

Does Opium have Benefit for Coronary Artery Disease? A Systematic Review

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Abstract

Opium is a plant with euphoria effect. People from some parts of the world traditionally use opium for cardioprotective effects. We did a systematic review to assess the effect of opium on coronary artery disease (CAD). A systematic database search was conducted in PubMed, Web of Science, Google Scholar, Cochrane library, Scopus, and SID from their onset up to June 2016. The quality of the studies was assessed with a standardized scoring system. Articles assessing the effect of opium consumption as orally or smoked were included in this review. Outcome was defined as age on CAD disease, risk of CAD, and morbidity from CAD. Poor methodological studies, animal studies, and studies on cardiovascular risk factors or serum markers were excluded from the review. Three case-control, three cohort, and eight cross-sectional studies were included in this systematic review. The age at the occurrence of myocardial infarction, coronary bypass surgery, and percutaneous intervention in opium users was significantly lower than that of nonusers. Odds ratio of opium consumption for CAD ranged from 1.3 to 3.8 in different studies. Hazard ratio of opium consumption for ischemic heart disease was 1.90 (1.57–2.29) with modification by sex, ethnicity, education level, marital status, residential place, and cigarette smoking. We concluded, in spite of the traditional belief, that the current evidence did not support the protective effect of opium on CAD. Future well-designed studies concerning probable confounders in Iran and other similar parts of world are required.

Keywords: Coronary artery disease, mortality, opium, smoking

INTRODUCTION

Papaver somniferum is a kind of plant which has euphoria effect called opium. Opium is used for medical or recreational purposes in many parts of the world including the Middle East region and in many Asian countries.^[1,2] Tragic reports in 2014 indicated that >20 million people used opium in different forms such as inhalation (vapor, sikh-sang) or oral.^[3] Near to 19% of patients with a history of myocardial infarction reported opium consumption.^[4] Previous studies suggested several health effects of opium such as analgesic, hypnagogic, anticough, and antidiarrheal effects.^[5] Studies showed that patients with chronic disease such as diabetes, hypertension, and ischemic heart disease more use opium than the general population due to traditional medicinal effect of opium on cardiovascular risk factors.^[6] It is worth mentioning that, such belief was common among some health-care workers, especially older physicians. Finding this answer can help physicians to give a correct consultation to patients. Many studies were conducted

about the relationship between opium consumption and coronary artery disease (CAD). Till now, to our knowledge, no systematic review of these studies has been published. However, in 2016, a perspective article mentioned about the hazardous effects of opium consumption on cardiovascular risk factors.^[7] The purpose of this systematic review is to assess the effect of opium consumption on CAD.

METHODS

Data sources

We searched the following electronic database including PubMed, Web of Science, Google Scholar, Cochrane library,

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Scopus, and SID in English and Persian languages from their onset up to June 2016 for studies reporting the relationship between opium use and CAD. We defined PICO frame of our review as P: Opium user, C: Nonopium user, O: CAD risk, age on cardiac event. Two independent authors (TH and AS) searched database with the terms (“opium” [tiab] OR “Papaver” [tiab]) AND (“cardiovascular disease” [tiab] OR “Coronary Artery Disease” [tiab] OR “myocardial infarction” [tiab] OR “coronary artery bypass surgery” [tiab] OR “percutaneous coronary intervention” [tiab]). Studies about synthetic opioids such as morphine and fentanyl did not enter into our review. All reference lists of relevant articles were reviewed to identify further reports that could be included in the systematic review. In addition, relevant congress and dissertation research projects registry were searched for identifying unpublished literature such as Proquest and Iranian Registry of Clinical Trials.

Study selection

After excluding the repeated studies, an initial screen of titles and abstracts was independently conducted by two reviewers (BSH and ER) based on inclusion criteria. A high degree of agreement in the selected literature was reported (kappa coefficient: 0.82). Then, the full articles of the remaining studies were reviewed for further evaluation. This review included observational studies determining the relationship between opium consumption and incidence, disease severity, re-admission, re-vascularization, and mortality from CAD. We included studies reporting opium consumption as orally or smoking. Outcome was defined as age on CAD disease, risk of CAD, severity of CAD and mortality from CAD. We excluded article if it falls under the following criteria: (1) reporting the effect of passive opium, (2) poor methodological quality score, (3) reporting opium effect of cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and serum marker, and (4) studying the effect of opium on animals. Quality assessment of selected studies was conducted by two independent (TH and AS) reviewers by the scoring guideline which is used in previous studies [Table 1].^[8,9] Every question of scoring system was defined as positive (1), negative (0), or unclear (?), with a highest potential grade of 100%. If there is any disagreement, a third reviewer (SS) made a final decision. A score higher than mean (50%) was defined as of high quality. Details of quality score related to each included study are summarized in Table 2.

Data extraction

Two independent authors (TH and BSh) extracted data using predetermined forms. Data extraction table included first author name, publication year, study location, study design, sample size, frequency of opium consumption, as well as the relationship/association between opium and cardiovascular disease and variables for which the results were controlled by statistical adjustments [Table 3].

RESULTS

The search to find relative papers located 412 possible references (including duplication between databases). After

Table 1: Details of methodological quality scoring criteria

Item	Criterion	Study type
Study population		
1	Selection before disease was present or at uniform point	CH/CC/CS
2	Cases and controls were drawn from the same population	CC
3	Participation rate ≥80% for cases/cohort	CH/CC/CS
4	Participation rate ≥80% for controls	CC
5	Sufficient description of baseline characteristics	CH/CC/CS
Assessment of risk factor		
6	Exposure assessment was blinded	CH/CC/CS
7	Exposure was measured identical for cases and controls	CC
8	Exposure was assessed prior to the outcome	CH/CC/CS
Assessment of outcome		
9	Opium use/outcome was assessed identical in studied population	CH/CC/CS
10	Opium use/outcome was assessed reproducibly	CH/CC/CS
11	Opium use/outcome was assessed according to standard definitions	CH/CC/CS
Study design		
12	Prospective design was used	CH/CC/CS
13	Follow-up time ≥2 years	CH
14	Withdrawals ≤20%	CH
Analysis and data presentation		
15	Appropriate analysis techniques were used	CH/CC/CS
16	Adjusted for at least age and sex	CH/CC/CS

CH: Applicable to cohort studies, CC: Applicable to case-control studies, CS: Applicable to cross-sectional studies

title screening, we excluded several studies which investigated the opium epidemiology, association between opium and cancer, arrhythmia, or other nonrelevant issues. Furthermore, after abstract screening, some studies were nonrelevant and excluded as follows: 11 studies due to assessing the relation between opium and cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia,^[6,23-32] two animal studies,^[33,34] five narrative review articles,^[35-39] one qualitative study,^[40] two studies on serum marker,^[41,42] and nine on poor methodological quality studies [Figure 1].^[43-51]

In total, we included 14 studies in this systematic review [Table 2]. Of these, one study was case-control, 11 were cross-sectional, and two were cohort studies. One included study related to the US population and other reviewed studies were conducted in Iran. The total number of patients in reviewed studies was 59,020, and sample size ranged from

Table 2: Details of quality score of the selected articles

Author name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total score	
cc																		
Massomi (45)	0	1	?	?	1	0	1	0	1	1	1	0	-	-	1	1	57%	
Nadimi (49)	1	1	?	?	1	0	1	0	1	1	0	1	0	-	1	1	64%	
cs																		
Bafghi (4)	0	-	?	-	1	0	-	0	1	1	1	0	-	-	1	1	54%	
Dehghani (40)	0	-	?	-	1	0	-	0	1	1	1	0	-	-	1	1	54%	
Davood (39)	0	-	?	-	1	0	-	0	1	1	1	0	-	-	1	1	54%	
rooh afza (41)	0	-	?	-	1	0	-	0	1	1	1	1	-	-	1	1	63%	
Sadeghian (43)	0	-	?	-	1	0	-	0	1	1	1	0	-	-	1	1	54%	
Sadeghian (38)	0	-	?	-	1	0	-	0	1	1	1	0	-	-	1	1	54%	
Safai (47)	0	-	?	-	1	0	-	0	1	1	1	0	-	-	1	1	54%	
Marmor (50)	1	-	0	-	1	0	-	0	1	1	1	0	-	-	1	1	63%	
Masoom (22)	1	1	?	?	1	0	1	0	1	1	?	1	-	-	1	1	64%	
CH																		
Khademi (51)	?	-	1	-	1	1	-	1	0	1	1	1	1	1	1	1	84	
Sharifi (44)	1	-	?	-	1	0	-	1	1	1	1	1	0	1	1	1	90	
Azarasa (48)	0	-	?	-	1	0	-	1	1	1	1	1	0	1	1	1	69%	

Each items was scored as positive (1), negative (0), or unclear (?)

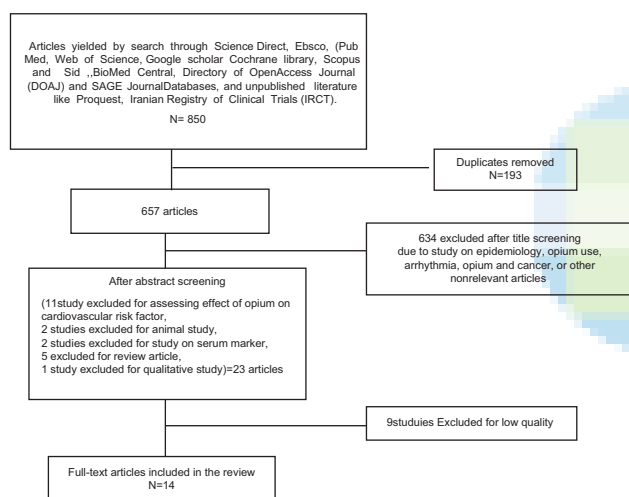


Figure 1: PRISMA flow diagram of various stages of selecting articles for present systematic review

91 in a cross-sectional study to 50,045 in a cohort study. The mean age of CAD patients in opium users and nonusers was 53.3 (10.1) and 66.3 (10.4) years, respectively. Several probable confounders, such as age, sex, and cigarette smoking, were adjusted in some studies.

Four studies investigated the relationship between opium and mortality, angiographic findings, functional class, and the need for revascularization in patients with acute myocardial infarction (AMI).^[4,52-54] Five studies examined the opium prevalence, CAD severity, and mortality in patients who underwent coronary angiography (CAG).^[12-14,16,55] Two studies assessed the prevalence of opium consumption, in-hospital mortality, rehospitalizations, and postoperative complications in coronary artery bypass graft (CABG) surgery patients.^[15,21] One cross-sectional study with 125 patients in two groups

assessed the relationship between opium addiction and microvascular angina.^[10] One cross-sectional study assessed the severity of coronary disease in two groups of patients with and without opium or opiate consumption history.^[19] And, in a large cohort study with median 4.7-year follow-up per participant, the association of opium consumption with risk of mortality from circulatory disease was investigated.^[17]

Frequency of opium user

Prevalence of the opium consumption in patients with AMI ranged from 17% in Isfahan,^[54] central area of Iran, to 51% in Kerman, south part of Iran, in 2013.^[53] Opium user rate in CAG reports was about 50% (15.7%–44%).^[12-14,16,55] Seventeen percent of the Golestan cohort population reported opium usage.^[17] Moreover, approximately 20% of the CABG patients were opium users.^[15,21] Furthermore, opioid consumption rate in microvascular coronary dysfunction (MCD) patients was more prevalent than individuals without MCD (23.2% vs. 7.2%, $P < 0.001$, respectively).^[10]

Age at cardiac event

In four cross-sectional studies with totally sample size of 1745, opioid consumption decreased the age at AMI: three^[4,53,54] significantly and one^[52] nonsignificantly. In one cross-sectional study with follow-up component,^[15] the age of 782 CABG patients in opium users was significantly lower than nonusers (48.0 ± 8.3 vs. 54.4 ± 10.2 , $P = 0.004$, respectively). In another study conducted on 600 CABG and cardiac valve surgery patients, the age at the surgery was similar in opium users and nonusers.^[21] In a recent study conducted in patients undergoing percutaneous coronary intervention (PCI), the age at PCI in opium user was lower than nonusers.^[12] In four studies conducted on CAD patients who underwent CAG, there was no report about age in opium users and nonusers [Table 2].^[13,14,16,44]

Table 3: Information of the included studies in present review

Author, year	Place of study	Design	Participants	Number of opium user	Result	Adjusted factors
Bafghi, 2005 ^[4]	South Iran	Cross-sectional	556 male patients hospitalized due to acute myocardial infarction	105 (18%)	Age at AMI in opium user was lower than in non user (60.1±12.54, 6±11, respectively $P<0.0001$), OR for in-hospital mortality among opium users compared to non opium users (OR: 2.2; 95% CI, 0.9 to 5.1, $P=0.05$)	Smoking, diabetes, age
Davoodi, 2006 ^[39]	Tehran, iran	Cross sectional	160 male with AMI	44 (27.5%)	Age at AMI in opium user similar to nonuser. : 55.87±9.7, 59.50±12.42, respectively, $P>0.05$, no significant difference in EF, angiographic findings, , in-hospital mortality, need for readmission, 6 months mortality, functional class and the need for revascularization in opium user was not worse except duration of admission	-
Dehghani, 2013 ^[40]	South Iran	Cross sectional	460 patients with AMI	239 (51%)	Age at AMI in opium user was lower than in non user :55.5±11.4, 60.8±12.1, respectively, $P<0.001$, in-hospital mortality: similar, anterior MI and early mortality were higher in non user	-
Roohafza, 2013 ^[41]	Central Iran	Cross sectional	569 men with AMI and 121 out-of-hospital SCD	118 (17.1%)	age at which AMI or SCD in opium user was lower than non user (3.6, 95% CI 1.2-6) years, frequency of cardiovascular risk factors, ejection fraction , post-AMI mortality and morbidity was not lower in opium consumer	Smoking, hospital, death or living status, income, education, family size
Masoomi, 2010 ^[22]	South Iran	Cross sectional	91 patients underwent CAG (58 CAD+, 31 CAD-)	19 (32%) in CAD+, 3 (9%) in CAD	The frequency of opium addiction was 3.8 folds greater in CAD patients, angiographic finding, ejection fraction didn't differ between addicted and non-addicted patients. Opium abuse was independent risk factor for CAD in non-cigarette smoking cases (OR=3.8, 95% CI=2.7-531.7)	Smoking
Masoomi 2009 ^[45]	South Iran	Case-control	299 patients underwent CAG, 215 CAD+, 84 CAD-	94 (44%) in CAD+, 24 (28%) in CAD	Frequency of opium user in severe CAD was higher than non CAD. odds of severe CAD in current user (OR=1.82, CI 95% 0.93-3.58	Sex, cigarette smoking, diabetes, hypertension, family history of CAD, obesity and hyperlipidemia
Sadeghian, 2009 ^[43]	Tehran, Iran	Cross sectional	940 patients underwent CAG (637 CAD+, 303CAD-)	100 (15.7%) in CAD+, 12 (3%) in CAD	in all subjects odds ratio of opium consumption for CAD OR: 2.65, CI: 1.31_5.35, PV: 0.007, in men OR was: 4.47	-
Sadeghian 2007 ^[38]	Tehran, Iran	Cross-sectional	2405 patients underwent CAG (2025 CAD+, 380 CAD-)	300 (14.8%) in CAD+, 22 (5%) in CAD-	Odds ratio of opium consumption for CAD :1.8, p: 0.01,	Smoking
Sharafi, 2013 ^[44]	Tehran, Iran	Cohort	1545 underwent PCI	350 (22%)	Age at PCI in opium user was lower than non-user (55.7 (9.2) ,58.4 (10.8), respectively, $P<0.001$), Adjusted hazard ratio of one year's MACE was 0.715 (95%CI: 0.372-1.371; $P=0.312$)	EF, DM, history of non-fatal myocardial infarction

Contd...

Table 3: Contd...

Author, year	Place of study	Design	Participants	Number of opium user	Result	Adjusted factors
Safaii, 2010 ^[47]	West Iran	Cross sectional with longitudinal component	782 patients underwent isolated CABG	56 (7%) current user, 18 (2%) past user	Age at CABG in opium user was lower than non-user ($P < 0.004$), current opium user was a significant predictor ($P < 0.0001$) of cardiovascular rehospitalization, Rates of postoperative complications, ICU readmission, postoperative length of stay, and in-hospital mortality were similar in user and non-user	-
Azarasa, 2009 ^[48]	Northwest Iran	Cross sectional	600 patients underwent CABG and cardiac valve surgery	72 (12%)	Age at CABG, postoperative complications, in hospital mortality in opium user and non-user was similar	-
Nadimi, 2016 ^[49]	South Iran	Cross sectional	250 patient, (125 patients with MCD, 125, normal coronary)	23.3% in MCD, 7.2% in normal coronary	Opium addiction was risk factor of MCD (adjusted OR: 3.575 1.418–9.016 $P = 0.006$)	Age, sex, BMI
Marmor, 2004 ^[50]	USA	Cross sectional	98 decedents with M/O, 97 decedents without M/O		Moderate CAD 8.2% in M/O and 10.3% in without M/O, OR: 0.8 CI: 0.23–1.98, Severe CAD 6.1% in M/O and 16.5% in without M/O, OR: 0.32 CI: 0.10–0.92	Gender, race, age
Khademi, 2012 ^[51]	North eastern Iran	Cohort	50045 people aged 40-75 from Golestan cohort	8487 opium user	The hazard ratio for death from circulatory disease was 1.81	Sex, ethnicity, education level, marital status, residential place, and cigarette smoking

AMI: Acute MI, OR: Odds ratio, CI: Confidence interval, EF: Ejection fraction, MI: Myocardial infarction, SCD: Sudden coronary death, CAG: Coronary angiography, CAD: Coronary artery disease, PCI: Percutaneous coronary intervention, DM: Diabetes mellitus, CABG: Coronary artery bypass grafting, ICU: Intensive Care Unit, MCD: Microvascular coronary dysfunction, M/O: Methadone or opiates, BMI: Body mass index, MACE: Major adverse cardiac event

Risk of coronary artery disease

In three cross-sectional^[13,16,55] and one case-control^[14] study with 3735 CAD patients, opium use was a significant risk factor for CAD. Odds ratio (OR) of opium consumption for CAD ranged from 1.3 in Sadeghian study^[13] to 3.8 in Masoomi study.^[16] Opium consumption was an independent risk factor for CAD in nonsmokers after adjusting for conventional risk factors (OR = 3.8, 95% confidence interval [CI] = 2.7–53.17).^[14] A large cohort study reported the hazard ratio of opium consumption for ischemic heart disease as 1.90 (1.57–2.29) with modification by sex, ethnicity, education level, marital status, residential place, and cigarette smoking.^[17] Furthermore, another case-control study reported opium addiction was an important effective factor of MCD (adjusted OR = 3.575, 95% CI = 1.418–9.016, $P = 0.006$) based on multivariable logistic regression analysis.^[10] On the other hand, multiple logistic regression analysis in Marmor's study^[19] indicated a significant protective effect of opium or opiate against moderate or severe CAD (OR = 0.8, 95% CI = 0.23–0.198 and OR = 0.32, 95% CI = 0.10–0.92, respectively).

Complication after cardiac event

In a cross-sectional study,^[4] in-hospital mortality after AMI was 18.6% in those patients with a history of opium consumption

versus 6.2% in those without ($P = 0.02$). However, in three studies conducted in AMI patients, in-hospital mortality was similar with regard to opium consumption.^[52–54] Also, in-hospital mortality after CABG in two studies was not different between opium users and nonusers.^[15,21]

Re-admission frequency,^[52] revascularization rate,^[52] Intensive Care Unit (ICU) re-admission,^[15] postoperative complications including respiratory, neurological, infective, and renal complications, and ICU time and hospital stay^[15,21] were not lower in opium users compared to nonusers.

Among 782 CABG patients in Safaii *et al.*'s study, opium was an effective factor ($P < 0.0001$) of readmission due to cardiac event.^[15] The study by Sharafi *et al.*^[12] found that opium was not a significant factor on the incidence of the major adverse cardiac event (11 [3.1%] vs. 53 [4.4%]; $P = 0.286$), in patients undergoing PCI. There were no difference in angiographic findings^[16,52] and ejection fraction^[16,52,54] between opium users and nonusers in three of the twelve included studies.

DISCUSSION

The present systematic review suggests that opium usage cannot delay the age of onset of CAD and decrease the risk

of CAD. As well as, in-hospital mortality in opium users was not lower than nonusers. The results of most included studies were adjusted for some effective variables such as age, smoking, and diabetes on CAD. Almost all studies were conducted in Iran with approximately 8% opium users.^[11,22] Valuable data from large Golestan prospective cohort study showed the increased risk of death from circulatory disease associated with opium consumption.^[17] According to Ghazavi's study,^[20] serum inflammatory markers such as high-sensitivity C-reactive protein (CRP) and some complementary factors and nitric oxide in opium smokers were greater than nonusers. Hence, opium could have harmful effect on the cardiovascular system. However, the results of a cadaver study showed that the long-term exposure to opium or opiate is associated with decreased severity of CAD.^[19] The finding of Marmor's study was related to both opium and opiate consumption, whereas, in other reviewed article, only opium usage effect on cardiovascular disease was studied. It is worth nothing that valuable evidence indicated that the second cause of death in opium user was CAD after accident.^[18] According to a study on 5900 individuals, using opium could not reduce the odds of diabetes, hypertension, and hypercholesterolemia.^[28] Although blood pressure decreases shortly after opium consumption due to vasodilatation, this is an acute reaction. Furthermore, a few hours before the time of next dose of opium consumption, the blood pressure and heart rate elevate. According to Asgary *et al.*'s study,^[20] some risk factors for premature atherosclerosis such as HbA1c, high-density lipoprotein-cholesterol, Lpa, apo-B, factor VII, fibrinogen, apo-A, and CRP in opium users were higher than that in nonusers.

Our findings are parallel with that of a recent review which suggested that several types of cancers such as esophagus, stomach, larynx, lung, and urinary bladder was associated with opium usage.^[56] In addition to the adverse cardiac effect of opium, Shirani *et al.*, suggested opium as a risk factor for carotid stenosis.^[50] Moreover, Masoudkabar *et al.*, in a prospective article reported that opium not only has no cardioprotective effects, but it might have adverse effect.^[7]

Some issues must be considered: (1) Traditionally, most opium users smoked tobacco. Hence, the cigarette smoking should be considered as a confounding factor. The results of some included studies in this review were adjusted for smoking, but opium remain risk factor for CAD, (2) There are different ways of opium consumption like inhalation (vapor, sikh- sang), oral, and intravenous with various absorption and blood level of its main sub extract, i.e., morphine. Hence, different cardiovascular effects might be expected. However, in large Golestan cohort study,^[17] this adverse cardiac effect of opium was present for various forms of opium and for various methods of consumption, (3) In spite of pure opiates such as heroin, opium is a combination of various materials that may produce different effects. People believe opium (Taryak) in past years was more effective and pure than these days. Therefore, we cannot investigate

the health related of opium itself, (4) There are difference in amount of opium consumption and duration of usage among opium user. Some individuals take orally opium in seed bead size or lentil once or twice a day. These probable confounding factors should be considered in designing of the study, in analyzing or interpretation the results, and (5) majority of studies were conducted in Iran except one study from the US. The high prevalence of opium in Iran allows us conducting epidemiological study. These studies conducted in the different parts of Iran with various races and climate. Although, some of them were poor quality, but the result of favorable studies did not support the cardioprotective effect of opium.

CONCLUSION

The results of this systematic review did not support the protective effect of opium use on CAD. Future well-designed studies concerning probable confounders in Iran and other similar parts of world are required.

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Conflicts of interest

There are no conflicts of interest.

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