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Review Article

Opium and cardiovascular health: A devil or an angel?

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ABSTRACT

Opioids have the highest rate of illicit drug consumption after cannabis worldwide. Opium, after tobacco, is still the most commonly abused substance in the Middle East. In addition to the ease of availability, one reason for the high consumption of opium in Asian countries might be a traditional belief among Eastern people and even medical staff that opium may have ameliorating effects on cardiovascular diseases (CVDs) as well as diabetes mellitus, hypertension, and dyslipidemia. Over the last decade, many studies have been performed on humans and animals to evaluate the interplay between opium consumption and stable coronary artery disease, acute coronary syndromes, and atherosclerosis. In this review, we conclude that opium consumption should be considered a risk factor for CVDs. Healthy individuals, as well as cardiac and diabetic patients, should be informed and educated about the hazardous effects of opium consumption on cardiovascular and other chronic diseases.

1. Introduction

Papaversomniferum L. is amongst the oldest medicinal plants, and the dried latex of its poppy, opium, has been used for medicinal or recreational purposes conventionally.[1] Opioids have the highest rate of illicit drug consumption after cannabis worldwide. In 2017, the United Nations Office on Drugs and Crime reported that 29 million persons, 50% higher than estimates, had used opiates in the preceding year globally.[2] Notably, opium, after tobacco, is still the most commonly abused substance in the Middle East.[3] One of the reasons for the high use of opium in this region might be the ease of access and also the location in the main pathway of the opium transit as the main opium-producing countries such as Afghanistan, and to a lesser extent, Myanmar, and Laos are located in this region. In addition to the ease of availability, another reason might be a traditional belief among Eastern people and even medical staff that opium may have ameliorating effects on cardiovascular diseases (CVDs) as well as diabetes mellitus, hypertension, and dyslipidemia.[4–9]

Over the last decade, many studies have been performed on humans and animals to evaluate the effect of opium consumption on blood lipid and glucose profiles, and also on CVDs. In 2013, we published the first review article on the cardio-metabolic effects of opium consumption.[1] In this review, we aimed to collect and integrate the newest evidence with our previous knowledge to clarify the effects of opium on CVDs and its underlying mechanisms.

2. Pharmacotoxicology

The word opium (*lachrymapapaveris,* Teriak) is derived from the Greek name for juice; a milky juice extracted by incising the unripe capsules (poppy) of *Papaversomniferum L.*[10] After being exposed to air, it becomes a brown, sticky, or crumbly substance. It is a complex

Abbreviations: CABG, Coronary artery bypass grafting surgery; CAD, Coronary artery disease; CI, Confidence interval; CRP, C-reactive protein; CVD, Cardiovascular disease; HR, Hazard ratio; INR, International normalized ratio; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiac events; MI, Myocardial infarction; M/O, Methadone or opiate; OR, Odds ratio; PAI-1, Plasminogen activator inhibitor-1.

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cocktail of substances that, in addition to water, contains more than 40 alkaloids[11] and over 70 components.[12] Only five of these alkaloids account for virtually all of the quantitative alkaloid content of opium (Fig. 1), including morphine (8–17% by weight), noscapine (1–10%), papaverine (0.5–1.5%), codeine (0.7–5%), and thebaine (about 0.2%).[11] Morphine and codeine are effective pain relievers through the activation of the μ (mu) opioid receptor. However, they are also abused for recreational purposes because the activation of the μ receptor causes euphoria and drowsiness.[13] Noscapine (formerly known as narcotine) is an antitussive agent.[14] Papaverine has no morphine-like actions, but as it relaxes smooth muscles, it is commonly used for the prevention and treatment of vasospastic diseases such as the spasm of coronary artery bypass grafts.[11,14]

Opium is used through different routes. It can be ingested orally or smoked after direct heating with burning charcoal in specialized devices such as an opium pipe (*Vafour*). In another route (*Sikh-Sang*), a stick is heated and the opium is put on the heated stick with a hairpin, and then the smoke is inhaled.[15] When opium is ingested, the onset of action is delayed.[1] This is while, in the case of opium smoking, morphine reaches the brain within seconds due to the rapid absorption of its vapor across the pulmonary capillaries into the bloodstream. Therefore, the onset of action is much more rapid and intense after smoking, but the duration of action is longer after oral intake because the absorption from the intestine, although slower, continues over a prolonged period.[14]

3. Stable coronary artery disease

3.1. Clinical studies

In the very first study on the association between opiates and coronary artery disease (CAD), investigators compared 98 decedents with methadone or opiate (M/O) in their blood at the time of autopsy and 97 decedents without M/O, and found a decreased severity of CAD among the former.[16] Although they concluded that long-term opiate exposure might mitigate CAD severity and its fatal consequences, they called for caution while interpreting their results based on several limitations, including a lack of data on the decedents' smoking histories, lipid profiles, and lifestyles.[16] Subsequently, majority of studies except few found that opium consumption is associated with more severe and extensive involvements of coronary arteries, even after adjustments for

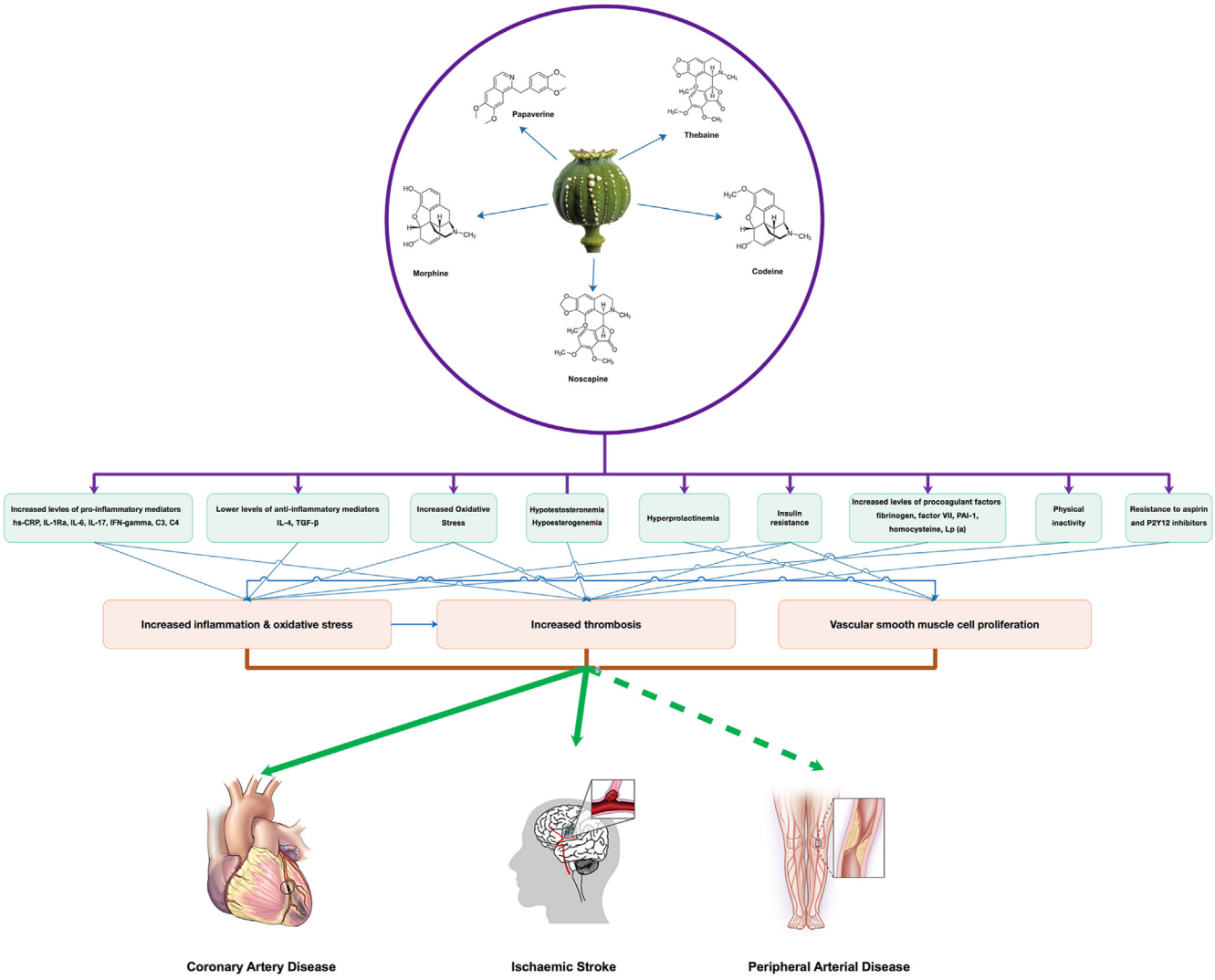

Fig. 1. Central illustration: Chemical structure of five main alkaloids of opium (*Papaversomniferum L.*) and the potential mechanisms of the harmful effects of opium consumption on coronary artery disease, ischemic stroke, and peripheral arterial disease. hs-CRP, high sensitivity C-reactive protein; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IFN-γ, interferon-γ; Lp (a), lipoprotein (a); PAI-1, plasminogen activator inhibitor-1; TGF-β, transforming growth factor-β.

possible confounders (Table 1).[10,17–22] A cross-sectional study found no association between opium consumption by any route and ischemic heart diseases.[23] However, the authors called for caution while interpreting their results as the opium dosage, the mean duration of opium consumption, and the purity of opium were not assessed in their study (Table 1).[23] A recent meta-analysis showed that opium consumption was associated with a significantly greater risk of CAD (odds ratio [OR]: 2.77, 95% confidence interval [CI]: 2.04 to 3.75).[24]

Besides studies evaluating the association between opium consumption and the presence, severity, and extension of stable CAD, opium abuse has been demonstrated to be related to coronary microvascular dysfunction. Opium abuse was an independent predictor of coronary microvascular dysfunction (OR: 3.575, 95% CI: 1.418 to 9.016; $p = 0.0069$) in a cross-sectional study on patients with documented microvascular dysfunction.[25] Further, another recent study revealed that opium consumption was an independent risk factor for CAD and coronary artery ectasia.[26]

3.2. Animal studies

It has been demonstrated that opium addiction has aggravating effects on the progression of atherosclerosis in the aorta of hypercholesterolemic rabbits.[4] However, this atherogenic effect was limited to hypercholesterolemic rather than normocholesterolemic conditions.[4] Concordantly, four weeks of opium smoking increased the atherogenic index in hypercholesterolemic rabbits and not in normocholesterolemic ones.[27] Another study showed that despite the attenuation of myocardial necrosis in rabbits with myocardial ischemia, opium exposure aggravated ischemia susceptibility, myocardial congestion, and hemorrhage.[28]

In summary, there is consistent evidence supporting the association between opium consumption and stable CAD.

4. Acute coronary syndromes

Although there is an agreement among current studies that opium consumption is positively associated with the presence and severity of CAD, there is controversy about the association between opium consumption and acute myocardial infarction (MI).[29] Some investigations have reported detrimental effects,[30,31] while others have shown neutral effects (Table 2).[32]

Despite the controversy regarding the association between opium consumption and the incidence of acute MI, there is an agreement regarding the impact of opium consumption on the in-hospital and mid-term outcomes of acute MI. Research has demonstrated that opium use is not correlated with increased rates of post–MI mortality, morbidity, and readmission.[6,31,33–35] Nevertheless, a few investigators have reported remarkably longer hospital lengths of stay,[35] higher readmission rates,[36] and borderline significantly higher in-hospital mortality rates (11.5% vs.

Table 1
Summary of studies evaluating the association of opium consumption with stable coronary artery disease and its outcomes.

Study	Methodology	Consumption pattern	Population	Results
Sadeghian et al, 2007	Cross-sectional	Use of opium≥1 time in life	$n = 2405$ (322 opium user and 2083 non-opium users)	• A higher prevalence of CAD in opium users than non-users (OR = 1.8, $p = 0.01$), even after the exclusion of cigarette smokers ($p < 0.001$) • A significant dose–response relationship between the dose of opium consumption and severity of CAD by clinical vessel score ($r = 0.2$)
Safaei, 2008	Cohort	Opium user	$n = 200$ post-CABG patients (14 current opium user, 9 past opium user, and 177 non-opium users)	• Similar post-operation complications and hospital stay • Higher readmission rates (26.1% versus 4%) in opium users than non-opium users during 6 months follow-up
Masoomi et al, 2010	Cross-sectional	Addicted	$n = 299$ (118 opium-addicted and 181 non-opium users)	• After adjustment for potential confounders like age, sex, and smoking, patients who regularly consume the opium are more likely to have severe CAD borderlinely (OR = 1.82, $p = 0.08$)
Masoomi et al, 2010	Nested case–control	Addicted	$n = 91$ (58 CAD and 33 normal coronary)	• Opium addiction was an independent risk factor for CAD in non-cigarette smoking cases (OR = 38, 95%CI = 2.7–531.7), but in cigarette smokers, opium was not a significant risk factor (OR = 13.2, 95%CI: 0.85–206.5).
Sadeghian et al, 2010	Cross-sectional	Opium user	$n = 940$ (387 men aged<45 years)	• Opium consumption was the most important risk factor for CAD in male patients under the age of 45 years in an Iranian sample (OR = 4.47, $p < 0.01$).
Hosseini et al, 2011	Cross-sectional	Use of opium for ≥3months[a]	$n = 456$ (228 diabetic opium users and 228 age, sex, and smoking matched diabetic non-opium users)	• Greater severity of CAD measured by Gensini's score among opium users than non-users (86.9 versus 59.6, respectively, $p < 0.0001$) • More extensive atherosclerotic plaques among opium users than non-users • A significant independent dose–response relationship between the dose of opium and the Gensini's score ($\beta = 0.27$, $p = 0.038$)
Rezvani et al, 2011	Cross-sectional	Addicted	$n = 558$ (161 opium-addicted and 397 non-opium users)	• No association between opium consumption by any route and CAD
Hosseini, 2012	Cross-sectional	Opium user	$n = 5442$ (2874 opium users and 2568 non-opium users)	• Opium was an independent risk factor for CAD (OR = 1.31, 95% CI: 1.01–1.69)
Khademi et al, 2012	Cohort	Use of opium at least once a week for ≥6 months	$n = 50,045$ (8487 opium users and 41,558 non-opium users)	• Increased risk of all-cause mortality in opium users (adjusted HR = 1.86, 95% CI: 1.68–2.06) • Increased risk of death from ischemic heart disease in opium users (adjusted HR = 1.9, 95% CI: 1.57–2.29) • A dose–response association between the duration of opium use and cardiovascular as well as all-cause mortality
Rahimi Darabad et al, 2014	Cross-sectional	Addicted	$n = 1170$ (121 opium-dependents and 1049 non-opium users)	• Opium dependence was independently associated with the presence of CAD (OR = 2.08).

CABG, Coronary artery bypass grafting surgery; CAD, Coronary artery disease; CI, Confidence interval; HR, Hazard ratio; OR, Odds ratio.
[a] 97.3% of opium users (222 out of 228) were using opium for ≥12 months (unpublished data).

Table 2
Summary of studies evaluating the association of opium consumption with acute coronary syndrome and its outcomes.

Study	Methodology	Consumption pattern	Population	Results
Azimzade-Sarwar et al, 2005	Case-control	Addicted	$n = 300$ (150 acute MI and 150 controls)	• No statistically significant association between opium addiction and acute MI (OR = 1.4, $p > 0.05$)
Davoodi et al, 2005	Cohort	Addicted	$n = 160$ acute MI patients (45 opium-dependents and 115 non-opium dependents)	• Longer hospital stay in opium-dependents than non-opium dependents • Similar rates of in-hospital mortality and major adverse cardiac events during 6-months follow up
Sadr-Bafghi et al, 2005	Nested case –control	Use of opium for >12months	$n = 556$ acute MI patients (106 opium users and 450 non-opium users)	• No significant difference in in-hospital mortality (OR = 2.2, 95% CI: 0.9 –5.1).
Niaki et al, 2013	Case-control	Use of opium for ≥12months	$n = 236$ (118 Acute MI and 118 controls)	• Opium consumption is a major risk factor for acute MI (adjusted OR = 26.3, 95% CI: 7.5–92.4, $p < 0.0001$)
Dehghani et al, 2013	Cross-sectional	Addicted	$n = 460$ (239 opium addicts and 221 non-addicts)	• Total in-hospital mortality was not significantly different between the opium-addicted and non-addicted groups. • Opium addiction was associated with a lower occurrence of anterior wall MI (26.4% versus 36.4% in non-addicted patients) and its related early mortality.
Roohafza et al, 2013	Cross-sectional Cohort[a]	Addicted	$n = 690$ (118 opium-dependents and 572 non-opium users) $n = 252$ post-acute MI patients (126 opium-dependents, and 126 age and smoking matched non-dependents)	• Opium dependence independently causes 3.6 (95% CI: 1.2–6.0) years decrease in the age at which the acute MI/sudden cardiac death occurs • Opium dependents and non- dependents had similar rates of post-acute MI morbidity, mortality, and readmission rates during 12 months of follow up.
Javadi et al, 2014	Cross-sectional	Addicted	$n = 304$ (152 opium-dependents and 152 non-opium users)	• Opium dependents and non-user had similar rates of post-acute MI arrhythmia, hospital stay, and in-hospital mortality
Harati, 2015	Retrospective cohort	Addicted	$n = 400$ (78 opium dependents and 322 non-opium users)	• Opium dependents had borderline significantly higher in-hospital mortality rate (11.5% versus 5.9%, $p = 0.072$) and significantly higher rehospitalization rates than non-users (38.5% versus 13.7%, $p < 0.001$).

CI, Confidence interval; MI, Myocardial infarction; OR, Odds ratio.
[a] An opium dependent and a non-dependent group (age- and smoking-matched) of alive post–MI patients were followed up for 12 months.

5.9%;$p = 0.072$)[36] in opium-dependent patients with acute MI rather than non-opium users (Table 2).

Altogether, not only is there no evidence for supporting a decreased risk of acute MI or a favorable post–MI outcome in opium-dependent patients but also it may be associated with more post–MI complications.

4.1. Clinical studies on patients undergoing revascularization

Some studies on coronary artery bypass grafting surgery (CABG) candidates have demonstrated that opium consumption is not correlated with increased in-hospital mortality rates, postoperative complication rates, or hospital lengths of stay.[37–40] However, others have shown that opium use is directly correlated with intra- and post-operative bleeding,[41] readmission,[38] and longer hospital lengths of stay.[40] Recently, we studied 28,691 patients who underwent CABG for a median of 56 months to evaluate the effects of opium consumption and cessation on the long-term outcomes of these patients.[42] In this cohort, 3636 patients continued opium consumption after surgery, while 1436 patients stopped opium use. After adjustments for possible confounders, we found that in comparison with the never users of opium, persistent opium consumption after CABG was associated with increased 5-year all-cause mortality (hazard ratio [HR]:1.28, 95% CI:1.06 to 1.54; $p = 0.009$) and 5-year major adverse cardiac events (MACE) (HR: 1.25, 95% CI: 1.13 to 1.40; P<0.0001). Still, those who quitted opium use after surgery were not at an increased risk of mortality (HR: 1.09, 95% CI: 0.83 to 1.43; $p = 0.514$) or MACE (HR: 1.03, 95% CI: 0.88 to 1.21; $p = 0.645$) at five years compared with the never users of opium.[42]

In a retrospective cohort study, opium consumption was not associated with 12-month MACE among male patients after elective percutaneous coronary interventions, and none of the components of MACE, consisting of target vessel revascularization, target lesion revascularization, CABG, and non-fatal MI, was different between opium users and non-users.[43] Nonetheless, it should be noted that while age is an important predictor of MACE, especially mortality, the authors did not make adjustments for the confounding effect of age on MACE despite the significantly lower age of the opium users by comparison with the non-users (55.7 versus 58.4 years, respectively; $p < 0.001$). This bias might potentially underestimate MACE in the opium user group.[43]

Altogether, it appears that opium consumption not only has no ameliorating effect on patients undergoing coronary revascularization but also may have hazardous effects on mid-term and long-termoutcomes.

5. Stroke

There are scarce reports about the correlation between opium and stroke (Table 3). In a case–control study, opium abuse was independently associated with ischemic stroke.[44] Other studies have demonstrated that opium addiction is associated with increased intima-media thickness, more atherosclerotic plaques, and a greater pulsatility index and mean flow velocity of the middle cerebral artery, which are the markers of cerebral atherosclerosis.[45–47] In a study on male CABG candidates, there was no difference in the prevalence of significant carotid artery stenosis between opium-addicted and non-addicted patients.[48] Nevertheless, there is a significant bias in this study as the authors reported a higher prevalence of diabetes (17% versus 11.4%) and hypertension (88.6% versus 11.4%) as well as a lower prevalence of smoking (27.1% versus 65.5%) in the non-addicted patients than in the opium-addicted ones, respectively. Indeed, no conclusion can be drawn about the association between opium consumption and carotid stenosis without adjusting for such important confounding factors (Table 3).[48]

In summary, the currently limited evidence suggests the detrimental effects of opium on cerebral atherosclerosis and hemodynamic abnormalities, and its association with ischemic stroke.

Table 3
Summary of studies evaluating the association of opium consumption with stroke and its outcomes.

Study	Methodology	Consumption pattern	Population	Results
Shirani et al, 2010	Cross-sectional	Addicted	$n = 939$ CABG-candidate male patients	• Similar prevalence of significant carotid artery stenosis between opium-addicted and non-addicted patients
Ebrahimi et al, 2018	Case-control	Addicted	$n = 965$ (672 patients with ischemic stroke and 293 controls)	• Opium abuse was an independent risk factor of ischemic stroke (OR = 2.36, 95% CI: 1.16–4.85, $p = 0.018$)
Hamziee-Moghadam et al, 2018	Case-control	Addicted	$n = 94$ (47 opium-addicted and 47 healthy controls)	• Greater adjusted intima-media thickness in opium-addicted persons compared to the control group (0.84 versus 0.62 mm, $p = 0.018$)
Moadabi et al, 2019	Cross-sectional	Addicted	$n = 353$ patients with ischemic stroke	• Opium addiction is an independent predictor of the pulsatility index of the middle cerebral artery (adjusted OR = 9.615, p<0.001) • Opium addiction is an independent predictor of the mean flow velocity of the middle cerebral artery (OR = 3.246, $p = 0.002$)
Mousavi-Mirzaei et al, 2019	Cross-sectional	Addicted	$n = 133$ patients with ischemic stroke	• More atherosclerotic plaques (OR = 1.42, $p = 0.005$) in opium-addicts rather than non-addicts • Greater internal media thickness (OR = 2.48, $p = 0.01$) in opium-addicts rather than non-addicts

CABG, Coronary artery bypass grafting surgery; CI, Confidence interval; OR, Odds ratio.
*An opium dependent and a non-dependent group (age- and smoking-matched) of alive post–MI patients were followed up for 12 months.

Nonetheless, further studies are needed to elucidate the association between opium consumption and stroke.

6. Peripheral arterial disease

Despite several studies assessing the relationship between opium consumption and CAD, there is limited data regarding the association between opium consumption and peripheral arterial disease. In a study on patients with peripheral arterial disease who underwent lower extremity vascular reconstruction surgery, investigators observed that the patency rate was significantly lower in opium users than non-users (32% versus 67%, respectively).[49] However, the authors failed to adjust this finding for potential confounders.[49] Future well-designed studies should elucidate the exact role of opium consumption in peripheral arterial disease.

7. Heart failure

The association between opium consumption and left ventricular systolic dysfunction has been evaluated in many recent studies. The current evidence implies that opium consumption is not associated with a decreased functional class.[23,33,34,37–39,50–52] Nevertheless, there are conflicting results regarding the association between opium consumption and the left ventricular ejection fraction (LVEF). Some studies have shown that opium users, with or without CAD, are more likely to have reduced LVEF than non-users,[50,51,53,54] while others have found a neutral effect in this regard.[10,20,23,31,33–35,37-39,43,52,55] A recent meta-analysis showed that opium use was associated with significantly lower LVEF in opium users who were candidates for CABG (mean differences = −2.15, 95% CI: −3.31 to −1).[24] However, this statistically significant difference of 2%, maybe of no or minimal clinical significance. Moreover, this correlation did not reach statistical significance in other subgroups of patients with CAD (mean differences = 0.29, CI: −0.57 to 1.14).[24] Taken all these lines of evidence together, we may conclude that opium consumption has neutral effects on the LVEF and functional class of individuals with heart failure.

8. Cardiac arrhythmias

Studies have demonstrated that opium use is associated with a higher incidence of ventricular arrhythmias in the post–MI course, even after adjustments for confounders,[52,56] while another study showed a neutral effect in this regard.[34] Whereas a study showed that opium addiction was linked with higher post-CABG arrhythmias,[53] another study found protective effects for opium use in terms of post-CABG atrial fibrillation.[57] Despite these controversies in clinical studies, animal studies[27,58] have consistently indicated a proarrhythmic effect for opium.[29] Future well-designed prospective clinical studies should elucidate the exact role of opium consumption in inducing or preventing cardiac arrhythmias.

9. Interactions with cardiovascular drugs

The current evidence shows that opiates can interfere with cardiovascular medications through alterations in their pharmacokinetics or pharmacodynamics.[59] In a large study, an analysis of prescriptions for patients with non-valvular atrial fibrillation who were under treatment with warfarin and had a stable international normalized ratio (INR) indicated that the consumption of opiates, including natural opium, buprenorphine, and tramadol, was associated with an increased INR in these patients, which might suggest a clinically important interaction.[60] Furthermore, it has been shown that the concomitant use of opium and digoxin may increase the risk of digoxin toxicity.[61] Another clinically relevant interaction of opium is with antiplatelets. Research has shown that the administration of opioids such as opium, methadone, and morphine attenuates the antiplatelet actions of aspirin,[62] ticagrelor,[63–65] prasugrel,[64,66] and clopidogrel.[67,68] This list of potentially lethal interactions between opium and cardiovascular drugs suggests that cardiologists and cardiac surgeons act cautiously when prescribing antiplatelets, digoxin, and warfarin for an opium-abusing patient.

10. Temporal relationship between opium consumption and cardiovascular diseases

Although the clinical studies on the association between opium consumption, and CAD and stroke have established a scientific base in the evidence pyramid, there are two common limitations in their methodologies that call for caution in interpreting their results. First, all of these studies have case–control or cross-sectional designs. Some patients with CAD or stroke likely start using opium because of their symptoms or their beliefs about the beneficial effects of opium use on CVDs following the development of their diseases. Hence, while we observe a higher prevalence of opium consumption among patients with CVDs than healthy individuals, we cannot make a causal interpretation because the temporal

relationship between opium consumption and CVDs cannot be determined in these studies. Another limitation is the possible prevalence-incidence bias, which should be considered in cross-sectional and case–control studies. If opium consumption affects the survival of patients with ischemic heart diseases, then the results of cross-sectional studies with prevalent rather than incident cases could be biased. Community-based cohort studies can overcome these two limitations and help us to make causal interpretations of the relationship between opium and CVDs. With the increasing use of opioids for chronic non-cancer pain, a large nested case–control study demonstrated that the use of opioids was associated with an increased risk of MI (OR: 1.28, 95% CI: 1.19 to 1.37).[69]

In our opinion, the most supportive evidence for a possible hazardous role of opium consumption in CVDs came from the Golestan Cohort Study.[70] The Golestan Cohort Study recruited 50,045 people aged 40–75 years from January 2004 to June 2008 from Golestan Province, located in North Iran. As detailed exposure data, a systematic follow-up approach, and the ascertainment of the cause of death were available, the investigators evaluated the association between opium consumption and all-cause mortality and major categories, including circulatory causes for mortality after a median follow-up of 4.7 years. The adjusted HR for all-cause mortality associated with ever use of opium was 1.86 (95% CI: 1.68 to 2.06). They also observed that opium users were at an increased risk of death from ischemic heart diseases (adjusted HR: 1.90; 95% CI: 1.57 to 2.29). Moreover, after excluding the persons who started opium use after receiving a diagnosis of major illnesses, namely ischemic heart diseases, cerebrovascular events, diabetes mellitus, and hypertension, they found a dose–response association between the duration of opium use and cardiovascular as well as all-cause mortality. Unlike previous cross-sectional and case–control studies, the Golestan Cohort Study was not subject to the aforementioned major limitations and, therefore, it is reasonable to conclude causality based on its findings.

11. Association between opium consumption and cardiovascular diseases: independent or confounded by smoking?

Cigarette smoking is one of the major risk factors for CVDs. It has been shown in all previous studies that opium abusers smoke cigarettes more frequently.[10,36,48] Thus, it is not clear whether the association between opium consumption and CVDs is a dependent association confounded by smoking or opium consumption is an independent risk factor for CVDs. Numerous studies have tried to answer this question. In a propensity score matched analysis, the study revealed that diabetic opium users had more severe CAD than matched diabetic non-users.[10]A large cross-sectional study indicated a higher prevalence of CAD in opium users than non-users, even after the exclusion of cigarette smokers (Table 1).[17] In a nested case–control study, opium addiction was an independent risk factor for CAD among non-smokers, while this association was not significant in cigarette smokers.[20] Hence, we can conclude that the relationship between opium consumption and CVDs is independent.

12. Why should opium consumption be associated with cardiovascular diseases?

Current knowledge is scarce about the effects of opium on blood glucose, dyslipidemia, and hypertension.[71] Although animal studies demonstrate the hazardous effects of opium on the aforementioned risk factors, there are some discrepancies in clinical studies.[71] Thus, it calls for future well-designed clinical studies to address this gap of knowledge. Here, we will focus on other risk factors and novel mechanisms of opium effects on CVD.

Studies have demonstrated that opium exerts its harmful effects on CVDs through increased inflammation and oxidative stress, increased thrombosis, and vascular smooth cell hyperplasia (Fig. 1). Although there is a complex relationship, we briefly discuss these interwoven factors here.

Recent studies have increasingly reported that opium addicts have elevated levels of pro-inflammatory mediators[15,72–76] and lower levels of anti-inflammatory cytokines.[74,75] On the other hand, it has been shown in several studies that morphine and heroin induce systemic oxidative stress and reduce the total antioxidant capacity independent of cigarette smoking.[77]

Hypotestosteronemia and hypoestrogenemia in opium addicts[78] may result in CVDs through all of the aforementioned mechanisms. These hormonal imbalances are associated with increased levels of procoagulant factors and insulin resistance.[79–86] Studies have also demonstrated that opium-addicted individuals have remarkably higher levels of procoagulant factors than non-addicted individuals.[15,87–90] Additionally, research has proven a state of insulin resistance, similar to patients with type 2 diabetes mellitus,[91] which causes CVDs.[79–86,89,92,93] Opium abusers have hyperprolactinemia,[78,94] which results in the proliferation of vascular smooth muscle cells and CVDs.[95] Another mechanism is the reduction of physical activity due to the depressant effects of opium on the central nervous system,[96] which is associated with an increased risk of CVDs.[97–100]

Last but not least, is the resistance to aspirin and P2Y12 inhibitors in opium users. We previously discussed that opium consumption blunts the pharmacological effects of aspirin,[62] ticagrelor,[63–65] prasugrel,[64,66] and clopidogrel.[67,68] These findings may render opium users with previous CVDs more vulnerable to acute thrombotic events and might be a novel justification for higher risks of MI and stroke in these patients.

13. Strategies for the treatment of opioid dependence

For the successful treatment of opioid dependence, we should employ pharmacological interventions besides psychosocial supportive measures. There are two approaches toward pharmacological treatment: 1) opioid agonist maintenance treatment with long-acting opioids such as methadone or buprenorphine, which is the most effective and the preferred method, and 2) detoxification, followed by treatment with long-acting opioid antagonists such as naltrexone, to prevent relapses. Other than these medications, alpha-2 adrenergic agonists such as clonidine for the treatment of opioid withdrawal and naloxone for the treatment of opioid overdose should be available.[101]

14. Conclusion

People have used opium for many years not only as a habit, but based on their traditional beliefs about its beneficial effects on diabetes mellitus, dyslipidemia, hypertension, and CVDs. Considering the current evidence, opium not only has no ameliorating effect on CVDs, but the clinical, animal, and prospective cohort studies consistently indicate that opium consumption is associated with CVDs and cardiovascular mortality. Moreover, the rapidly growing biological explanations for a causal relationship between opium consumption and CVDs underscore the warning that opium consumption should be considered a risk factor for CVDs. Unfortunately, false beliefs regarding the beneficial effects of opium are common, and it is the responsibility of health professionals[102] and

Box 1
Highlights.

- There is consistent evidence supporting the association between opium consumption and stable coronary artery disease.
- Persistent opium consumption after coronary artery bypass grafting surgery is associated with increased long-term risks of mortality and major adverse cardiac events.
- The currently limited evidence suggests the detrimental effects of opium on cerebral atherosclerosis, and hemodynamic abnormalities and its association with ischemic stroke.
- A dose–response association exists between the duration of opium use and all-cause and cardiovascular mortality.
- Opium consumption should be considered a risk factor for cardiovascular diseases.
- Physicians should battle against false beliefs about the beneficial effects of opium.

health authorities to battle against these false beliefs. Healthy people, as well as cardiac and diabetic patients, should be informed and educated about the hazardous effects of opium consumption on cardiovascular and other chronic diseases (Box 1).

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Declaration of competing interest

All authors have none to declare.

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