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SYSTEMATIC REVIEW AND META-ANALYSIS

Association of Nonacute Opioid Use and Cardiovascular Diseases: A Scoping Review of the Literature

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BACKGROUND: In this scoping review, we identified and reviewed 23 original articles from the PubMed database that investigated the relationship between nonacute opioid use (NOU) and cardiovascular outcomes.

METHODS AND RESULTS: We defined NOU to include both long-term opioid therapy and opioid use disorder. We summarized the association between NOU and 5 classes of cardiovascular disease, including infective endocarditis, coronary heart disease (including myocardial infarction), congestive heart failure, cardiac arrythmia (including cardiac arrest), and stroke. The most commonly studied outcomes were coronary heart disease and infective endocarditis. There was generally consistent evidence of a positive association between community prevalence of injection drug use (with opioids being the most commonly injected type of drug) and community prevalence of infective endocarditis, and between (primarily medically indicated) NOU and myocardial infarction. There was less consensus about the relationship between NOU and congestive heart failure, cardiac arrhythmia, and stroke.

CONCLUSIONS: There is a dearth of high-quality evidence on the relationship between NOU and cardiovascular disease. Innovative approaches to the assessment of opioid exposure over extended periods of time will be required to address this need.

Key Words: cardiovascular disease ■ epidemiology ■ opioids

Exposure to opioid drugs in the United States[1,2] has increased exponentially over the past 30 years.[3,4] This includes use of prescription opioids for medical purposes as directed by a physician—such as treatment of opioid dependence, cancer-related pain, or noncancer chronic pain—as well as non–medically indicated use of prescription opioids and illicit opioid use. Opioid treatment, initially restricted to patients with cancer, expanded over time to include the treatment of non–cancer-related pain. A growing awareness of the problem of undertreated pain resulted in standards, issued by the Joint Commission on Accreditation of Healthcare Organizations in 2001, requiring greater monitoring and treatment of pain.[5,6] Pharmaceutical companies aggressively marketed opioid medications for treatment of chronic pain,[7] citing flawed research studies as evidence of the safety of these medications.[8] As a result of these and other factors, opioid prescribing in the United States increased nearly 7-fold between 1997 and 2007. The increase in opioid availability was accompanied by steep increases in fatal and nonfatal overdoses[9] and opioid use disorder (OUD).[2,10]

Long-term opioid therapy—such as for the treatment of chronic pain or opioid addiction—has been defined as use of opioids on most days for >3 months.[11] Long-term exposure to opioids may also result from the nonmedical use of prescription or illicit opioids because of dependence or addiction, leading to an OUD. We use the term *nonacute opioid use* (NOU) to encompass both long-term opioid therapy and OUD.

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Nonstandard Abbreviations and Acronyms

ER-HPO	extended-release high-potency opioid
IE	infective endocarditis
NOU	nonacute opioid use

Researchers have begun to investigate possible effects of long-term opioid use on health outcomes other than addiction and misuse. Of specific interest is cardiovascular disease, which remains a leading cause of death, physician and emergency department visits, and hospitalization in the United States.[12,13] Trends in hospitalized cases of infective endocarditis[14] have been shown to mirror trends in opioid overdose and injection drug use (IDU).[15] Observational studies have also reported an association of opioid drug use with increased risk of cardiovascular events, including myocardial infarction (MI) and heart failure.

However, it is unclear what the biological pathways between long-term exposure to opioids and cardiovascular disease (CVD) might be. Opioid receptors have been discovered in the heart, and their activation by short-term administration of opioid drugs before acute ischemic events has been shown to have a cardioprotective effect.[16] However, the association between chronic opium use and increased levels of low-density lipoproteins and triglycerides could provide a pathway to coronary artery disease.[17,18] High and increasing prevalence of NOU and a sustained high burden of cardiovascular disease have prompted this scoping review of the literature to systematically examine the association of NOU with cardiovascular outcomes.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

We identified original, peer-reviewed research articles on the relationship between NOU involving any prescription medication containing opioids, or any illicit opioid drug, and CVD. We conducted a keyword search and a Medical Subject Headings (MeSH) term search of the PubMed database for articles published on or before September 2, 2019. The keyword search included the following strings and logic: ("Heart Failure" OR "Endocarditis" OR "Myocardial infarction" OR "Atrial fibrillation" OR "cardiac arrhythmia" OR "myocardial ischemia" or "coronary heart disease" or "cardiac arrest" or "stroke" or "coronary artery disease") AND Opioid AND epidemiology. For the MeSH term search, the strings and logic were: ("Analgesics, Opioid" [Majr] OR "Opioid-Related Disorders/epidemiology" [Majr]) AND ("Cardiovascular Diseases/epidemiology" [Majr] OR "Stroke/epidemiology" [Majr]). We included the term *epidemiology* in both keyword and MeSH term searches to exclude basic science and nonhuman studies. Additional articles were identified from the reference lists of retrieved articles.

Inclusion and Exclusion Criteria

We included original articles that investigated the association of NOU with ≥1 of the following 5 cardiovascular outcomes: infective endocarditis (IE); coronary heart disease, including MI; congestive heart failure; cardiac arrythmia, including cardiac arrest; and stroke. We excluded studies that lacked an appropriate comparison group. In most cases, this meant individuals who did not experience NOU. In the case of endocarditis, it meant either individuals who did not inject opioids or a time period during which injection opioid use was expected to be substantially lower because of a policy change. The details of inclusion and exclusion are listed in Table 1.

One author (J.S.) reviewed the entire list of identified references, while 2 authors (A.K.N. and E.L.A.) each reviewed a mutually exclusive half of the references. Disagreement in the classification of records by the 2 independent reviewers was adjudicated by group consensus. A flow diagram summarizes article selection procedures (Figure).

Table 1. Inclusion and Exclusion Criteria for Studies

Inclusion Criteria	Exclusion Criteria
• Investigates the relationship between a history of long-term (medical or nonmedical) exposure to opioids (prescription or illicit) and subsequent cardiovascular disease • Investigates the relationship between history of opioid use and cardiovascular outcomes following a (not necessarily cardiovascular) medical procedure (eg, kidney transplant, orthopedic surgery)	• Basic science studies • Nonhuman studies • Case study or case series • Review articles • Nonoriginal research including editorials, letters, and protocols • Short term opioid use • Studies of the effect of brief exposures to opioid medications (eg, for analgesia or anesthesia related to a surgical procedure or other medical events) • Studies of the relationship between opioid use and any cardiovascular events other than those of interest

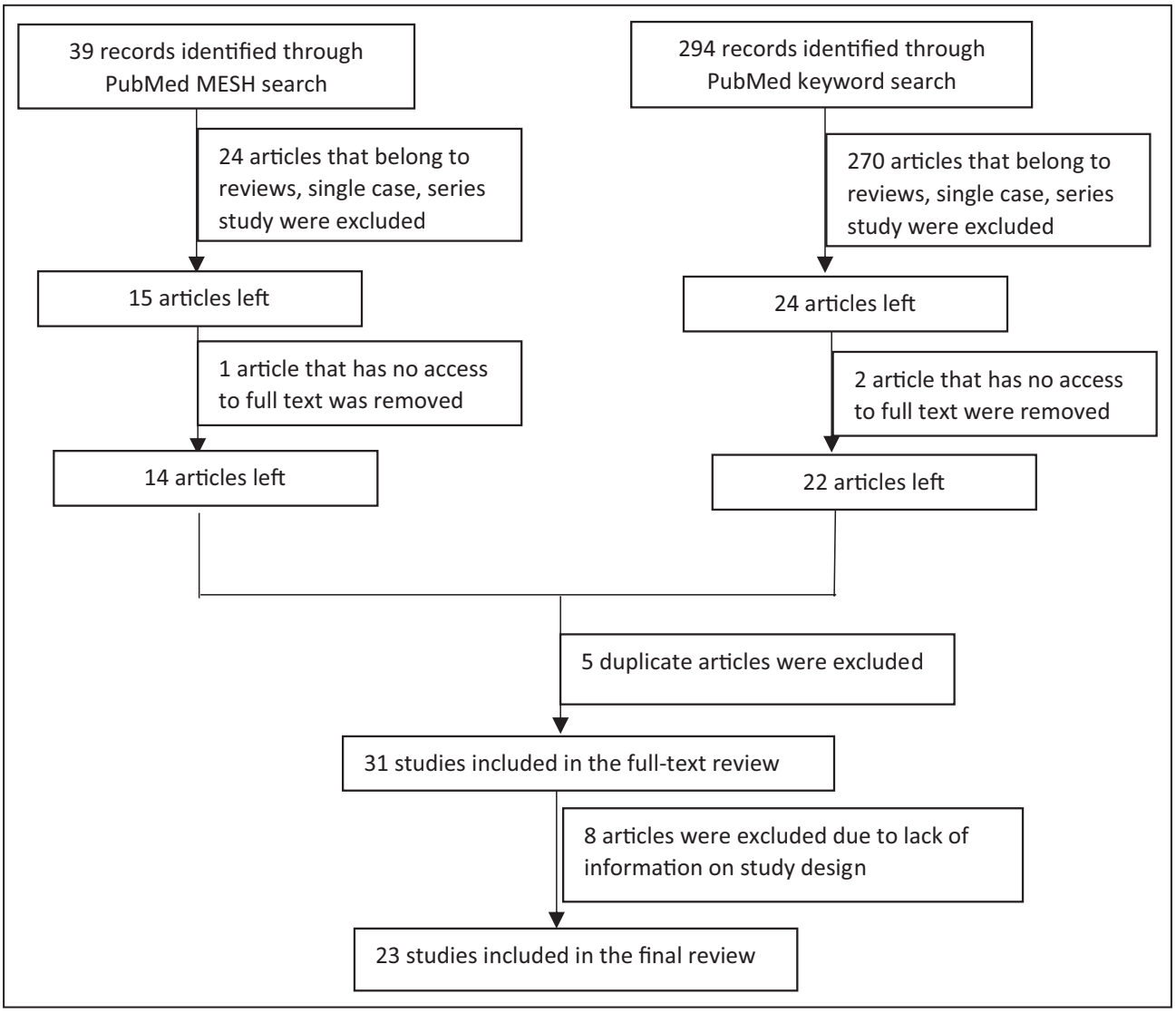

Figure. Flow diagram of included studies.
MESH indicates Medical Subject Headings.

RESULTS

A total of 39 articles were identified from the MeSH term search and 294 articles from the keyword search. After excluding reviews and case series, articles that did not address NOU or any of our outcomes of interest, those that did not include a comparison group, and those for which full text could not be retrieved, and after and resolving duplicates that were retrieved through both search protocols, 23 studies remained for review. Fourteen articles were from the United States, 2 from Iran, 2 from Canada, and 1 each from of the following countries: United Kingdom, Italy, Germany, Spain, and Taiwan. There were 10 cohort studies,[19–28] 5 case-control studies,[29–33] 3 cross-sectional studies,[34–36] and 5 trend analyses[37–41] (Table 2, Table S1). All included studies used retrospective designs.

Myocardial Infarction

Of the 10 studies that reported on the association of opioid use with MI, 4 used data from retrospective cohorts,[19,34–36] 2 were cross-sectional studies,[23,25] and 4 were nested case-control studies.[29,31–33] Among older adults with chronic obstructive pulmonary disease, when restricting to opioid-only formulation, positive associations were observed for coronary artery disease (CAD)-related mortality (hazard ratio [HR], 1.83; 95% CI, 1.32–2.53), and for CAD-related emergency room visit or hospital admission (HR, 1.38; 95% CI, 1.08–1.77). Carman et al[19]

Table 2. Selected Major Studies of the Association of Nonacute Opioid Use With Endocarditis, MI, Congestive Heart Failure, Arrhythmia, and Stroke

Study	Study Design	Year Frame	N	Exposure	Outcome	Effect Estimate
Bates, 2019,[41] United States	RTA	2008–2015	462	Illicit drug use	Endocarditis	Relative risk increase, 0.06%; *P*=0.001
Carman, 2011,[19] United States	RCS	2002–2005	148 657	Overall chronic opioid [I] therapy for nonmalignant pain	Myocardial infarction	IRR, 2.66; 95% CI, 2.3–3.08
				Low-dose chronic opioid therapy for nonmalignant pain	Myocardial infarction	IRR, 1.21; 95% CI, 1.02–1.45
				High-dose chronic opioid therapy for nonmalignant pain	Myocardial infarction	IRR, 1.89; 95% CI, 1.54–2.33
Gray, 2018,[37] United States	RTA	2000–2016	510	Injection drug use (no mention of opioid name)	Endocarditis	Prevalence ratio of IDU per year, 1.09; 95% CI, 1.05–1.14
Hartman, 2016,[38] United States	RTA	2009–2014	127	Injection drug use [II]	Endocarditis	Percentage of endocarditis increases from 14% in 2009 to 56% in 2014
Jain, 2008,[20] United States	RCS	1996–2003	238	Injection drug use [III]	Tricuspid valve IE	OR, 4.37; *P*=0.001
				Injection drug use	Mitral valve IE	OR, 4.37; *P*=0.001
				Heroin	Tricuspid valve IE	OR, 4.37; *P*=0.001
Jobski, 2017,[29] Germany	CC	2006–2011	309 936	Current or recent use of ER-HPO[IV] (referent: past use)	Myocardial infarction	OR, 1.17,
						95% CI, 1.09–1.26
				Recent discontinuation of any ER-HPO (referent: past use)	Myocardial infarction	OR, 1.11; 95% CI, 0.98–1.25
				Recent switch of substance (referent: past use)	Myocardial infarction	OR, 1.38; 95% CI, 1.02–1.86
				Current or recent use of ER-HPO (referent: past use)	Stroke	OR, 0.95; 95% CI, 0.88–1.02
				Recent discontinuation of any ER-HPO (referent: past use)	Stroke	OR, 1.14; 95% CI, 1.02–1.27
				Recent switch of substance (referent: past use)	Stroke	OR, 1.19; 95% CI, 0.89–1.58
Keeshin, 2016,[21] United States	RCS	1999–2009	392	Injection opioid use [V]	Endocarditis	Endocarditis cases increase 2-fold
				Injection opioid use	HCV antibody prevalence	HCV antibody prevalence increase 3-fold
				Injection opioid use	Positive opiate toxicology screens	Positive opiate toxicology screens increase 6-fold

(*Continued*)

Table 2. Continued

Study	Study Design	Year Frame	N	Exposure	Outcome	Effect Estimate
Khodneva, 2016,[34] United States	CS	2003–2007	29 025	Prescription opioid [VI] use for nonmalignant chronic pain	Stroke	HR, 1.04; 95% CI, 0.78–1.38
				Prescription opioid use for nonmalignant chronic pain	Coronary artery disease in all	HR, 1.03; 95% CI, 0.83–1.26
				Prescription opioid use for nonmalignant chronic pain	Coronary artery disease in female	HR, 1.38; 95% CI, 1.05–1.82
				Prescription opioid use for nonmalignant chronic pain	Coronary artery disease in male	HR, 0.7; 95% CI, 0.5–0.97
Lee, 2013,[30] Taiwan	CC	1998–2010	6040	Treatment with morphine for all cancer-related pain	Stroke: all stroke	OR, 1.13; 95% CI, 0.97–1.31
				Treatment with morphine for prostate cancer-related pain	Stroke: all stroke	OR, 3.02; 95% CI, 1.68 to 5.42
				Treatment with morphine for prostate cancer-related pain	Stroke: hemorrhagic	OR, 4.24; 95% CI, 1.03 to 17.4
				Treatment with morphine for prostate cancer-related pain	Stroke: ischemic	OR, 2.9; 95% CI, 1.58 to 5.35
Lentine, 2015,[22] United States	RCS	2006–2008	16 322	Pretransplant prescription narcotic use with living donor	Ventricular arrhythmia	HR, 1.38; 95% CI, 0.14 to 13.42
				Pretransplant prescription narcotic use with deceased donor	Ventricular arrhythmia	HR, 5.58; 95% CI, 2.19 to 14.21
				Pretransplant prescription narcotic use with living donor	Cardiac arrest	HR, 1.83; 95% CI, 0.94 to 3.54
				Pretransplant prescription narcotic use with deceases donor	Cardiac arrest	HR, 1.31; 95% CI, 0.85 to 2.01
Lewer, 2017,[39] United Kingdom	RTA	1997–2016	1 052 444	Injection opioid use	Endocarditis	Hospital admissions for infections related to injection drug use increased annually from 2012 to 2016
Li, 2013,[31] United States	CC	1990–2008	56 590	Any opioid prescription [VII] at current use (≤30 d)	Myocardial infarction	OR, 1.28; 95% CI, 1.19 to 1.37
				Any opioid prescription cumulative use 11–50 Rx	Myocardial infarction	OR, 1.38; 95% CI, 1.28 to 1.49
				Any opioid prescription cumulative use >50 Rx	Myocardial infarction	OR, 1.25; 95% CI, 1.11 to 1.4
				Buprenorphine prescription	Myocardial infarction	OR, 1.71; 95% CI, 1.09 to 2.68
				Morphine prescription	Myocardial infarction	OR, 2.15; 95% CI, 1.24 to 3.74
				Meperidine prescription	Myocardial infarction	OR, 1.46; 95% CI, 1.22 to 1.76
Marmor, 2004,[23] United States	RCS	1998	98	Serologic evidence of methadone or opiates (as proxy for long-term exposure to opioids)	Coronary artery disease	OR, 0.43; 95% CI, 0.2 to 0.94

(*Continued*)

Table 2. Continued

Study	Study Design	Year Frame	N	Exposure	Outcome	Effect Estimate
Meisner, 2019,[24] United States	RCS	2013–2017	1921	Injection drug use	Endocarditis	Endocarditis percentage change, 238%
Menendez, 2015,[25] United States	RCS	2002–2011	9 307 348	Opioid use disorder (opioid abuse or dependence)	Myocardial infarction	OR, 1.9; 95% CI, 1.3 to 2.6
Mirzaiepour, 2012,[26] Iran	RCS	2010–2011	200	Opium addiction (as defined by DSM-IV criteria for substance dependence)	Arrhythmia and cardiac arrest	OR, 21.9; 95% CI, 9.58 to 50.01
Omran, 2019,[27] United States	RCS	1993–2015	5283	Opioid	Stroke	Stroke percentage change from 1993 to 2008, 1.9%; 95% CI, −2.2% to 6.1%
					Stroke	Percentage change from 2008 to 2015, 20.3%; 95% CI, 10.5 to 30.9%
Pontes, 2018,[1] Spain	CC	2008–2012	22 652	Opioid analgesic therapy for osteoarthritis-related pain	Myocardial infarction	OR, 1.13; 95% CI, 1.03 to 1.24
Roberto, 2015,[33] Italy	CC	2002–2012	12 483	Current use of acetaminophen or/and an acetaminophen-codeine combination (0–90 d) (referent=nonuse, defined as more than 365 d since last use)	Myocardial infarction	OR, 1.22; 95% CI, 0.92 to 1.63
				Recent use	Myocardial infarction	OR, 1.12; 95% CI, 0.8 to 1.55
				Past use	Myocardial infarction	OR, 1.13; 95% CI, 0.86 to 1.48
Sadeghian, 2009,[35] Iran	CS	2006–2008	4398	Opioid dependence (according to DSM-IV criteria)	Myocardial infarction	RR, 0.34; 95% CI, 0.02 to 3.23
				Opioid dependence (according to DSM-IV criteria)	Arrhythmia and cardiac arrest	RR, 0.65; 95% CI, 0.43 to 1.03
Solomon, 2010,[28] United States	RCS	1996–2005	31 375	Incident opioid therapy [VIII] for nonmalignant pain	Nonspecific	RR, 1.62; 95% CI, 1.27 to 2.06
Vozoris, 2017,[36] Canada	CS	2008–2013	149 094	Incident opioid use [IX]	Heart failure	HR, 0.84; 95% CI, 0.73 to 0.97
				Incident opioid use	Coronary artery disease	HR, 2.15; 95% CI, 1.5 to 3.09
Weir, 2019,[40] Canada	RTA	2006–2015	60 529	Intervention: removal of controlled-release oxycodone from Canadian market (2011 Q4)	Endocarditis	No quantitative estimates provided

Opioid names listed in the Exposure column in Table 2 with roman numerals are listed in Table S1. CC indicates case control; CS, cross sectional; DSM-IV, Diagnostic and Statistical Manual, 4th edition; ER-HPO, extended-release high-potency opioid; HCV, hepatitis C virus; HR, hazard ratio; IRR, incidence rate ratio; MI, myocardial infarction; OR, odds ratio; RCS, retrospective cohort study; RR, relative risk; and RTA, retrospective trend analysis.

reported a positive association between chronic opioid therapy for nonmalignant pain and MI incidence in a commercially insured cohort, with greater risk observed at higher doses (incidence rate ratio, 2.66; 95% CI, 2.30–3.08). Within a group of patients who underwent coronary artery bypass grafting,[35] a relative risk of 0.34 (95% CI, 0.02–2.32), was reported for perioperative MI, among patients with preoperative opioid dependence. However, the extremely wide CI indicates the possibility of a sparse data bias.

In a case-control study of primary care patients with physician-diagnosed osteoarthritis,[32] Pontes et al reported a positive association between the odds of MI and use of opioid analgesics for treatment of osteoarthritis (odds ratio [OR], 1.13; 95% CI, 1.03–1.24), with odds increasing as the mean monthly dose of opioids increased. Jobski et al[29] reported associations with recent (within 30 days of index MI) discontinuation of extended-release high-potency opioid (ER-HPO) therapy (OR, 1.11; 95% CI, 0.98–1.25) and recent (within 30 days of index MI) switch (OR, 1.38; 95% CI, 1.02–1.86) of ER-HPO medication type. Within a group of general practice patients with osteoarthritis, Roberto et al[33] reported no statistically significant association with acetaminophen–codeine for treatment of osteoarthritis pain (OR, 1.22; 95% CI, 0.92–1.63). Li et al[31] reported a positive association between MI and current opioid use (OR, 1.28; 95% CI, 1.19–1.37), 2-year cumulative prior use consisting of 11 to 50 prescriptions (OR, 1.38; 95% CI, 1.28–1.49), and 2-year cumulative prior use consisting of >50 prescriptions (OR, 1.25; 95% CI, 1.11–1.40).

Findings from Marmor's cross-sectional study of serologic evidence of methadone or opioid use at autopsy, and its relationship to coronary artery plaque, suggest a protective effect with respect to CAD (OR, 0.43; 95% CI, 0.20–0.94).[23] However, the study did not provide information on duration of opioid use or of methadone treatment of opioid addiction. Among hospital inpatients undergoing major elective orthopedic surgery, Menendez et al[25] reported a positive association between preoperative opioid abuse or dependence and in-hospital MI (OR, 1.90; 95% CI, 1.30–2.60).

Conversely, data from the REGARDS (Reasons for Geographic And Racial Differences in Stroke) study[34] suggest no association overall between prescription opioid use for nonmalignant chronic pain and coronary heart disease over the course of 4 to 7 years of follow-up (HR, 1.03; 95% CI, 0.83–1.26). In an analysis stratified by sex, the authors report a modest increase in coronary heart disease risk among women (HR, 1.38; 95% CI, 1.05–1.82), but a decrease in risk among men (HR, 0.70; 95% CI, 0.50–0.97) with evidence of opioid use.

Heart Failure

There were no studies of NOU and heart failure identified in our search.

Arrhythmia

Of the 3 studies that reported on the association of opioid use with arrhythmia, 2 used data from retrospective cohorts,[22,35] and 1 was a cross-sectional study.[26] In a cohort of hospital patients who underwent coronary artery bypass surgery, Sadeghian et al[35] reported a protective association between atrial fibrillation and opium addiction that was not statistically significant (OR, 0.65; 95% CI, 0.43–1.03). In hospital patients admitted with acute MI, Mirzaiepour et al[26] reported a strong, positive association between post-MI arrhythmia and opium addiction (OR, 21.9; 95% CI, 9.58–50.0). In a cohort of patients undergoing kidney transplantation, Lentine et al[22] reported a positive association between ventricular arrhythmia and pre-transplant opioid use at a dose >23.8 mg/kg morphine equivalents (HR, 5.58; 95% CI, 2.19–14.21).

Stroke

Of the 4 studies reporting on the association of opioid use and ischemic or hemorrhagic stroke, 2 used data from a retrospective cohort,[27,34] and 2 were nested case-control studies.[29,30] Jobski et al[29] reported an association with recent (within 30 days of index MI) discontinuation of ER-HPO therapy (OR, 1.14; 95% CI, 1.02–1.27). No association was reported for current opioid use or recent switch of opioid type. Omran et al[27] reported percentage of stroke among hospitalized patients changed 20.3% (95% CI, 10.5%–30.9%) from 2008 to 2015 with the combination of opioid abuse. Khodneva et al reported no association between prescription opioid use for nonmalignant chronic pain and stroke over a median[34] of 5.2 (1.8) years of follow-up in the REGARDS study (HR, 1.04; 95% CI, 0.78–1.38). Lee et al[30] reported a positive association between morphine use for cancer-related pain and hemorrhagic stroke (OR, 1.36; 95% CI, 1.02–1.82) but not ischemic stroke (OR, 1.08; 95% CI, 0.92–1.27). When restricted to patients with prostate cancer only, the association with hemorrhagic stroke was higher (OR, 4.24; 95% CI, 1.03–17.4), and a significant association with ischemic stroke was reported (OR, 2.90; 95% CI, 1.58–5.35).

Infective Endocarditis

Seven studies investigated the association between opioid use and IE. Five of these were trend analyses, of which 4 reported a temporal association between IDU and IE,[24,37–40] and 1 reported a temporal association between mixed drug use and IE.[41] Jain and colleagues[20] reported an association between IDU and tricuspid valve IE. Keeshin and colleagues[21] suggested that increases in hospital admissions for IE may provide an indirect surveillance marker for IDU within the surrounding community.

DISCUSSION

There has been a growing interest in the possible cardiovascular effects of opioid drugs. Khodneva et al[34] described self-reported, baseline CVD in a cohort of community-dwelling adults consisting of 1851 participants with prescription opioid use and 27 174 nonusers. They found that coronary heart disease (22.8% versus 17.4%), stroke (13.2% versus 8.5%) and corrected QT interval prolongation (3.3% versus 2.8%) were more commonly reported by participants with prescription opioid use. Studies have investigated the link between methadone treatment for OUD and elongation of the QT interval/torsade de pointes, which can lead to cardiac arrhythmias and cardiac arrest.[42,43] Solomon et al[28] reported different relative risk of cardiac events after the start of different opioid therapy. Moreover, several studies have reported a small or moderate increase in the risk of MI in people with chronic exposure to opioids attributable to abuse/dependence or long-term opioid therapy for chronic pain.[19,25,46] Conversely, it has been suggested that long-term opiate exposure may mitigate the severity of coronary artery disease.[23]

We set out to summarize systematically previous research on the association between NOU and 5 CVD outcomes. The amount and strength of the evidence varied across the outcomes. The most commonly studied outcomes were MI (10 reports) and IE (7 reports). Across studies included in this review was generally consistent evidence of a positive association between community prevalence of injection drug use (with opioids being the most commonly injected type of drug) and community prevalence of IE, and between nonacute opioid exposure (primarily for medical reasons) and MI incidence. The other 4 outcomes were less commonly studied (3 reports each for CAD, arrhythmia, and stroke; 1 for heart failure), and there was less consensus about their relationship with opioid use. Many of the studies, for all outcomes, lacked detailed information on the duration and dose of opioid exposure. Several studies have reported a temporal association between the prevalence of IDU and the prevalence of IE in a community, suggesting an increase in the prevalence of IE with increasing prevalence of IDU. The sharing of needles and other materials promotes the spread of microbial infections, with IE cases frequently resulting from staphylococcal infection.[45] Prescription opioids and heroin are among the most commonly injected drugs.[46] Thus, increasing exposure to opioids in a population can lead to greater prevalence of IE, by increasing the prevalence of IDU within that population.

CAD is the most common cause of MI but is directly observable only by invasive procedures, such as cardiac catheterization or coronary angiogram, or at autopsy. This may explain why we identified 7 studies with MI as the end point but only 3 with CAD. Only 4 studies[19,29,31,33] described detailed assessment of dose and duration of opioid exposure, and all of these studies reported an association between opioid use and MI.

Cardiac opioid receptors have been identified,[47] but possible biological pathways between NOU and MI or CAD are still not well understood. Li et al[31] speculated about possible relationships between opioids, hormones (including testosterone), and coronary atheroma, but their study did not explore these connections. Although some studies, such as that of Tanaka et al,[48] attempt to address from a molecular perspective the role of endogenous and exogenous opioids and cardiac opioid receptors in limiting cardiac damage in patients with acute MI (ischemic preconditioning, opioid-induced cardio protection), our findings suggest that long-term opioid exposure is associated with an increase in the incidence of acute MI.

In a systematic review of opioid use and arrhythmia, Behzadi et al[49] reported that some opioids, including methadone, tramadol, and oxycodone, are associated with increased risk of long QT syndrome, which in turn may lead to dangerous arrhythmias including torsade de pointes. While arrhythmia was one of the cardiovascular conditions included in our review, we found only 3 studies of the relationship between NOU and cardiac arrhythmia that met our inclusion criteria. Our initial query returned a number of articles on opioids and the QT interval, which, upon review, turned out to lack an appropriate control group. As a result, those studies were excluded. Moreover, we excluded studies of arrhythmias associated with acute opioid exposure as in, for example, studies conducted among patients undergoing surgery or patients with acute MI. Thus, although there is a body of evidence linking use of certain opioids with the long QT syndrome, we found little high-quality, epidemiologic evidence examining directly the association of NOU with cardiac arrhythmias per se. This appears to be a gap in need of future attention.

We found no studies that addressed the association of NUO with the risk of stroke or heart failure in a general cohort that included a reliable assessment of dose and duration of opioid use. The identified studies had ≥1 serious limitations, including highly selective cohorts or a primary focus on short-term exposures, such as recent use, change of medication, discontinuation of medication, or inadequate assessment of dose and duration. There remains a need for high-quality studies examining the relationship between NOU and stroke and congestive heart failure.

Much of the research on opioids and CVD has focused on acute exposures related to surgical procedures or other treatment for acute medical conditions. Examples include opioids used for anesthesia during

surgery or for postoperative analgesia and morphine as part of treatment for acute MI. There has been relatively little high-quality research on nonacute opioid exposure and its relationship with cardiovascular conditions. A significant challenge for this type of research is the accurate assessment of the duration and intensity of opioid exposure over an extended period of time. For example, it is estimated that the period between the appearance of major risk factors for CAD—high serum cholesterol and high systolic blood pressure—and their effects on mortality may be ≥10 years.[50] Exposure to prescription opioids is well documented in administrative claims databases, but members may be lost to follow-up if they change insurance plans. Moreover, exposure to nonmedical use of opioids is practically impossible to assess through secondary data sources.

CONCLUSIONS

In conclusion, this review of the literature on the association of NOU with the risk of cardiovascular events provides summative evidence that such exposure poses a risk not only for cardiac disorders associated with infections caused by needle reuse, such as infective endocarditis, but may also predispose people to chronic cardiovascular disorders, including MI and arrhythmias. There is a dearth of high-quality evidence on the relationship between NOU and CVD. Many of the identified studies lacked detailed information on the duration and intensity of opioid exposure and all were retrospectively conducted. This is understandable, as the challenges to accurate assessment of NOU are considerable. Innovative approaches to opioid exposure assessment will be required.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Specific opioids used in the 23 reviewed studies (cf Table 2).

References	Opioid name
I	Codeine, codeine, dihydrocodeine, dihydrocodone, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tramadol,
II	Heroin, oxycodone, oxymorphone
III	Heroin and methadone
IV	Morphine, oxycodone, oxycodone-naloxone, hydromorphone, tapentadol, fentanyl, Buprenorphine
V	Heroin
VI	Diphenoxylate, hydrocodone, hydromorphone, meperidine, morphine sulfate, oxycodone, pentazocine, tramadol, fentanyl, codeine
VII	Any prescribed opioid: buprenorphine, morphine, meperidine, tramadol, codeine, dihydrocodeine, propoxyphene, meptazinol
VIII	Hydrocodone bitartrate, codeine phosphate, oxycodone hydrochloride, propoxyphene hydrochloride, tramadol hydrochloride
IX	Anileridine, codeine phosphate, hydromorphone HCL, morphine HCL, meperidine HCL, oxycodone HCL, codeine sulfate, codeine phosphate, acetaminophen-caffeine-codeine, acetaminophen-codeine phosphate, fentanyl transdermal, acetaminophen-codeine, acetylcalicylic acid-codeine-caffeine, acetylsalicylic acid-codeine, oxycodone-HCL-acetaminophen, oxycodone HCL-acetylsalicylic acid, morphine HCL, morphine sulfate