 | 14.6 | 6.7 | <0.001 |
| Major bleeding | 0.7 | 0.5 | 0.6 | 1.5 | 0.6 | 0.1 |
| Stroke | 1.2 | 0.5 | 0.003 | 1.0 | 0.8 | 0.7 |
| Ventilation | 5.5 | 3.6 | 0.003 | 10.6 | 6.2 | 0.02 |
| VF/VT | 6.0 | 2.3 | <0.001 | 4.8 | 2.0 | 0.02 |

VF/VT indicates ventricular fibrillation/ventricular tachycardia.

neuronal uptake inhibitor cocaine.[22] Khat-induced coronary spasm is further supported by the fact that amphetamine, cocaine, and 3,4-methylenedioxymethamphetamine (known as MDMA or ecstasy), which are structurally and/or functionally similar to cathinone, are believed to increase the risk of ACS through the induction of coronary artery spasm.[23–28]

ACS among khat chewers may also result from the hypercoagulable state. Gebhard et al[29] recently demonstrated the induction of tissue factor with amphetamine, and Steffel et al[30] reported an increase in endothelial tissue factor accompanied by a reduction in tissue factor pathway inhibitor with cocaine. Because amphetamine and cocaine are related to cathinone, it may be hypothesized that cathinone also contributes to excess cardiovascular events through the hypercoagulable state in addition to the vasoreactivity effect. A cathinone effect of catecholamine-induced platelet aggregation is another potential mechanism,[31] which could be mediated by $\beta_2$-adrenoceptors, as suggested by Broadley.[32] Thus, it is possible that, by releasing catecholamines, cathinone can have a proaggregatory action. Alkadi et al[33] reported a significant reduction in bleeding time with aspirin use among khat chewers with acute MI compared with non–khat chewers (2.3 versus 8 minutes). de Ridder et al[34] reported acute MI and cerebral infarctions resulting from thrombus occlusions of the cerebral artery and proximal right coronary artery in a 28-year-old male khat chewer. In addition, the case reported by Saha and Dollery[35] showed on admission the presence of myocardial infarction and stenosis in the left anterior descending coronary artery and filling defects consistent with thrombus formation.

Premature coronary atherosclerosis is another potential mechanism. Wijetunga et al[25] found that 5 of 6 patients with amphetamine-associated MI had obstructive coronary artery disease in amphetamine-associated MI. Similar observations were reported by Turnipseed et al.[26] Both normal and advanced coronary atherosclerosis was reported with cocaine-induced AMI.[28,36] In the present study, although the overall use of coronary angiography was low, 32 of the total 172 khat chewers (18.3%) who had coronary angiography had normal coronary arteries or nonsignificant lesions, and the remaining patients had evidence of significant coronary artery stenosis. We can hypothesize that long-term exposure to hypercatecholamine might induce or exacerbate atherosclerosis in khat chewers.

## Khat Chewing and ACS

We and others have previously reported the association between khat chewing and ACS. In the present study, khat chewers represented 19% of the overall ACS population studied; these khat chewers originated mainly from Yemen. Furthermore, among Yemeni patients studied in Gulf RACE-2, 75.5% were khat chewers. This high prevalence among Yemeni patients is attributed to the legality and socially acceptable use of khat in Yemen and is consistent with previous reports.[12,19,33] Khat use in other Gulf states is illegal and confined mainly to individuals originating from Yemen and East Africa. Alkadi et al[33] reported 79% prevalence of khat chewing among patients hospitalized with MI in Yemen in 2002, which was significantly higher than in control subjects (20.8%; $P<0.001$). Furthermore, the vast majority of events (70.1%) occurred either during or immediately after completion of a khat-chewing session. The investigators proposed considering khat chewing a risk factor for MI. Similar observations were reported by Al-Motarreb et al[19] in a study conducted between 1995 and 1997 that involved 150 MI patients. Seventy-nine percent of patients were khat chewers, of whom 92% consumed khat daily and almost 90% consumed khat for >3 hours daily. The most striking observation was the differences in the time of onset of symptoms. The peak period of presentation among khat chewers was between 3 and 11 PM, coinciding with the timing of khat-chewing sessions, whereas in non–khat chewers, the peak time was between 3 and 9 A[SCAP]M. The association between ACS and khat chewing was further supported by the dose-response relationship between the quantity of khat chewed and risk of MI. Heavy khat chewers were shown to have 39-fold increased risk of MI.[37] The present study extends these observations in a much larger cohort of patients. Furthermore, it reports the safety and probable efficacy of $\beta$-blocker and thrombolytic therapy use among these patients. Finally, it reports increased mortality rate at 1 month and 1 year among khat-chewing compared with non–khat chewing ACS patients.

**Table 5. Univariate and Multivariate Analyses for the Predictors of In-Hospital, 1-Month and 1-Year Mortality in Acute Coronary Syndrome Patients**

| Variables | Unadjusted OR | 95% CI | Adjusted OR | 95% CI |
|---|---|---|---|---|
| Mortality (in-hospital) | | | | |
| Age | 1.04* | 1.04–1.06 | 1.04* | 1.03–1.06 |
| Female sex | 1.78* | 1.42–2.03 | 1.58* | 1.08–2.32 |
| BMI | 0.99 | 0.97–1.01 | 1.01 | 0.98–1.04 |
| Hypertension | 0.99 | 0.80–1.23 | 0.87 | 0.61–1.23 |
| Diabetes mellitus | 1.12 | 0.91–1.40 | 1.01 | 0.71–1.44 |
| Smoking | 0.61* | 0.48–0.78 | 0.79 | 0.55–1.15 |
| STEMI | 2.91* | 2.31–3.65 | 11.00* | 3.19–37.88 |
| Renal failure | 2.73* | 1.88–3.96 | 5.60* | 2.48–12.60 |
| Killip class >1 | 5.50* | 4.43–6.83 | 3.03* | 2.18–4.21 |
| β-blocker | 0.17* | 0.14–0.21 | 0.33* | 0.24–0.45 |
| Thrombolytic therapy | 0.48* | 0.36–0.63 | 0.67* | 0.47–0.95 |
| Prior aspirin | 1.06 | 0.85–1.31 | 1.05 | 0.69–1.61 |
| Prior statin | 0.81 | 0.64–1.03 | 0.99 | 0.60–1.66 |
| Khat chewing | 2.07* | 1.63–2.62 | 1.02 | 0.71–1.45 |
| Mortality (1 mo) | | | | |
| Age | 1.04* | 1.03–1.05 | 1.03* | 1.02–1.04 |
| Female sex | 1.54* | 1.26–1.85 | 1.31 | 0.92–1.85 |
| Hypertension | 0.97 | 0.82–1.16 | 0.83 | 0.61–1.12 |
| Diabetes mellitus | 1.12 | 0.94–1.33 | 1.06 | 0.78–1.43 |
| Smoking | 0.68* | 0.56–0.82 | 0.84 | 0.63–1.14 |
| STEMI | 2.20* | 1.84–2.62 | 11.15* | 3.72–33.47 |
| Renal failure | 2.28* | 1.65–3.14 | 6.60* | 2.74–15.89 |
| Killip class >1 | 4.19* | 3.51–4.98 | 2.45* | 1.82–3.31 |
| β-blocker | 0.10* | 0.08–0.12 | 0.11* | 0.09–0.15 |
| Thrombolytic therapy | 0.47* | 0.37–0.60 | 0.67* | 0.50–0.89 |
| Khat chewing | 2.68* | 2.22–3.24 | 1.69* | 1.24–2.30 |
| Mortality (1 y) | | | | |
| Age | 1.05* | 1.04–1.06 | 1.04* | 1.02–1.05 |
| Female sex | 1.64* | 1.37–1.92 | 1.26 | 0.91–1.75 |
| Hypertension | 1.14 | 0.98–1.33 | 0.93 | 0.70–1.23 |
| Diabetes mellitus | 1.28* | 1.10–1.50 | 1.20 | 0.91–1.59 |
| Smoking | 0.63 | 0.53–0.75 | 0.94 | 0.71–1.24 |
| STEMI | 1.55* | 1.33–1.81 | 3.90* | 1.85–8.23 |
| Renal failure | 2.50* | 1.87–3.32 | 5.33* | 2.30–12.36 |
| Killip class >1 | 3.45* | 2.95–4.03 | 2.18* | 1.66–2.88 |
| β-blocker | 0.17* | 0.14–0.20 | 0.18* | 0.14–0.23 |
| Thrombolytic therapy | 0.48* | 0.39–0.60 | 0.66* | 0.50–0.86 |
| Khat chewing | 1.92* | 1.62–2.28 | 1.46* | 1.10–1.94 |

OR indicates odds ratio; CI, confidence interval; BMI, body mass index; and STEMI, ST-segment–elevation myocardial infarction.

*$P<0.05$.

The traditional therapy with β-blockers was definitely shown to improve outcomes in MI patients.[38] This could be controversial in drug- or khat-associated ACS. The beneficial reduction in blood pressure, heart rate, and arrhythmia could be attenuated with the unopposed α-adrenergic effects that might exacerbate coronary spasm. Earlier on, there was an official recommendation against their use in cocaine-associated ACS[39]; this concept has recently been challenged by 2 recent studies by Rangel et al[14] (331 patients) and Dattilo et al[15] (363 patients), who reported safety and/or improved long-term outcome with β-blocker therapy among patients with chest pain and cocaine use. Indeed, Rangel et al reported 70% reduction in cardiovascular mortality over the long term in patients who were prescribed β-blockers at discharge. Data on the efficacy and safety on β-blocker use among amphetamine-associated ACS are limited to case reports and case series that included a small number of amphetamine users. Ragland et al[23] reported exacerbation of amphetamine-induced acute MI in a 37-year-old woman by propranolol that later was relieved by nifedipine, and cardiac catheterization revealed a normal coronary angiogram.

In terms of khat, although the α1-adrenoceptor antagonist indoramin failed to block the khat-induced increase in blood pressure, the β-blocker atenolol was shown to reduce blood pressure and heart rate in a previous study involving non-ACS patients.[17] The present study demonstrates lower mortality rates in patients who received β-blocker therapy in a large cohort of khat chewers (overall 1408 khat chewers), of whom 927 received β-blocker therapy on admission and 989 were prescribed β-blocker therapy at discharge. This lower mortality rate may be attributed to selection bias in that the treating clinicians were more likely to prescribe β-blocker therapy to the lower-risk group. In all circumstances, β-blocker use was safe and not associated with increased complications. This finding extends the observations from smaller registry groups of beneficial β-blocker use in patients using cathinone-like drugs cocaine or amphetamine.

## Outcome

In the present analysis, khat chewing was associated with a higher mortality rate and complications such as cardiogenic shock, heart failure, recurrent ischemia, and stroke despite a lower prevalence of cardiovascular risk factors, including diabetes mellitus and prior cardiovascular disease. This worse outcome may be attributed to multiple factors. First, there was a significant delay in patients presenting after symptom onset, resulting in less likelihood of receiving reperfusion therapy; this delay may be due in part to the analgesic effect of khat biochemical constituents.[40,41] Second, thrombolytic therapy has reduced efficacy, probably because of the prothrombotic effects of cathinone. Third, the risk of ischemic cardiomyopathy is higher. We hypothesize that long-term exposure to the catecholamine-like effects of khat increased the risk of ischemic cardiomyopathy once the patient develops ACS. This detrimental effect is similar to that induced by methamphetamine and amphetamine. The exposure to these compounds is potentially associated with structural and functional changes in myocytes, as well as clinical manifestations of cardiomyopathy and congestive heart failure.[42–44] This hypothesis is supported by the observations from the present study of advanced Killip class and a higher incidence of systolic dysfunction at presentation with a subsequent increased risk of heart failure and cardiogenic shock among khat chewers. Fourth, the higher risk of recurrent myocardial ischemic as observed in our study also may be attributed to the prothrombotic effects of khat. Fifth, the risk of other

complications, including stroke, is higher, which is consistent with our recent observations from the Gulf RACE-1 registry.[12] Finally, we found that khat chewing is an independent predictor of stroke among ACS patients. Acute cerebral infarctions and stroke-like complications were reported with khat[45,46] and with sympathomimetic drugs such as cocaine and amphetamine.[47,48] Khat chewing may predispose to stroke by increasing thrombogenicity and vasospasm, the 2 similar postulated mechanisms that induced ACS, with a subsequent increased risk of hemorrhagic transformation.

The present findings contradict conclusions made by previous investigators who suggested that drug-induced MI is associated with a lower mortality rate[25,26,49,50]; however, in contrast to the present study, those conclusions were based on either case reports or small registries from which firm conclusions cannot made. Moreover, although drugs that cause MI such as amphetamine or cocaine were used primarily by young individuals, khat chewing occurs across the spectrum of young and old male and female individuals; hence, the average age of khat chewers with MI is higher than the age of those reported with drug-induced MI, and age has been shown to be powerful predictor of outcome, including death. This worse outcome is further supported by the recent observations of increased risk of myocardial ischemia, stroke, and death with the use of drugs similar to khat in either structure or function, specifically sibutramine, hagigat, and mephedrone. Sibutramine, a diet medication that is a centrally acting serotonin-norepinephrine reuptake inhibitor and is structurally related to amphetamines, was associated with 16% increased risk of MI and stroke mainly in patients with a history of cardiovascular disease in the Sibutramine Cardiovascular Outcomes Trial (SCOUT).[51] In an observational study in Israel, hagigat was found to cause myocardial ischemia, pulmonary edema necessitating mechanical ventilation, and hemorrhagic stroke.[3] Finally, mephedrone (4-methylmethcathinone; also known as 4-MMC or meow meow), a new synthetic derivative of cathinone entering the recreational drug market in the developed world, was identified as causing sympathomimetic toxicity and was identified in 48 related cases at postmortem in a UK registry.[52,53]

## Limitations

Our data were collected from an observational study. However, well-designed observational studies provide valid results. Although long-term follow-up is available, it is limited to overall mortality; moreover, detailed data on khat chewing use at follow-up are unavailable, so it is possible that those who continued to chew khat had higher cardiac events at follow-up. Second, although the present study represents the largest study that evaluates the clinical characteristics, therapy, and outcome of khat-chewing ACS patients to date, it is limited by the fact that khat chewers were mainly of Yemeni origin and mainly of Middle Eastern Arab ethnicity. Future studies involving patients of multiple ethnicities, especially African blacks, are needed.

## Conclusion

Our data confirm earlier observations and reveal that khat-associated ACS is associated with worse outcomes. This observational report underscores the importance of improving education concerning the cardiovascular risks of khat chewing.

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## Disclosures

None.

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## CLINICAL PERSPECTIVE

Chewing the leaves of the plant *Catha edulis* (khat) likely dates to times of antiquity and may precede the use of coffee. Twenty million people worldwide are believed to be using khat for its stimulant effects. The use of khat was previously confined to East Africa and the Arabian Peninsula. It initially was thought to be of limited concern to Western populations because of its complicated cultivation and distribution systems. However, overnight delivery systems and the immigration of khat chewers contributed to the globalized distribution of khat. Moreover, to make distribution of khat easier and to preserve its efficacy for a longer time, several synthetic forms, including *hagigat* and *graba*, were made. Although khat chewing is illegal in the United States, numerous seizures of fresh and dried khat have been made recently. Cathinone, cathine, and norephedrine are the main ingredients of the plant. Cathinone is structurally similar to amphetamine and functionally similar to cocaine and ecstasy (3,4-methylenedioxymethamphetamine). Cathinone, the most active khat alkaloid, has been shown to have multiple cardiovascular effects, including increasing heart rate and blood pressure and inducing coronary artery spasm. The present study suggests khat chewers presenting with acute coronary syndrome have fewer cardiovascular risk factors and present late compared with non–khat chewers. This late presentation may be attributed to the analgesic effect of khat. Khat chewers presenting with acute coronary syndrome have increased risk of morbidity and mortality. Increased awareness of endemic practices is paramount in the context of increasing global migration.