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GENERAL SECTION

Original Research Articles

Prescription Opioid Use and Risk of Coronary Heart Disease, Stroke, and Cardiovascular Death Among Adults from a Prospective Cohort (REGARDS Study)

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Abstract

Objective. Despite unknown risks, prescription opioid use (POU) for nonmalignant chronic pain has grown in the US over the last decade. The objective of this study was to examine associations between POU and coronary heart disease (CHD), stroke, and cardiovascular disease (CVD) death in a large cohort.

Design, Setting, Subjects. POU was assessed in the prospective cohort study of 29,025 participants of the REasons for Geographic and Racial Differences in Stroke study, enrolled between 2003 and 2007 from the continental United States and followed through December 31, 2010. CHD, stroke, and CVD death were expert adjudicated outcome measures.

Methods. Cox proportional hazards models adjusted for CVD risk factors were used.

Results. Over a median (SD) of 5.2 (1.8) years of follow-up, 1,362 CHD events, 749 strokes, and 1,120 CVD death occurred (105, 55, and 104, respectively, in the 1,851 opioid users). POU was not associated with CHD (adjusted hazard ratio [aHR]) 1.03 [95% CI 0.83–1.26] or stroke (aHR 1.04 [95% CI 0.78–1.38]), but was associated with CVD death (aHR 1.24 [95% CI 1.00–1.53]) in the overall sample. In the sex-stratified analyses, POU was associated with increased risk of CHD (aHR 1.38 [95% CI 1.05–1.82]) and CVD death (aHR 1.66 [95% CI 1.27–2.17]) among females but not males (aHR 0.70 [95% CI 0.50-0.97] for CHD and 0.78 [95% CI 0.54–1.11] for CVD death).

Conclusion. Female but not male POU were at higher risk of CHD and CVD death. POU was not associated with stroke in overall or sex-stratified analyses.

Key Words. Opioids; Cardiovascular Disease; Sex Differences

Introduction

Prescription opioid use (POU) is common in the US, with 6–20% of community-dwelling adults reporting therapeutic use of opioids [1,2]. POU has grown

substantially in the US: from 1997 to 2006, sales of hydrocodone and oxycodone increased by 244% and 732%, respectively [3], fueled in part by expanded therapeutic indications from cancer-related to noncancer causes of chronic pain [3–5]. Highly potent compounds such as oxycodone and methadone are widely prescribed for noncancer chronic pain [1,3,6].

While mortality and morbidity related to *opioid abuse, dependence*, and *overdose* have been extensively explored [5,7–9], health risks and safety of *therapeutic opioid use* for noncancer pain are unknown. Recent reports suggest elevated risk of acute coronary heart disease (CHD) among POU [10–12]. Compared to patients on nonsteroidal anti-inflammatory drugs (NSAIDs), opioid treated arthritis patients had two-fold higher risk of myocardial infarction (MI), five-fold higher risk of coronary artery revascularizations, and nearly double the risk of out-of-hospital cardiac death [10]. A United Kingdom study reported 1.28-fold higher risk of MI in opioid users compared to nonusers, with risks more pronounced in females than in males [12]. Opioids are found to affect myocardial contractility, conduction, and possibly reperfusion after MI [13–15], and adverse cardiac effects including QT interval prolongation prompted the FDA to withdraw *propoxyphene* from US markets in 2010 [15].

A very limited number of previous studies of cardiovascular effects of POU conducted to date did not account for important physiologic or self-reported CHD risk factors [10,12]. Associations between POU and stroke or cardiovascular disease (CVD) death in community populations are virtually unexplored. Therefore, we used data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study to examine cardiovascular risks of POU, controlling for other known risk factors of CVD. We hypothesized that POU will be associated with increased risk of acute CHD, stroke, and CVD death, overall and stratified by sex.

Methods

REGARDS Cohort Study Procedures

The REGARDS study is a prospective national cohort of 30,239 community-dwelling adults from all continental US states that examines regional and racial influences on stroke mortality. Details are described elsewhere; briefly, participants were enrolled between 2003 and 2007 using commercially available lists combining mail and telephone contacts to recruit English-speaking adults aged 45 years and older, who were living in the continental US [16]. Severe debilitating conditions and cancer were exclusion criteria [16]. Race and sex were balanced by design, with oversampling from the Southeastern US; the final cohort composition was 58% female and 42% black. Baseline data collection included computer-assisted telephone interviews on sociodemographics, health history, and health status. In-home examinations by trained staff followed standardized, quality-controlled protocols to collect fasting blood and urine samples; electrocardiograms; blood pressure (BP), anthropometric measures; and medication use by pill bottle review. Blood and urine samples were centrally analyzed at the University of Vermont. Electrocardiograms were centrally analyzed at Wake Forest University.

Living participants or their proxies were followed up every 6 months by telephone with retrieval of medical records for reported hospitalizations. Deaths were detected by report of next of kin or through online sources (e.g. Social Security Death Index) and the National Death Index. Proxies or next of kin were interviewed about the circumstances surrounding death, including the presence of chest pain. Death certificates and autopsy reports were also obtained to adjudicate cause of death. Events through December 31, 2010 were included in this analysis. The REGARDS study procedures were approved by the Institutional Review Boards at the participating centers and all participants provided informed consent.

Prescription Opioid Use

POU was defined as use of diphenoxylate, hydrocodone, hydromorphone, meperidine, morphine sulfate, oxycodone, pentazocine, tramadol, fentanyl, and codeine ascertained at pill bottle review. Because of known cardiotoxicity, propoxyphene users were excluded from analyses.

CHD, Stroke, and CVD Death

The outcomes in this study were acute CHD (nonfatal MI or acute death from CHD), stroke, and CVD death (acute death from CHD, stroke, heart failure, sudden death, vascular pathology, and other CVD causes). Outcomes were adjudicated by trained experts following published guidelines [17]. For MI, medical records were examined for signs or symptoms of ischemia; a rising and/or falling pattern in cardiac troponin or creatine phosphokinase-MB concentration over six or more hours with a peak concentration greater than twice the upper limit of normal; and electrocardiogram changes consistent with ischemia or MI, guided by the Minnesota code. Definite and probable MI events were included in analyses. Strokes were defined following the World Health Organization definition of the absence of possible non-neurologic causes and symptom duration $>$24 hours [18]. Events without non-neurologic causes but symptoms lasting $\leq$24 hours with neuroimaging consistent with acute ischemia or hemorrhage were classified as "clinical strokes" and were included in analyses. For deaths, medical history, hospital records, autopsy reports, interviews with next of kin or proxies, and death certificates or National Death Index data were reviewed to adjudicate the cause of death. Acute CHD deaths included out-of-hospital sudden deaths, in-hospital death with cardiac symptom within 6 h of hospital admission, and death within 28 days of definite or probable MI. For all adjudicated endpoints, κ for agreement between independent adjudicators was $>$0.80.

Covariates

Age, race, sex, annual household income, and educational attainment were self-reported. Annual income was dichotomized at <$35,000 and education was dichotomized at having a high school diploma. Cigarette smoking was categorized as current (now) vs past (smoking at least 100 cigarettes in a lifetime) or none. Physical activity was assessed by self-report of any exercise enough to work up a sweat vs none during a regular week. BP was the average of 2 measures using an aneroid sphygmomanometer taken after a 5 minutes seated rest. Hypertension was defined as BP ≥140/≥90 mmHg or report of current use of medication for high BP. Body mass index (BMI) was calculated using height and weight. Serum concentrations of total cholesterol and high-density lipoprotein cholesterol (HDL-C) were measured using colorimetric reflectance spectrophotometry. High-sensitivity c-reactive protein (hsCRP) was analyzed by particle-enhanced immunonephelometry (N High-Sensitivity CRP; Dade BehringInc). Urine albumin was measured by nephelometry using the BNII ProSpec nephelometer (Now Siemaless AG), and urine creatinine was measured by the rate Jaffé method using the Modular-P chemistry analyzer (Roche/Hitachi, Basel, Switzerland). Urinary albumin-to-creatinine ratio (ACR) was used in analyses. Diabetes was defined as use of insulin or oral antiglycemic agents, fasting blood glucose concentration of 126 mg/dL or higher, or nonfasting random plasma glucose concentration of 200 mg/dL or higher. History of atrial fibrillation was ascertained from self-report or via baseline electrocardiograms. Left ventricular hypertrophy (LVH) was identified by meeting Sokolow-Lyon LVH criteria on electrocardiogram [19]. History of CHD was defined as electrocardiogram evidence of MI or self-reported history of coronary artery bypass surgery, percutaneous coronary intervention, or MI. Prevalent CVD included history of CHD, self-reported diagnosis or intervention procedure for peripheral arterial disease, aortic aneurism, and/or stroke. Use of nonsteroidal anti-inflammatory drugs (NSAIDs), including inhibitors of cyclooxygenase 2 (COX-2), aspirin, statins, and antihypertensive medications was determined via self-report or pill bottle review. Depressive symptoms were assessed using the 4-item version of the Center for Epidemiological Studies Depression (CES-D) dichotomized at <4 [20]. Health status was defined using Short Form 12 (SF-12) physical component summary (PCS) and mental component summary (MCS) scores [21]. Pain was measured using the following question: "During the past 4 weeks how much did pain interfere with your normal work, including both work outside and housework?" [21] with responses dichotomized as moderate to severe chronic pain (pain interfered with work "extremely," "quite a bit" or "moderately") vs no or low pain ("not at all" or "a little bit"). QT intervals were corrected for heart rate using the formula QT + (154*[1–{60/heart rate}]) [22] and were prolonged if ≥450 ms for males and ≥460 ms for females [22].

Statistical Analysis

Chi-square and Student *t*-tests were used to compare baseline characteristics of POU with nonusers. Cox proportional hazards models estimated hazard ratios (HR) of three endpoints: CHD, stroke and CVD death, separately, as a function of POU. This was first done in the total sample as well as in analyses stratified by absence or presence of baseline CHD (for the CHD endpoint), stroke (for the stroke endpoint) and CVD (for CVD death). An initial model adjusted for age, sex, geographic region of residence (to account for the sampling scheme), income, and education. Model 2 included variables in the first model plus total cholesterol, HDL-C, use of statins, cigarette smoking, diabetes, systolic BP, use of antihypertensive medication, baseline CHD or CVD or stroke (depending on the endpoint). Model 3 included all covariates in model 2 plus exercise, BMI, log-transformed hsCRP, log-transformed ACR, depressive symptoms, regular aspirin use and NSAID use (including COX-2 inhibitors), moderate to severe pain in the last 4 weeks, and PCS. Finally model 4 added QTc interval to all other covariates. Multivariable-adjusted Cox proportional hazards models were fitted using imputed data to account for missing covariate data using multiple imputations by chained equations with 20 datasets.

We also conducted an additional analysis examining ischemic strokes exclusively, overall and stratified by sex analogous to analyses described above.

Another set of fully adjusted multivariable analyses examined the cardiovascular risk of separate opioid medications, namely oxycodone, hydrocodone, as well as combined opioid-acetaminophen preparations. In a separate sensitivity analysis, we included methadone users in the POU group.

Because of the possibility of confounding by indication, we conducted a secondary analysis using propensity scores indicating the probability of POU. To construct propensity scores we used all covariates described above in the multivariable adjusted main analyses plus additional variables as shown (Supplemental Table 1). Propensity scores for POU were calculated using logistic regression run on 30 datasets with missing data multiply imputed [23]. We fitted Cox proportional regression models within the quintile of the propensity score, overall and separately for males and females.

All analyses were conducted using SAS software version 9.3 (SAS Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).

Results

Study Participants

After excluding 569 individuals missing follow-up data, 69 participants missing medication data and 576 propoxyphene users, the sample included 29,025

participants. For stroke, the final sample included 29,018 because 7 participants had a stroke after the interview date, but before the in-home visit date and thus were excluded. Over the median (SD) follow-up time of 5.2 (1.8) years there were 1,362 acute CHD events, 749 strokes and 1,120 CVD deaths.

There were 1,851 (6.4%) POU (Figure 1). Hydrocodone was the most commonly used opioid medication (54% of POU).

Compared with the 27,174 nonusers, the 1,851 POU were younger and included fewer males and more blacks (Table 1). POU were more likely to smoke, have diabetes, hypertension, baseline CHD, CVD, and to report depressive symptoms. POU reported significantly lower physical functioning and higher levels of chronic pain despite opioid medication use compared with nonusers. Similar baseline differences were observed between male POU and nonusers and female POU and nonusers. Male POU were slightly younger than male nonusers. In contrast to the total sample, male POU did not differ from nonusers in systolic BP level or statin use.

Overall Analysis

Compared with nonusers, POU had higher age-adjusted incidence of acute CHD both overall and for those without baseline CHD (each $P < 0.001$) (Table 2). In multivariable analyses, the associations between POU and acute CHD were attenuated in the overall sample (fully adjusted HR 1.03, 95% CI 0.83–1.26) and for those without CHD at baseline (fully adjusted HR 1.06, 95% CI 0.80–1.41). POU was not significantly associated with recurrent acute CHD among those with CHD at baseline in both crude and fully adjusted models.

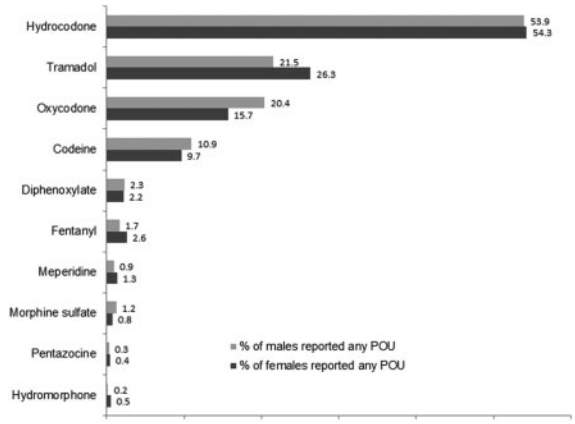

Figure 1 Use of individual opioid medications in REGARDS, separately by sex. Opioid users are defined as REGARDS participants who used diphenoxylate, hydrocodone, hydromorphone, meperidine, morphine sulfate, oxycodone, pentazocine, tramadol, fentanyl, and codeine. Opioid use was ascertained via pill bottle review during the in-home study visit. Each number on the figure represents a proportion of REGARDS males or females who used individual opioid medication of all males or females–opioid users. Sum of the proportions may exceed 100% because participants used several medications simultaneously. Abbreviation: POU-prescription opioid users.

The incidence of stroke was similar for POU and nonusers in the overall sample and those with and without baseline stroke examined separately. POU was not associated with risk of stroke in any analyses (Table 2). Analyses restricted to ischemic strokes revealed similar lack of associations (Supplemental Table 2).

The age-adjusted rates of CVD death among POU were higher in the overall sample (9.6 [95% CI 7.9–11.7] vs 5.2 [95% CI 4.8–5.7]) and among those with and without baseline CVD (Table 2). In the overall sample, the fully adjusted HR for CVD death was 1.24 (95% CI 1.00–1.53); among persons with a baseline history of CVD it was 1.40 (95% CI 1.08–1.82); but among those without baseline CVD, it was 0.99 (95% CI 0.69–1.41).

Sex Differences

There was no difference in age-adjusted incidence of acute CHD between male POU and nonusers in the overall sample and among those with and without baseline CHD (Table 3). In contrast, the incidence of CHD was higher among female POU vs nonusers for all three groups. There was a statically significant interaction of sex and POU in models testing associations between both incident and recurrent acute CHD (interaction *P*-values 0.07 and 0.004, respectively, Table 3). In the sex stratified fully adjusted analyses, POU was protective for CHD among males especially in those with baseline CHD, but POU was associated with higher risk in females (fully adjusted HR 1.38 [95% CI 1.05–1.82]) overall and in females with baseline CHD (fully adjusted HR 1.63 [95% CI 1.08–2.45]) (Table 3). Neither male nor female POU had higher risk of stroke compared with nonusers. The risk for CVD death was elevated for female but not male POU compared with nonusers, especially for females with baseline CVD (fully adjusted HR 2.14 [95% CI 1.51–3.03]). Overall and among participants with baseline CVD, the *P*-values for the sex*POU interaction term in the CVD death models were <0.01 (Table 3).

Effect of Separate Opioid Medications on Cardiovascular Endpoints

Overall, compared to nonusers of opioids, oxycodone users had a stronger association with acute CHD (fully adjusted HR [aHR] 1.24 [95% CI 0.81–1.90]) and CVD death (aHR 1.64 [95% CI 1.07–2.52]) than users of hydrocodone (aHR [95% CI] for acute CHD: 0.89 [0.65–1.27] and for acute CVD death 1.04 [0.76–1.42], respectively) or other opioids (aHR and [95% CI] for acute CHD: 1.01 [0.77–1.41] and for acute CVD death 1.33 [0.96–1.83], respectively) (Table 4). However, when

Table 1 Baseline characteristics of REGARDS participants taking and not taking prescription opioids

Variables	All			Males			Females		
	POU n = 1,851 n (%)*	Nonusers n = 27,174 n (%)	*P*	POU n = 651 n (%)	Nonusers n = 12,479 n (%)	*P*	POU n = 1,200 n (%)	Nonusers n = 14,695	*P*
Sociodemographics									
Age, years, mean (SD)	64.0 (9.4)	64.9 (9.4)	<0.001	64.1 (9.0)	65.7 (9.3)	<0.001	64.0 (9.5)	64.3 (9.5)	0.26
Female	1200 (64.8)	14695 (54.1)	<0.001	–			–		
African American	841 (45.4)	11,067 (40.7)	<0.001	257 (39.5)	4287 (34.3)	0.007	584 (48.7)	6780 (46.1)	0.09
Less than high school education	344 (18.6)	3213 (11.8)	<0.001	106 (16.3)	1365 (10.9)	<0.001	238 (19.8)	1848 (12.6)	<0.001
Annual income < $35,000	1,023 (55.2)	11,123 (40.9)	<0.001	316 (48.5)	4250 (34.1)	<0.001	707 (58.9)	6873 (46.8)	<0.001
Health behaviors									
Current smoking	423 (23.0)	3753 (13.9)	<0.001	178 (21.8)	1742 (14.0)	<0.001	336 (21.0)	2011 (13.7)	<0.001
Never exercises	886 (47.6)	8880 (33.8)	<0.001	258 (40.4)	3355 (27.3)	<0.001	608 (51.5)	5525 (38.1)	<0.001
Physiological CHD risk factors									
Body mass index, kg/m^2, mean (SD)	31.0 (7.3)	29.2 (6.1)	<0.001	29.8 (5.8)	28.5 (5.0)	<0.001	31.7 (7.8)	29.8 (6.8)	<0.001
Diabetes	535 (30.3)	5577 (21.3)	<0.001	189 (30.3)	2720 (22.5)	<0.001	346 (30.2)	2857 (20.3)	<0.001
Hypertension	1,261 (68.4)	15,822 (58.4)	<0.001	425 (65.4)	7189 (57.8)	<0.001	836 (70.2)	8633 (58.9)	<0.001
Systolic blood pressure, mmHg, mean (SD)	128.5 (17.7)	127.5 (16.5)	0.01	128.5 (16.7)	128.9 (16.1)	0.53	128.6 (18.1)	126.2 (16.8)	<0.001
Total cholesterol mg/dL,mean (SD)	189.7 (42.4)	192.2 (40.0)	0.02	179.3 (39.7)	182.9 (38.2)	0.02	195.4 (42.8)	200.1 (39.7)	<0.001
HDL-C, mg/dl, mean (SD)	51.0 (16.5)	51.8 (16.1)	0.04	43.8 (14.2)	45.5 (13.7)	0.002	55.0 (16.3)	57.3 (16.1)	<0.001
hsC-reactive protein, mg/L,median [25th, 75th %]	3.6[1.5–8.1]	2.1[0.9–4.8]	<0.001	2.8[1.1–6.4]	1.7[0.8–3.7]	<0.001	4.2[1.7–8.7]	2.7[1.1–5.9]	<0.001
Albumin to creatinine ratio,mg/g, median [25th, 75th %]	8.1[5.0–17.9]	7.4[4.6–15.9]	<0.001	7.4[4.4–18.6]	6.8[4.2–16.8]	0.08	8.4[5.2–17.6]	7.8[5.0–15.4]	0.005
Atrial fibrillation	224 (12.6)	2236 (8.4)	<0.001	78 (12.3)	1060 (8.7)	0.002	146 (12.7)	1176 (8.2)	<0.001
Left ventricular hypertrophy	188 (10.4)	2621 (9.8)	0.45	61 (9.5)	1139 (9.3)	0.85	127 (10.8)	1482 (10.3)	0.54
Baseline cardiovascular disease									
Coronary heart disease	413 (22.8)	4643 (17.4)	<0.001	177 (27.6)	2915 (23.7)	0.03	236 (20.1)	1728 (12.0)	<0.001
Stroke, peripheral artery Disease, or aortic aneurism	245 (13.2)	2315 (8.5)	<0.001	91 (14.0)	1293 (10.4)	0.003	164 (12.8)	1022 (7.0)	<0.001
QTc prolongation†	61 (3.3)	772 (2.8)	0.24	32 (4.9)	493 (4.0)	0.47	29 (2.4)	279 (1.9)	0.17
Medications									
Statin	679 (37.1)	8923 (33.2)	<0.001	234 (36.3)	4456 (36.0)	0.88	445 (37.6)	4467 (30.7)	<0.001
Antihypertensive medication	1,148 (62.8)	13,727 (51.1)	<0.001	379 (58.7)	6043 (48.7)	<0.001	769 (65.1)	7684 (53.1)	<0.001
Aspirin	766 (41.4)	11815 (43.5)	0.08	303 (46.6)	6312 (50.6)	0.05	463 (38.6)	5503 (37.5)	0.44
NSAID	504 (27.5)	3588 (13.3)	<0.001	154 (23.7)	1318 (10.6)	<0.001	350 (29.5)	2270 (15.5)	<0.001
Mental and physical health									
Depressive symptoms (CES- D≥4)	443 (24.1)	2677 (9.9)	<.001	104 (16.1)	856 (6.9)	<0.001	339 (28.4)	1821 (12.5)	<0.001
Chronic pain (moderate tosevere) in last 4 weeks	1094 (59.1)	5308 (19.5)	<.001	346 (53.2)	2006 (16.1)	<0.001	748 (62.3)	3302 (22.5)	<0.001
Perceived stress, median, [25th, 75th %]	4.0[1.0–7.0]	3.0[0–5.0]	<.001	3.0[1.0–6.0]	2.0[0–4.0]	<0.001	4.0[2.0–7.0]	3.0[1.0–6.0]	<0.001
MCS, median, [25th, 75th %]	53.8[42.9–59.0]	56.8[52.1–59.4]	<.001	55.9[45.9–59.7]	57.4[53.4–59.8]	<0.001	52.7[41.3–58.7]	56.0[50.7–59.1]	<0.001
PCS, median, [25th, 75th %]	34.9[26.2–46.1]	50.9[41.9–55.0]	<.001	37.6[28.4–48.2]	51.5[43.7–55.3]	<0.001	33.4[25.0–44.7]	49.7[40.3–54.8]	<0.001

Abbreviations: CES-D = Center for Epidemiological Studies Depression scale; CHD = coronary heart disease; HDL = high density lipoprotein; hsC-Reactive Protein = highly sensitive C-Reactive protein; MCS = medical component score on SF-12 scale; NSAID = nonsteroidal anti-inflammatory drugs; QTc = QT interval corrected for heart rate; PCS = physical component score on SF-12 scale; SD = standard deviation.

*Numbers are means and % unless indicated otherwise in the variables column.

†QT corrected interval > 450 ms for men or > 460 ms for women on baseline ECG.

Table 2 Association of baseline prescription opioid use (POU) with acute coronary heart disease (CHD), stroke, and cardiovascular disease (CVD) death among REGARDS participants

Acute CHD

	All N = 29,025		No baseline CHD N = 23,969		Baseline CHD N = 5,056	
	POU	Nonusers	POU	Nonusers	POU	Nonusers
Participants, n	1,851	27,174	1,438	22,531	413	4,643
Events, n	105	1257	56	712	49	545
IR (95%CI)‡	11.7 (10.6–15.0)**	8.3 (7.8–8.8)	8.0 (6.1–10.4)*	5.7 (5.2–6.2)	28.7 (21.7–38.0)	24.0 (22.0–26.2)
	HR (95%CI)†		*HR (95%CI)*		*HR (95%CI)*	
Model 1	**1.41 (1.15–1.72)**		**1.39 (1.06–1.82)**		1.19 (0.89–1.60)	
Model 2¶	1.17 (0.96–1.44)		1.28 (0.97–1.68)		1.14 (0.85–1.53)	
Model 3¶	1.03 (0.83–1.26)		1.08 (0.81–1.43)		0.96 (0.70–1.30)	
Model 4¶	1.03 (0.83–1.26)		1.06 (0.80–1.41)		0.95 (0.70–1.29)	

Stroke

	All N = 29,025		No baseline stroke N = 27,208		Baseline stroke N = 1,810	
	POU	Nonusers	POU	Nonusers	POU	Nonusers
Participants, n	1,850	27,168	1,685	25,523	165	1,645
Events, n	55	694	41	565	14	129
IR (95%CI)‡	5.9 (4.5–7.7)*	4.4 (4.0–4.7)	4.7 (3.5–6.5)	3.7 (3.3–4.0)	19.9 (11.8–33.5)	17.0 (14.2–20.2)
	HR (95%CI)†		*HR (95%CI)*		*HR (95%CI)*	
Model 1	1.29 (0.97–1.69)		1.24 (0.90–1.70)		1.15 (0.66–2.02)	
Model 2£	1.12 (0.85–1.48)		1.13 (0.81–1.54)		1.15 (0.65–2.01)	
Model 3£	1.04 (0.78–1.38)		1.07 (0.77–1.48)		0.97 (0.54–1.74)	
Model 4£	1.04 (0.78–1.38)		1.07 (0.77–1.49)		0.97 (0.54–1.75)	

CVD death

	All N = 29,025		No baseline CVD N = 22,403		Baseline CVD N = 6,622	
	POU	Nonusers	POU	Nonusers	POU	Nonusers
Participants, n	1,851	27,174	1,295	21,108	556	6,066
Events, n	104	1016	35	470	69	546
IR (95%CI)‡	9.6 (7.9–11.7)**	5.4 (5.0–5.8)	4.4 (3.2–6.2)*	3.0 (2.7–3.4)	27.1 (21.3–34.3)**	16.2 (14.7–17.7)
	HR (95%CI)†		*HR (95%CI)*		*HR (95%CI)*	
Model 1	**1.75 (1.43–2.15)**		**1.41 (1.00–1.99)**		**1.69 (1.31–2.18)**	
Model 2¥	**1.51 (1.23–1.86)**		1.35 (0.95–1.91)		**1.63 (1.27–2.10)**	
Model 3¥	**1.23 (1.00–1.52)**		1.01 (0.70–1.44)		**1.40 (1.07–1.81)**	
Model 4¥	**1.24 (1.00–1.53)**		0.99 (0.69–1.41)		**1.40 (1.08–1.82)**	

Abbreviations: CI = confidence interval; CHD = coronary heart disease; CVD = cardiovascular disease includes history of CHD, stroke, periphery artery disease or aortic aneurism; HR = hazards ratio; IR = incidence rate; POU = Prescription opioid user.

*Significant difference between POU and nonusers at $P < 0.05$; ** significant at $P < 0.001$.

†Hazard Ratio and (95% Confidence Interval) for POU.

‡Age-adjusted Incidence Rate per 1,000 person-years (95% confidence interval).

Model 1 adjusts for age, race, sex, geographical region, education, income.

Model 2¶ adjusts for Model 1 covariates + total cholesterol, HDL-cholesterol, use of statins, smoking, diabetes, systolic blood pressure, use of antihypertensive medication, history of CHD (only for overall analysis).

Model 3¶ adjusts for Model 2 covariates + exercise, body mass index, log-transformed CRP, log transformed ACR, depressive symptoms (CES-D=>4) physical functioning (physical health component of SF-12), regular aspirin and NSAIDS use and chronic pain (moderate to severe) at baseline.

Model 4¶ adjusts for model 3 covariates + QT interval, corrected for heart rate.

Model 2£ adjusts for Model 1 covariates + total cholesterol, HDL-cholesterol, use of statins, smoking, diabetes, systolic blood pressure, use of antihypertensive medication, history of stroke (only in overall analysis), atrial fibrillation, left ventricular hypertrophy, history of CHD, periphery artery disease or aortic aneurism.

Model 3£ adjusts for Model 2 covariates + exercise, body mass index, log-transformed CRP, log transformed ACR, depressive symptoms (CES-D=>4) physical functioning (physical health component of SF-12), regular aspirin and NSAIDS use and chronic pain (moderate to severe) at baseline.

Model 4£ adjusts for model 3 covariates + QT interval, corrected for heart rate.

Model 2¥ adjusts for Model 1 covariates + total cholesterol, HDL-cholesterol, use of statins, smoking, diabetes, systolic blood pressure, use of antihypertensive medication, history of CVD (only for overall analysis).

Model 3¥ adjusts for Model 2 covariates + exercise, body mass index, log-transformed CRP, log transformed ACR, depressive symptoms (CES-D=>4), physical functioning (physical health component of SF-12), regular aspirin and NSAIDS use and chronic pain (moderate to severe) at baseline.

Model 4¥ adjusts for model 3 covariates + QT interval, corrected for heart rate. Bold $P < 0.05$.

Table 3 Sex specific associations between prescription opioid use and acute coronary heart disease, cardiovascular death, stroke

	All		No baseline CHD		Baseline CHD	
	POU	Nonusers	POU	Nonusers	POU	Nonusers
Acute coronary heart disease						
MALES, n	651	12,479	474	9,564	177	2,915
Events, n	38	842	22	446	16	396
Age-adjusted IR (95%CI)‡	12.5 (9.1–17.3)	12.1 (11.3–13.0)	9.9 (6.5–15.0)	8.2 (7.4–9.1)	21.1 (17.5–34.5)	27.7 (25.1–30.6)
HR (95%CI)†	**0.70 (0.50–0.97)**		0.89 (0.57–1.39)		**0.53 (0.32–0.87)**	
FEMALES, n	1,200	14,695	964	12,967	236	1,728
Events, n	67	415	34	266	33	149
Age-adjusted IR (95%CI)‡	11.1 (8.7–14.2)**	5.1 (4.6–5.7)	7.0 (5.0–9.9)**	3.8 (3.3–4.3)	33.7 (24.0–47.6)**	17.7 (14.9–20.9)
HR (95%CI)†	**1.38 (1.05–1.82)**		1.22 (0.84–1.77)		**1.63 (1.08–2.45)**	
Sex x POU *P*-interaction¶	**0.001**		0.07		**0.004**	
Stroke						
MALES, n	650	12,476	594	11,615	56	861
Events, n	22	378	14	305	8	73
Age-adjusted IR (95%CI)‡	7.1 (4.7–10.8)	5.2 (4.7–5.8)	4.8 (2.9–8.2)	4.4 (3.9–5.0)	34.6 (17.3–69.4)	18.3 (14.5–23.1)
HR (95%CI)†	1.07 (0.69–1.67)		0.92 (0.53–1.59)		1.59 (0.72–3.50)	
FEMALES, n	1200	14,692	1021	13,908	109	784
Events, n	33	316	27	260	6	56
Age-adjusted IR (95%CI)‡	4.8 (2.9–8.2)	4.4 (3.9–5.0)	4.6 (3.1–6.7)	3.1 (2.6–3.5)	12.4 (5.6–27.7)	15.4 (11.8–20.2)
HR (95%CI)†	0.98 (0.68–1.43)		1.16 (0.77–1.76)		0.53 (0.21–1.32)	
Sex x POU *P*-interaction§	0.90		0.38		0.08	
Cardiovascular death						
MALES, n	651	12,479	422	8,883	220	3,596
Events, n	32	651	12	265	20	386
Age-adjusted IR (95%CI)‡	9.1 (6.4–12.9)	7.5 (6.8–8.3)	5.1 (2.9–9.1)	4.0 (3.4–4.7)	19.0 (12.3–29.5)	19.2 (17.2–21.4)
HR (95%CI)†	0.78 (0.54–1.11)		0.83 (0.46–1.51)		0.75 (0.47–1.18)	
FEMALES, n	1,200	14,695	873	12,225	327	2,470
Events, n	72	365	23	205	49	160
Age-adjusted IR (95%CI)‡	9.6 (6.5–10.6)**	3.6 (3.1–4.1)	4.0 (2.6–6.1)*	2.3 (1.2–2.7)	32.0 (24.0–42.7)**	11.9 (10.0–14.1)
HR (95%CI)†	**1.66 (1.27–2.17)**		1.15 (0.73–1.81)		**2.14 (1.51–3.03)**	
Sex x POU *P*-interaction#	**0.0001**		0.17		**0.0001**	

Abbreviations: CI = confidence interval; CHD = coronary heart disease; CVD = cardiovascular disease includes history of CHD, stroke, periphery artery disease or aortic aneurism; HR = hazards ratio; IR = incidence rate; POU = Prescription opioid user.
*Significant difference between POU and nonusers at $P < 0.05$; ** significant–at $P < 0.001$.
†Hazard Ratio and (95% Confidence Interval) for POU in the fully adjusted model (model 4) stratified by gender.
‡Age-adjusted Incidence Rate per 1,000 person-years (95% confidence interval).
¶From the fully adjusted model (model 4) of acute CHD.
§From the fully adjusted model (model 4) of stroke.
#From the fully adjusted model (model 4) of CVD death.
Bold $P < 0.05$.

compared directly with each other, the difference in the effects of hydrocodone and oxycodone use was not statistically significant in either of the analyses (Table 4).

About a half of POUs in REGARDS were taking combined opioid-acetaminophen medications at baseline: 48% of women POU and 42% of men POU (*P*-value for sex difference 0.004). The combination of POU-acetaminophen displayed a stronger association with cardiovascular endpoints than those of pure opioids or pure acetaminophen compared to nonusers of both (Table 5). This was observed especially among females. Females on opioid-acetaminophen combined preparations were 1.7 times as likely to have acute CHD and 2.1 times as likely to die from cardiovascular causes as nonusers of both, whereas females on pure opioids did not demonstrate statistically significant associations with the endpoints (Table 5). Males on opioid-acetaminophen combination had a nonsignificant association with stroke (fully adjusted HR 1.42, [95% CI 0.81–2.51]. Acetaminophen alone was not associated with cardiovascular endpoints in REGARDS.

The sensitivity analysis including methadone users resulted in the addition of 56 individuals to the POU group, and the analyses resulted in very similar findings.

Propensity Score Analysis

The propensity score analysis confirmed the results reported above, but with less pronounced and nonsignificant associations for CVD death (for the overall

Table 4 Association of Hydrocodone, Oxycodone, both and other prescription opioids with acute coronary heart disease, cardiovascular death, stroke

	All participants					
	Acute CHD		Stroke		Cardiovascular death	
	Events among POU, n/POU, n	aHR (95%CI)	Events among POU, n/POU, n	aHR (95%CI)	Events among POU, n/POU, n	aHR (95%CI)
Model 1. Separate medications vs nonusers (referent)						
Hydrocodone	44/940	0.89 (0.65–1.27)	30/940	1.15 (0.79–1.67)	43/940	1.04 (0.76–1.42)
Oxycodone	22/265	1.24 (0.81–1.90)	8/264	1.02 (0.50–2.06)	22/265	**1.64 (1.07–2.52)**
Simultaneous use of Hydrocodone and Oxycodone	3/20	1.51 (0.48–4.78)	1/20	1.31 (0.18–9.36)	2/20	1.25 (0.31–5.09)
All other opioids	38/682	1.01 (0.77–1.41)	18/682	0.92 (0.57–1.48)	40/682	1.33 (0.96–1.83)
Model 2. Hydrocodone vs Oxycodone users (referent), excludes participants on other opioids or nonusers		0.74 (0.44–1.27)		1.25 (0.55–2.86)		0.62 (0.36–1.06)
	Females		Females		Females	
Model 1. Separate medications vs nonusers						
Hydrocodone	27/616	1.10 (0.73–1.64)	20/616	*	33/616	**1.57 (1.08–2.28)**
Oxycodone	15/154	**2.19 (1.29–3.72)**	5/154	*	12/154	**1.87 (1.13–3.57)**
Simultaneous use of Hydrocodone and Oxycodone	1/8	3.63 (0.50–26.41)	0/8	*	1/8	3.70 (0.51–27.00)
All other opioids	24/449	1.36 (0.89–2.07)	8/449	*	27/449	**1.67 (1.12–2.50)**
Model 2.Hydrocodone vs Oxycodone users (ref), excludes participants on other opioids or nonusers		0.54 (0.27–1.07)		1.24 (0.41–3.77)		0.84 (0.40–1.78)
	Males		Males		Males	
Model 1. Separate medications vs nonusers						
Hydrocodone	17/324	0.68 (0.42–1.11)	10/324	1.00 (0.39–1.63)	10/324	**0.49 (0.26–0.92)**
Oxycodone	7/111	0.64 (0.30–1.37)	3/110	0.89 (0.28–2.61)	10/111	1.39 (0.74–2.63)
Simultaneous use of Hydrocodone and Oxycodone	2/12	1.30 (0.32–5.33)	1/12	1.85 (0.25–13.49)	1/12	0.87 (0.12–6.37)
All other opioids	14/233	0.68 (0.41–1.19)	10/233	1.38 (0.28–2.81)	13/233	0.91 (0.52–1.58)
Model 2. Hydrocodone vs Oxycodone users (ref), excludes participants on other opioids or nonusers		1.64 (0.62–4.34)		*		0.50 (0.15–1.65)

Abbreviations: aHR = fully adjusted hazards ratio; CI = confidence interval; CHD = coronary heart disease; POU = Prescription opioid user; REF = referent group.
Bold $P < 0.05$.
*Model did not converge.

Table 5 Association of combination opioid/acetaminophen preparations, pure opioids, other acetaminophen medications with acute coronary heart disease, cardiovascular death, stroke

	All participants					
	Acute CHD		Stroke		Cardiovascular death	
	Events n/users, n	aHR (95%CI)	Events n/users, n	aHR (95%CI)	Events n/users, n	aHR (95%CI)
Opioid + Acetaminophen preparation users	53/872	1.14 (0.86–1.52)	35/872	1.40 (0.98–1.99)	56/872	**1.41 (1.07–1.86)**
Opioid alone preparation users	54/1035	0.89 (0.67–1.17)	22/1034	0.76 (0.50–1.18)	51/1035	1.04 (0.78–1.39)
Other Acetaminophen users	116/2462	0.96 (0.79–1.17)	71/2460	1.06 (0.82–1.35)	85/2462	0.81 (0.64–1.01)
Nonusers of both		REF		–		–
	Females		Females		Females	
Opioid + Acetaminophen preparation users	39/587	**1.72 (1.22–2.44)**	22/587	1.33 (0.85–2.09)	45/587	**2.12 (1.52–2.94)**
Opioid alone preparation users	28/640	1.12 (0.75–1.65)	11/640	0.63 (0.34–1.16)	28/640	1.22 (0.82–1.81)
Other Acetaminophen users	64/1656	1.22 (0.93–1.59)	42/1665	1.06 (0.76–1.47)	47/1656	0.93 (0.68–1.21)
Nonusers of both		REF		–		–
	Males		Males		Males	
Opioid + Acetaminophen preparation users	14/285	0.61 (0.36–1.04)	13/285	1.42 (0.81–2.51)	11/285	0.61 (0.33–1.11)
Opioid alone preparation users	26/395	0.73 (0.49–1.09)	11/394	0.92 (0.50–1.70)	23/395	0.89 (0.57–1.34)
Other Acetaminophen users	52/806	0.79 (0.59–1.05)	29/805	1.04 (0.71–1.52)	38/806	0.72 (0.52–1.01)
Nonusers of both		REF		–		–

Abbreviations: aHR = fully adjusted hazards ratio; CI = confidence interval; CHD = coronary heart disease; REF = referent group.
Bold $P < 0.0.5$

sample, fully adjusted HR 1.14 (95% CI 0.92–1.40]; for those with CVD at baseline, fully adjusted HR 1.25 [0.96–1.62]; for those without CVD at baseline, fully adjusted HR 0.97 [0.68–1.29]) (Supplemental Table 3).

Discussion

This study contributes to a novel growing body of literature examining health risk of therapeutic use of opioids. POU in the overall study population was associated with elevated risk of CVD death, controlling for a host of CVD risk factors and concurrent medication use, such as NSAIDs. We observed important sex differences in the association of POU with cardiac endpoints in the REGARDS study: female POU were at increased risk for CHD and CVD death compared with nonusers, but male POU were at lower risk for CHD, with nonsignificant lower risks for CVD death. Both male and female POU had similar risks for stroke compared with nonusers. These findings raise concerns about the cardiovascular safety of the growing practice of prescribing opioids for chronic noncancer pain, especially for females as well as call for additional research efforts to examine sex difference in opioid cardiovascular risks. Combined opioid and acetaminophen preparations may have more deleterious cardiovascular effect than pure opioid compounds.

POU was common in REGARDS, similar to previous studies [1], and females were more likely to be POU than males. POU had more chronic health conditions, lower physical functioning, and more depressive symptoms consistent with previous studies [24,25]. Importantly, despite opioid use, POU still reported higher levels of chronic pain compared to nonusers.

Overall, after adjustment for numerous covariates, risks for CHD were similar for POU and nonusers in the REGARDS study, in contrast to a previous report of a 1.28-fold increased risk of incident MI among patients treated with opioids for noncancer pain [12]. However, we found a 1.24-fold increase of risk of CVD death among POU, consistent with a report of a 1.96 increased risk of sudden death among arthritis patients treated with opioids, although that endpoint is not fully comparable with our endpoint of CVD death [10]. POU in our study was not associated with increased risk for stroke. Similarly, Solomon, et al. also reported no association between POU and stroke compared to NSAID users [10]. Consistent with the study by Solomon, et al. study, we did not observe any significant difference in cardiovascular risk between hydrocodone (a weaker compound) and oxycodone (more potent compound) [10].

Our finding of increased risk for CVD death associated with POU is novel and concerning in light of several

molecular mechanisms. Opioid receptors have been described in human myocardial cells with recent research suggesting that chronic use or higher doses may increase ischemia and oxidative stress [13,26–28]; remifentanil in rat myocardium demonstrated dose-dependent increased susceptibility to reperfusion injury via superoxide anions [29]. Chronic methadone and oxycodone use has been linked to prolonged QT intervals and torsades de pointes in part via inhibition of human ether-a-go-go gene regulated potassium channels [14,30,31]. Other studies have found increased inflammatory markers such as CRP and accelerated artherosclerosis in chronic opioid users [32]. POU in our study had higher hsCRP levels than nonusers, but controlling for hsCRP did not completely attenuate the association between POU and CHD or CVD death. Methadone also increased platelet aggregation through stimulation of platelet/endothelial cell adhesion molecule-1 and glycoprotein IIb expression, decreasing protective effects of aspirin [33]. Together, these mechanisms suggest potential pathophysiologic plausibility for an association between opioid use and CVD.

This study is one of the first to report sex differences in the association of CVD and POU that were most pronounced in females with prevalent CHD or CVD. One prior study reported that higher cumulative use of opioids (>50 lifetime prescriptions) was associated with incident MI in females but not in males, and lower cumulative use (1–2 prescriptions) was associated with MI in males but not females [12]. We were unable to examine cumulative opioid use. One explanation of higher cardiac risks in females-opioid users may be related to the finding that chronic opioid use decreases hypothalamic-pituitary-ovarian axis activity and may decrease estrogen levels, potentially increasing CVD risk in women [34]. In addition, female POUs in REGARDS were slightly more likely to use combined opioid–acetaminophen preparations than male POU. The combination of acetaminophen with opioids may confer higher risk of CVD death than opioids used alone. Thus, greater use of combination medications among females may provide a partial explanation of the observed excess CVD mortality in female opioid users.

Our study's notable strengths included the large national sample of community-dwellers; availability of many variables, including physiologic and patient-reported characteristics; expert-adjudicated outcomes; and the propensity score analysis. Limitations include the observational design with limited opportunity for drawing causal inferences. Although we adjusted for baseline comorbidities, physical functioning, and chronic pain, and conducted a propensity score analysis, there is still a possibility of residual confounding by indication. We did not have information on duration of opioid use, dose, longitudinal repeated measures of pain, or information on whether opioid use was concordant with physician recommendations. Similarly, we had little information on opioid diversion or misuse. Some covariates (health behaviors, depressive symptoms) were self-reported, with known limitations. Although we had many psychosocial variables available, some important psychosocial characteristics were unavailable, such as history of prior substance dependence, and current substance use beyond smoking and alcohol use.

Conclusion

POU among adults from this community sample was common, with females using opioids more than males (7.5% vs 5.0%, respectively). Overall POU was not significantly associated with CHD or stroke, but it was associated with CVD death even after adjusting for a host of baseline CVD risk factors and concurrent medication use that included NSAIDs and COX-2 inhibitors. In the sex-stratified analyses female but not male POU had higher risk of CHD and CVD death than nonusers, especially among those with baseline CHD or CVD. We were not able to account for opioid dosages or duration of use; therefore, more studies are needed to confirm the sex-specific cardiovascular risks of opioids. The combination of opioids with acetaminophen was particularly deleterious in this study. Physicians should use caution when prescribing opioid medications for noncancer pain, especially for females with known CVD.

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Supplemental Data

Supplemental Data may be found online at http://painmedicine.oxfordjournals.org

Supplemental Table 1. Variables included in calculation of propensity score indicating probability of opioid prescription at baseline.

Supplemental Table 2. Association of baseline prescription opioid use (POU) with ischemic stroke (hemorrhagic strokes excluded).

Supplemental Table 3. Association of baseline prescription opioid use with acute coronary heart disease, cardiovascular death, stroke among REGARDS participants, matched within quintiles of propensity score representing propensity of receiving opioids at baseline (Hazard Ratios for POU compared to nonusers).