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ORIGINAL ARTICLE

Prescribed opioid use is associated with adverse cardiovascular outcomes in community-dwelling older persons

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Abstract

Aims Prescribed opioids are commonly used in the older community-dwelling population for the treatment of chronic pain. Although the harmful effects of opioid abuse and overdose are well understood, little is known about the long-term cardiovascular (CV) effects of prescribed opioids. The aim of this study was to investigate the CV effects associated with prescribed opioid use.

Methods and results A post hoc analysis of participants in the Aspirin in Reducing Events in the Elderly (ASPREE) trial was conducted. Participants in the ASPREE trial included community-dwelling older adults without a prior history of CV disease (CVD). Prescribed opioid use was defined as opioid use at baseline and/or at the first annual visit (AV1). Cox proportional hazards regression was used to calculate hazard ratios and 95% confidence intervals (95% CI) for associations between opioid use and CVD events following AV1. Of the 17 701 participants included (mean age 75.2 years, 58.2% female), 813 took opioids either at baseline or at AV1. Over a median follow-up period of 3.58 years (IQR 2.50–4.62), CVD events, most notably heart failure hospitalization, occurred in 7% (n = 57) amongst opioid users and 4% (n = 680) amongst non-opioid users. After adjustment for multiple covariates, opiate use was associated with a 1.67-fold (CI 1.26–2.23, $P < 0.001$) increase in the hazard ratio for CVD events.

Conclusions These findings identify opioid use as a non-traditional risk factor for CVD events in community-dwelling older adults.

Keywords Opioids; Cardiovascular disease; Epidemic; Heart failure

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Introduction

Cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease, and heart failure, is a leading cause of death and disability globally.[1] Although there are several traditional risk factors for CVD, including hypertension, smoking, dyslipidaemia, obesity, and diabetes, recent research is exploring the potential impact of non-traditional, potentially modifiable factors.[2]

The respiratory and psychosocial impacts of opioid abuse and overdose are well known; however, limited studies have investigated the potential cardiovascular (CV) effects of prescribed opioid use.[3–7] Findings from these limited studies remain conflicting, with some suggesting opioids increase the risk of CVD events, whereas others propose a potential cardioprotective effect.[8–10] Furthermore, opioids are frequently used as analgesia for the acute management of CV events, such as acute myocardial infarction (MI) to relieve chest pain

and discomfort. Their analgesic effects are theoretically through the reduction in blood pressure and heart rate, thereby decreasing myocardial oxygen demand. Although their impact on CV outcomes is limited, increasing evidence suggests that their use in patients presenting with acute coronary syndromes is associated with higher mortality even after risk adjustment and matching.[11–13]

Despite the current uncertainty around the CV effects of chronic opioid use, the use of opioids is increasing in the geriatric community-dwelling population worldwide.[14] In 2017, opioid prescription was highest (26.8%) amongst people aged at least 65 years in the USA.[15] This high prevalence can largely be attributed to the frequent occurrence of chronic non-cancer pain, which ranges between 25 and 50% in this population.[16] The most common causes of chronic non-cancer pain in this population include osteoarthritis, musculoskeletal and neuropathic pain.[17] Prescribed opioids have a high potential to lead to psychological and physical dependence, with one in four adults who take opioid prescriptions for chronic non-cancer pain struggling with lifelong addiction.[18,19] In 2018, at least 1 million elderly adults were estimated as having a substance use disorder with a concurrent rise in admission rates for substance use disorders in this population.[20,21]

This study sought to describe the prevalence of chronic opioid use amongst community-dwelling people aged at least 65 years and the risk of CV outcomes associated with their use.

Methods

Data source and study population

The trial design, methods, and main results of the ASPREE trial have been published previously.[22–25] The Aspirin in Reducing Events in the Elderly (ASPREE) trial was an international, multicentre, double-blind, randomized controlled clinical trial that compared daily 100 mg aspirin with placebo. Participants were community-dwelling adults living in Australia and the USA who were ≥70 years of age (≥65 years amongst US participants) and had no prior CVD events, or dementia, and major physical disability or any other chronic illness expected to limit survival to less than 5 years. The ASPREE trial concluded in 2017, after a median follow-up of 4.7 years, and the study included annual clinic visits.[22–25]

Ascertainment of regular opioid exposure

All participants enrolled into the ASPREE trial completed two baseline visits to finalize eligibility and, after randomization, were seen annually for trial assessments conducted by trained staff. Opioid use was defined as use either at baseline or at the AV1. Participants who started opioids before AV1 and had a new diagnosis of cancer were adjusted for in the analysis. Information on opioid use (including types), along with the use of other concomitant prescription medications, were recorded at ASPREE trial entry and updated at annual intervals during follow-up. Use of non-steroidal anti-inflammatory drugs (NSAIDs) was defined as use of salicylic acid and derivatives or non-steroidal anti-inflammatories (WHO ATC codes N02BA and MO1A).[26] The information was collected by asking participants to bring all current or recently used medications to study visits.

Outcome measures

The primary outcome of the ASPREE trial was disability-free survival, and results have been previously reported.[24] Incident CVD was a prespecified, composite secondary endpoint of ASPREE, consisting of fatal coronary heart disease (death from MI, sudden cardiac death, cardiac failure death, or any other death in which the underlying cause was considered to be coronary heart disease), non-fatal MI, fatal or non-fatal stroke (haemorrhagic or ischaemic), non-coronary cardiac or vascular death, or hospitalization for heart failure.[22] All CVD events were adjudicated by a panel of experts blinded to treatment group assignment.

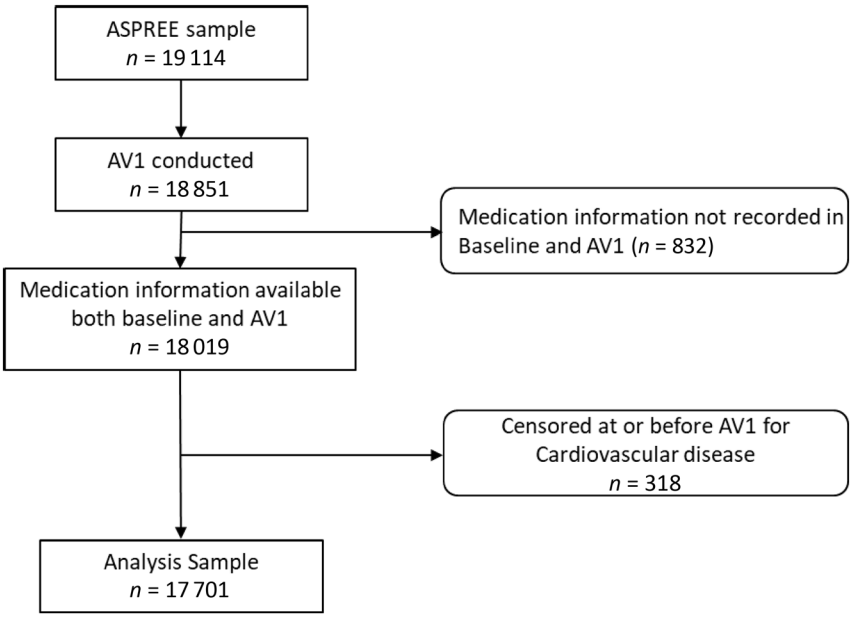
In this post hoc analysis, we primarily used the prespecified composite CVD endpoint to explore the association between opioid use and incident CVD events.[23] This outcome was measured after AV1 and any CVD events that occurred before AV1 were censored (*Figure 1*). We also explored the association of baseline opioid use with individual endpoints—ischaemic stroke, heart failure hospitalization, MI (non-fatal/fatal), and all-cause mortality.

Statistical analyses

Continuous variables are presented as means ± standard deviations. Variables that were non-normally distributed are recorded as median [interquartile range (IQR)]. Categorical data are presented as counts and percentages. For comparisons between opioid users and non-users, Pearson's chi square (x^2) test or Fisher's exact test was used as appropriate for categorical variables. *T*-tests (for symmetrically distributed data) or non-parametric tests (e.g. Mann–Whitney tests for non-symmetrically distributed data) were used for continuous variables.

Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for time to the first CVD event occurring during the follow-up period after AV1. The unadjusted Cox proportional hazards model was followed with adjustment for accumulating sets of covariates, which included age and sex (Model 1); BMI,

Figure 1 Analysis sample. Of the 19 114 individuals enrolled into ASPREE, 18 851 attended AV1; of these individuals, 18 019 had medication information available at baseline and AV1. There were 318 individuals who were censored at or before AV1 for CVD, resulting in a final sample of 17 701.



diabetes, hypertension, eGFR, smoking (current), country of residence, ethnicity, and aspirin use (Model 2); depression, frailty, dyslipidaemia, and other NSAID use (Model 3); and cancer (Model 4). In addition, cumulative incidence of the CVD endpoint as well as the other individual endpoints was computed according to the complement of the Kaplan–Meier estimates of event-free survival. Cumulative incidence functions were computed for individual endpoints to account for competing risks. Analyses were repeated and stratified by sex.

Further, propensity-matched samples based on propensity scores was used as a sensitivity analysis to minimize the effect of bias and confounding as well as the difference in the number of participants with or without opioid use at baseline. We used a 1:1 nearest neighbour approach to select similar numbers of samples for both groups. Briefly, the propensity score was generated for each participant based on key baseline characteristics: age, sex, hypertension, obesity, diabetes, dyslipidaemia, depression, and frailty status (Model 1) and further adjusted for smoking and other NSAID use (Model 2).

Results

Of the original 19 114 individuals enrolled into ASPREE, 18 851 attended AV1; of these individuals, 18 019 had medication information available at baseline and AV1. There were 318 individuals who were censored at, or before AV1 for CVD, resulting in a final sample of 17 701 (*Figure 1*). In the sub-analysis of participants who had started opioid use at AV1 (n = 342), 300 had been diagnosed with cancer before AV1.

The mean (SD) age of included participants was 75.1 (4.5) years and 58.2% females. Prescribed opioids either at baseline or at AV1 were present in 813 participants. *Table 1* shows the baseline characteristics clinical characteristics of the participants, stratified by opioid users and non-users. Compared with participants who did not take opioids, those who used opioids were more likely to be female (70.7% vs. 56.6%, $P < 0.001$); have diabetes (13.5% vs. 10.9%, $P = 0.018$), hypertension (81.1% vs. 75.3%, $P < 0.001$), obesity (45.8% vs. 29.3%, $P < 0.001$), and smoke (6.9% vs. 3.4%, $P < 0.001$); and demonstrated increased frailty (62% vs. 40.3%, $P < 0.001$).

Opioid users also used more concomitant medications (*Tables 2* and S1), including beta-blockers (10.9% vs. 8.3%, $P = 0.007$), angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) (52.5% vs. 43.2%, $P < 0.001$), lipid-lowering drugs (40.6% vs. 35.2%, $P = 0.002$), psychotropic medications (5.2% vs. 2.4%, $P < 0.001$), and chemotherapy agents (3.9% vs. 1.8%, $P < 0.001$). This group were more likely to use other analgesics such as NSAIDs (43.1% vs. 20.5%, $P < 0.001$) and pregabalin (14.9 vs. 2.2%, $P < 0.001$). In addition, opioid users also had increased usage of anxiolytics including benzodiazepines (13.9% vs. 5.2%, $P < 0.001$).

Following AV1, over a median follow-up period of 3.58 years (IQR 2.50–4.62), CVD events occurred in more opi-

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Table 1 Patient baseline characteristics based on baseline opioid use

	All (n = 17 701)	Opioid use		
		Yes (n = 813)	No (n = 16 888)	P-value
Age (mean ± SD), years	75.1 ± 4.5	75.80 ± 4.76	75.12 ± 4.50	<0.001
Male (%)	42.8	29.3	43.4	<0.001
Weight (mean ± SD), (kg)	77.0 ± 15	80.0 ± 17.1	76.9 ± 14.9	<0.001
Height (m)	1.65 ± 0.1	1.63 ± 0.1	1.65 ± 0.1	<0.001
BMI (kg/m^2)	28.1 ± 4.7	30.2 ± 5.9	28.1 ± 4.6	<0.001
BSA(m^2)	3.6 ± 0.8	3.6 ± 0.9	3.6 ± 0.8	0.093
Diabetes (%)	11.0	13.5	10.9	0.001
Hypertension (%)	75.6%	81.1%	75.3%	<0.001
Systolic blood pressure (mmHg)	139.3 ± 16.5	138.4 ± 17.8	139.3 ± 16.4	0.417
Diastolic blood pressure (mmHg)	77.3 ± 10	76.7 ± 11	77.3 ± 10	0.411
Baseline heart rate	70.8 ± 10.7	72.2 ± 11.2	70.7 ± 10.7	0.051
Baseline eGFR	72.7 ± 13.9	72.0 ± 15.0	73.0 ± 13.8	0.149
Smoking status (%)	3.6%	6.9%	3.4%	<0.001
Familial history of coronary artery disease (%)	61.3%	62.5%	61.3%	0.49
Dyslipidaemia (%)	66.2%	66.7%	66.1%	0.757
Total cholesterol (mmol/L)	5.23 ± 0.98	5.19 ± 1.05	5.23 ± 0.98	0.006
HDL (mmol/L)	1.58 ± 0.46	1.60 ± 0.50	1.58 ± 0.46	0.500
LDL (mmol/L)	3.03 ± 0.88	2.90 ± 0.92	3.04 ± 0.87	<0.001
Triglycerides (mmol/L)	1.33 ± 0.66	1.51 ± 0.82 s	1.32 ± 0.65	<0.001
Frailty				<0.001
Not frail	58.8%	38.0%	59.8%	
Pre-frail	39.1%	55.1%	38.3%	
Frail	2.2%	6.9%	2.0%	

BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; HDL, high-density lipoproteins; LDL, low-density lipoproteins.
Hypertension: Based on patient's Participant Medical History-Baseline form. Diabetes: Based on patient's Participant Medical History-Baseline form. Frailty: Baseline frailty according to modified Fried criteria.

Table 2 Concomitant medication exposure

	All (n = 17 701)	Opioid use		
		Yes (n = 813)	No (n = 16 888)	P-value
Aspirin (%)	11	12.7	10.9	0.120
Beta-blockers (%)	8.4	10.9	8.3	0.007
ACE inhibitors/ARB (%)	43.6	52.5	43.2	<0.001
Anti-hyperlipidaemics (%)	35.5	40.6	35.2	0.002
NSAID use (%)	21.5	43.1	20.5	<0.001
Benzodiazepine (%)	5.6	13.9	5.2	<0.001
Psychotropic medications (%)	2.5	5.2	2.4	<0.001
Pregabalin (%)	2.8	14.9	2.2	<0.001
Chemotherapy (%)	1.9	3.9	1.8	<0.001
Alcohol use				<0.001
Current (%)	76.8	70.8	77.1	
Former (%)	5.8	7.8	5.7	
Never (%)	17.4	21.4	17.2	

NSAID use: Salicylic acid and derivatives or non-steroidal anti-inflammatories (WHO ATC codes N02BA and MO1A); benzodiazepine (WHO ATC codes NO5CD); psychotropic medications (WHO ATC codes NO5A); pregabalin (WHO ATC codes NO3AX); chemotherapy (WHO ATC codes LO1).[21]

oid users compared to non- users: 21.2 per 1000-person-years vs. 11.5 per 1000-person-years, $P < 0.001$. In all, 57 (7%) opioid users compared with 680 (4%) of non-users experienced one of the components of the composite CVD endpoint (*Figure 2* and *Table 3*). In the univariate analysis (Model 1), a significantly increased risk for CVD events was observed, which persisted when analyses were adjusted for body mass index (BMI), diabetes, hypertension, estimated glomerular filtration rate (eGFR), smoking (current), country of residence, ethnicity, and aspirin use (Model 2) and further adjusted for depression, frailty, dyslipidaemia, and other NSAID use (Model 3) and cancer (Model 4). The increased risk of CVD events continued even after adjustment for other concomitant substances such as alcohol and benzodiazepines and the use of other medications such as psychotropic medications, pregabalin, and chemotherapy agents (Model 5) (*Table 3*). Propensity-matched findings (*Table 4*) were consistent, with an increased incidence of CVD events associated

Figure 2 Cumulative incidence of first CVD event occurring after AV1. Following AV1, CVD events occurred in more opioid users compared with non-users: 21.2 per 1000-person-years vs. 11.5 per 1000-person-years, P < 0.001. In all, 57 (7%) opioid users compared with 680 (4%) of non-users experienced one of the components of the composite CVD endpoint. AV1, Annual Visit 1; CVD, cardiovascular.

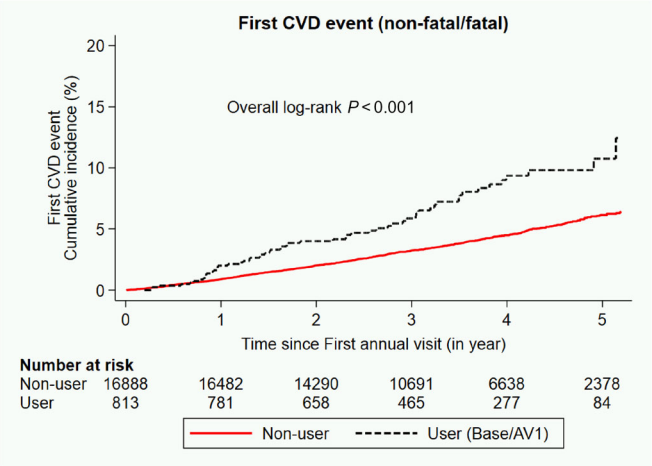

Table 3 Association between opioid use and CVD events occurring after AV1

	All			Male			Female		
	Opioid use			Opioid use			Opioid use		
CVD, *N*	Yes (*n* = 813)	No (*n* = 16 888)	*P*-value	Yes (*n* = 238)	No (*n* = 7330)	*P*-value	Yes (*n* = 575)	No (*n* = 9558)	*P*-value
Observed CVD events, *N* (%)	57 (7.0%)	680 (4.0%)		18 (7.6%)	386 (5.3%)		39 (6.8%)	294 (3.1%)	
Event rate per 1000-person-years	21.2	11.5	$P < 0.001$	24.3	15.2	$P = 0.067$	20.1	8.7	$P < 0.001$
Hazard ratio (95% CI)									
Model 1	1.94 (1.48–2.54)		$P < 0.001$	1.56 (0.97–2.50)		$P = 0.067$	2.19(1.57–3.06)		$P < 0.001$
Model 2	1.82 (1.37–2.41)		$P < 0.001$	1.37 (0.83–2.27)		$P = 0.222$	2.12 (1.50–2.99)		$P < 0.001$
Model 3	1.69(1.26–2.24)		$P < 0.001$	1.26 (0.75–2.10)		$P = 0.381$	1.95(1.37–2.77)		$P < 0.001$
Model 4	1.67 (1.26–2.23)		$P < 0.001$	1.26 (0.75–2.10)		$P = 0.38$	1.93 (1.36–2.74)		$P < 0.001$
Model 5	1.67(1.25–2.23)		$P < 0.001$	1.30 (0.77–2.17)		0.325	1.90(1.33–2.72)		$P < 0.001$

CVD, cardiovascular disease.
Model 1: Adjusted for age and gender. Model 2: Model 1 plus adjustment for BMI, diabetes, hypertension, eGFR, smoking (current), country of residence, ethnicity, and aspirin use. Model 3: Model 2 plus adjustment for depression, frailty, dyslipidaemia, and other NSAID use. Model 4: Model 3 plus adjustment for cancer. Model 5: Plus adjustment for alcohol use, concomitant use of benzodiazepine, psychotropic medications, pregabalin, and chemotherapy.

Table 4 CVD amongst propensity-matched sample

	Coefficient	95%CI
CVD events, median (IQR)		
Model 1[a]	1.74	1.13, 2.67 ($P = 0.011$)
Model 2[b]	1.88	1.21, 2.91 ($P = 0.005$)

[a]Unadjusted.
[b]Adjusted for smoking and other NSAIDs.

with opioid use (HR = 1.74, CI 1.13–2.67, $P = 0.011$) compared with non-users (Model 1). The propensity-matched sample was further adjusted for smoking and other NSAID use with an HR 1.88 (IQR 1.21–2.91, $P = 0.005$) (Model 2).

In the analysis of other individual end points following AV1, there were higher heart failure hospitalizations [18 (2.2%) vs. 123 (0.72%), $P < 0.001$], ischaemic strokes [17 (2.1%) vs. 224 (1.3%), $P < 0.001$], and deaths [67 (8.2%) vs. 762 (4.5%), $P < 0.001$] in opioid users compared with the non-users (*Table 5*). The incidence of heart failure hospitalizations and deaths remained significantly higher in opioid users despite full covariate adjustment. Myocardial infarction (non-fatal/fatal) was only significantly higher amongst opioid users in Model 1 HR = 1.77(1.11–2.83) P < 0.001 and Model 2 HR:1.68(1.03–2.73) $P < 0.001$, however not after further covariate analyses in Model 3 and 4. *Figure 3* shows the

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Table 5 Association between opioid use and individual components of CVD events occurring after AV1

	All			Male			Female		
	Opioid use			Opioid use			Opioid use		
Heart failure, *N*	Yes (*n* = 813)	No (*n* = 16 888)	*P*-value	Yes (*n* = 238)	No (*n* = 7330)	*P*-value	Yes (*n* = 575)	No (*n* = 9558)	*P*-value
Observed CVD events, *N* (%)	18(2.2%)	123 (0.73%)		6 (2.5%)	68 (0.93%)		12(2.1%)	55 (0.58%)	
Event rate per 1000-person-years	6.6	2.0	$P < 0.001$	7.9	2.6	$P = 0.067$	6.1	1.6	$P < 0.001$
Hazard ratio (95% CI)									
Model 1	3.27 (1.99–5.39)		$P < 0.001$	2.80 (1.21–6.47)		$P = 0.016$	3.58(1.92–6.68)		$P < 0.001$
Model 2	2.72 (1.61–4.58)		$P < 0.001$	2.26 (0.089–5.69)		$P = 0.085$	2.94(1.54–5.60)		$P = 0.001$
Model 3	2.37(1.39–2.36)		$P < 0.001$	1.79 (0.69–4.67)		$P = 0.231$	2.62(1.35–5.09)		$P = 0.005$
Model 4	2.35 (1.38–4.02)		$P = 0.002$	1.76 (0.68–4.58)		$P = 0.245$	2.61 (1.35–5.08)		$P = 0.005$
Model 5	2.36 (1.36–4.07)		0.002	1.86 (0.71–4.87)		0.204	2.58(1.30–5.10)		$P = 0.006$
	All			Male			Female		
	Opioid use			Opioid use			Opioid use		
Stroke, *N*	Yes (*n* = 813)	No (*n* = 16 887)	*P*-value	Yes (*n* = 238)	No (*n* = 7329)	*P*-value	Yes (*n* = 575)	No (*n* = 9558)	*P*-value
Observed CVD events, *N* (%)	17 (2.1%)	224 (1.3%)		3 (7.9%)	126 (17.2%)		14 (2.4%)	98 (1.0%)	
Event rate per 1000-person-years	6.2	3.7	$P = 0.056$	4.0	4.9	$P = 0.778$	7.1	2.9	$P = 0.004$
Hazard ratio (95% CI)									
Model 1	1.73 (1.05–2.83)		$P < 0.001$	0.80 (0.25–2.51)		$P = 0.70$	2.34 (1.34–4.10)		$P = 0.003$
Model 2	1.66(0.99–2.78)		$P = 0.053$	0.80 (0.25–2.53)		$P = 0.70$	2.20 (1.22–3.96)		$P = 0.008$
Model 3	1.61 (0.96–2.72)		$P = 0.073$	0.79 (0.25–2.52)		$P = 0.69$	2.15(1.18–3.92)		$P = 0.012$
Model 4	1.60 (0.95–2.70)		$P = 0.078$	0.79 (0.25–2.52)		$P = 0.69$	2.09 (1.15–3.81)		$P = 0.016$
Model 5	1.65 (0.97–2.79)		$P = 0.063$	0.82(0.26–2.64)		P = 0.742	2.17(1.18–3.98)		$P = 0.013$
	All			Male			Female		
	Opioid use			Opioid use			Opioid use		
Myocardial infarction (non-fatal/fatal), *N*	Yes (*n* = 813)	No (*n* = 16 887)	*P*-value	Yes (*n* = 238)	No (*n* = 7329)	*P*-value	Yes (*n* = 575)	No (*n* = 9558)	*P*-value
Observed CVD events, *N* (%)	19(2.3%)	262 (1.6%)		9(3.8%)	173(2.4%)		10 (1.7%)	89 (0.93%)	
Event rate per 1000-person-years	6.9	4.4	$P = 0.067$	11.9	6.8	$P = 0.117$	5.0	2.6	$P = 0.066$
Hazard ratio (95% CI)									
Model 1	1.77 (1.11–2.83)		$P < 0.001$	1.73(0.89–3.38)		$P = 0.109$	1.80(0.94–3.46)		$P = 0.078$
Model 2	1.68 (1.03–2.73)		$P < 0.001$	1.54(0.75–3.14)		$P = 0.24$	1.78 (0.91–3.46)		$P = 0.091$
Model 3	1.57(0.96–2.57)		$P = 0.074$	1.40 (0.67–2.90)		$P = 0.368$	1.70(0.86–3.36)		$P = 0.127$
Model 4	1.57 (0.96–2.58)		$P = 0.073$	1.40(0.68–2.90)		$P = 0.37$	1.69(0.86–3.34)		$P = 0.13$
Model 5	1.52 (0.92–2.51)		$P = 0.102$	1.38(0.66–2.89)		$P = 0.39$	1.59 (0.79–3.18)		$P = 0.192$
	All			Male			Female		
	Opioid use			Opioid use			Opioid use		
All-cause mortality, *N*	Yes (*n* = 813)	No (*n* = 16 888)	*P*-value	Yes (*n* = 238)	No (*n* = 7330)	*P*-value	Yes (*n* = 575)	No (*n* = 9558)	*P*-value
Observed CVD events, *N* (%)	67 (8.2%)	762 (4.5%)		27 (11.3%)	423 (5.8%)		40 (7.0%)	339 (3.5%)	
Event rate per 1000-person-years	23.3	12.3	$P < 0.001$	34.2	4.9	$P < 0.001$	19.2	2.9	$P < 0.001$
Hazard ratio (95% CI)									

(*Continues*)

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Table 5 (continued)

All-cause mortality, *N*	All			Male			Female		
	Opioid use			Opioid use			Opioid use		
	Yes (n = 813)	No (n = 16 888)	*P*-value	Yes (n = 238)	No (n = 7330)	*P*-value	Yes (n = 575)	No (n = 9558)	*P*-value
Model 1	1.98 (1.54–2.55)		$P < 0.001$	2.13(1.45–3.15)		$P < 0.001$	1.90(1.37–2.63)		$P < 0.001$
Model 2	1.97 (1.52–2.56)		$P < 0.001$	1.97 (1.30–2.99)		$P = 0.002$	1.96 (1.40–2.73)		$P < 0.001$
Model 3	1.81(1.39–2.36)		$P < 0.001$	1.90 (1.24–2.91)		$P = 0.003$	1.73(1.23–2.43)		$P = 0.002$
Model 4	1.68 (1.29–2.18)		$P < 0.001$	1.84 (1.20–2.82)		$P = 0.005$	1.55(1.10–2.17)		$P = 0.012$
Model 5	1.63 (1.25–2.14)		$P < 0.001$	1.72(1.11–2.66)		$P = 0.014$	1.55(1.10–2.19)		0.012

cumulative incidence of ischaemic stroke, heart failure hospitalization, MI (non-fatal/fatal), and all-cause mortality.

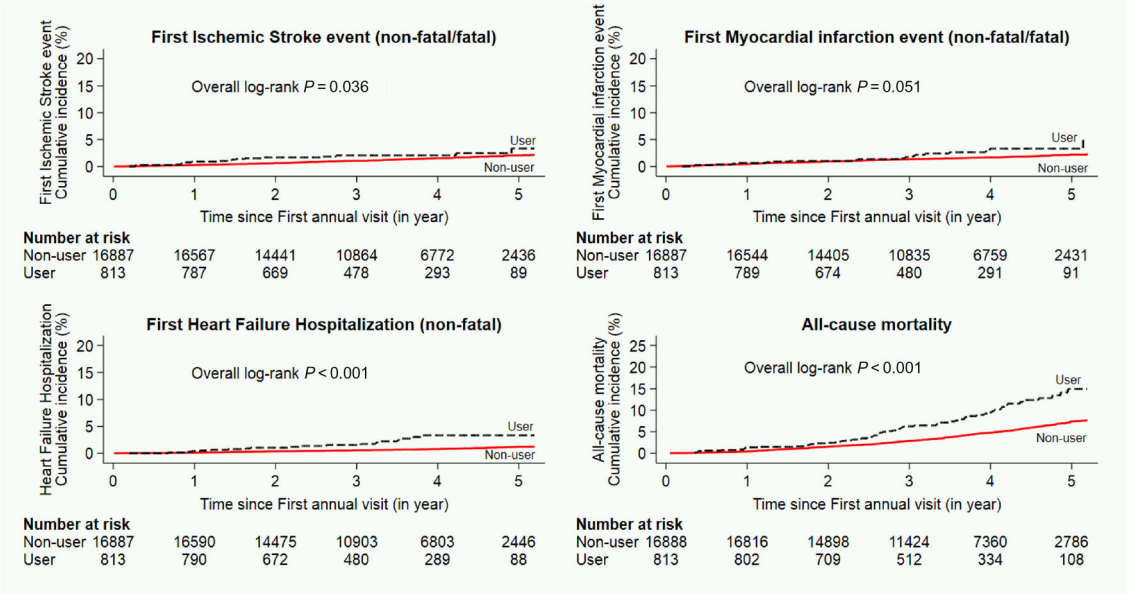
In the sub-analysis by sex, the rates of CVD and their individual components including heart failure, stroke, and all-cause mortality were significantly elevated in female opioid users compared with non-users (*Tables 3 and 5*). The rate of CVD events in females was 20.1 per 1000-person-years vs. 8.7 per 1000-person-years ($P < 0.001$) in opioid users compared with non-users. These findings were consistent across all models: Model 1 HR = 2.19 (IQR 1.57–3.06), $P < 0.001$; Model 2 HR = 2.12 (1.50–2.99), $P < 0.001$; Model 3 HR = 1.95 (IQR 1.37–2.77), $P < 0.001$; Model 4 HR = 1.93 (IQR 1.36–2.74), $P < 0.001$; and Model 5 HR = 1.90 (IQR 1.33–2.72), $P < 0.001$. The HR associated with heart failure, stroke, and all-cause mortality also remained significantly elevated after adjusting for all covariates. This contrasted to the male sub-analysis, whereby the rate of CVD events in male opioid users compared with non-users was not significantly different (24.3 per 1000-person-years vs. 15.2 per 1000-person-years, $P = 0.067$). Furthermore, within the individual components constituting CVD events, only all-cause mortality remained significantly elevated after adjusting for all covariates, HR = 1.84 (IQR 1.20–2.82), $P = 0.005$.

Discussion

In this adjusted post hoc analysis of the ASPREE trial, participants who took opioids were at increased risk of the composite CVD endpoint, which included fatal coronary heart disease, nonfatal MI, stroke, hospitalization for heart failure, or all-cause mortality. The risk of each of the individual endpoints including heart failure, stroke, and all-cause mortality was also significantly elevated in opioid users compared with non-users. We also observed important sex differences in the association of prescribed opioids and CVD endpoints. The impact of opioids on CVD is currently limited to observational data due to the unfeasibility of conducting randomized trials examining this relationship. As such, this study is integral to the growing body of literature highlighting the potential health risk in the use of therapeutic opioids, thereby steering clinical practice away from the prescription of opioids for chronic non-cancer pain, especially for females.

Recent reports have suggested a relationship between opioid use and increased risk of coronary artery disease.[3–5] Li *et al*. reported a 1.28-fold risk of MI in opioid users compared with non- users.[7] Carman *et al*. estimated that the incidence rate ratios for MI and MI/coronary revascularization in a cohort of chronic opioid users versus a matched cohort from the general population was 2.66 (95% CI, 2.3–3.08) and 2.39 (95% CI, 2.15–2.63), respectively.[27] Finally, a recent study by Khodneva *et al*. found that prescribed opioid use

Figure 3 Cumulative incidence of individual components of CVD events occurring after AV1. In the analysis of individual end points following AV1, there were higher heart failure hospitalizations [18 (2.2%) vs. 123 (0.72%), $P < 0.001$], ischaemic strokes [17 (2.1%) vs. 224 (1.3%), $P < 0.001$], and deaths [67 (8.2%) vs. 762 (4.5%), $P < 0.001$] in opioid users compared with the non-users.



was associated with significantly increased risk (1.24-fold) of CV death.[28]

Although the present study is associative in nature, findings are biologically plausible. A prior histopathologic study of myocardial samples from subjects dying from illicit drug-related deaths demonstrated a strong relationship between opioid use and myocardial fibrosis.[29] This observation would be consistent with the present study's finding of a significant increase in heart failure events in opioid users. Opioid receptors in human myocardium may also play a role in neural transmission and regulation of myocardial function.[30] Chronic and higher doses of opioid use have been shown to increase myocardial ischaemia and oxidative stress via opioid receptor-dependent mechanisms, which interfere with cellular function.[29] In rat myocardium, a dose-dependent increased susceptibility to reperfusion injury after administration of remifentanil has been identified.[31] Reese *et al.* noted increased inflammatory markers such as C-reactive protein and accelerated atherosclerosis in chronic opioid users.[32] Other potential pathophysiologic mechanisms include increased platelet aggregation through stimulation of the platelet/endothelial cell adhesion molecule 1 and glycoprotein IIb expression, thereby decreasing the protective effects of aspirin and perhaps providing an explanation for the observed increase in stroke rate.[33]

The relationship between chronic opioid use and the development of heart failure could potentially be attributable to the development of sleep-disordered breathing including sleep apnoea with long-term opioid use.[34] In a recent study, Solhjoo demonstrated that nocturnal oxygen saturation was significantly reduced in a dose dependent manner in patients on chronic methadone therapy.[35] Central sleep apnoea is present in 40% of patients with heart failure and is a strong independent marker of mortality.[36,37] The relationship between obstructive sleep apnoea and heart failure is complex but is likely attributable to increased sympathetic and neurohumoral activation secondary to hypoxia, coupled with increased oxidative stress, resulting in significant CV morbidity.[38–41]

Amongst participants using opioids, the use of concomitant NSAIDs was significantly higher (43.1% vs. 20.5%, $P < 0.001$). The use of NSAIDs is independently associated with an increase in the absolute risk of adverse CV events,[42–44] with higher doses and frequencies increasing the risk of MI.[45–47] Furthermore, the combination of prescribed opioid use with acetaminophen has been more strongly associated with CV endpoints compared with non-users of both.[27]

Chronic opioid use is often associated with polysubstance abuse, which could be a potential contributor to the development of heart failure and poorer outcomes in opioid users.[48–50] Long-term excess alcohol consumption is a known risk factor for the development of dilated cardiomyopathy.[51] Specka *et al.* reported that 90% of opioid users consumed at least one other psychoactive substance at admission into their study. Amongst those, alcohol and benzodiazepines were found to be the most common.[52] The use of concomitant substances with opioids could be attributed to the attenuation in processing of painful stimuli through sympathetic stimulation, hypothalamic–pituitary–adrenal axis dysregula-

tion, and pro-inflammatory immune-system activation, resulting in an increased sensitivity to pain or decreased pain tolerance.[53,54] The relationship between chronic opioid use and polysubstance abuse in our cohort was variable. Participants using opioids were less likely to be current alcohol drinkers (70.8% vs. 77.1%, $P < 0.001$), and a greater percentage had never used alcohol (21.4% vs. 17.2%, $P < 0.001$). However, the concomitant use of benzodiazepines was significantly higher in opioid users compared with non-users (13.9% vs. 5.2%, $P < 0.001$). The relationship between anxiolytics such as benzodiazepine use and heart failure has limited evidence.[55] However, Zwas *et al*. noted that the treatment of heart failure patients with anxiolytics portended a worse prognosis irrespective of concomitant depression, and it remained a predictor of mortality.[56] The possible confounding effect of both alcohol and benzodiazepine use was accounted for in the multi-variate analysis in Model 5. Despite this, chronic opioid use was still associated with increased CVD events, HR = 1.67(IQR 1.25–2.23), $P < 0.001$.

Mood, sleep, and personality disorders can also aggravate pain symptoms and are frequently comorbid in patients with chronic pain.[57–61] This was reflected in our study whereby participants using opioids had an increased use of psychotropic medications (5.2% vs. 2.4%, $P < 0.001$). Although mental health disorders have been independently associated with an increased risk of CV mortality, the use of psychotropic drugs themselves are also associated with an increased risk of sudden cardiac death.[62,63] Most notably, clozapine treatment is consistently linked with the development myocarditis and cardiomyopathy, with the risk of developing cardiomyopathy five times greater in patients treated with clozapine than the general population.[64,65] Depression, which is prevalent in 5–10% of community-dwelling adults aged 65 years and older, has been accepted as a psychosocial risk factor for coronary heart disease with the 2016 European Guidelines on CVD prevention in clinical practice recommending screening and treatment of depression.[66,67] Depression and the use of psychotropic medications were accounted for in Model 3 and Model 5 of the multi-variate analysis (*Table 3*); however, the risk of CVD events associated with opioid use was still elevated.

Sex differences in the association of CVD and opioid use, more pronounced in females, have been previously reported.[28] Compared with males, females are also more likely to be prescribed opioids or prescribed higher doses and to use opioids for longer periods of time.[57] One explanation for the higher CVD risks in female opioid users may be related to the finding that chronic opioid use decreases hypothalamic–pituitary–ovarian axis activity and may decrease oestrogen levels, potentially increasing CVD risk in females.[68] In the REGARDS study, female opioid users were also more likely to use combined opioid–acetaminophen preparations than males prescribed opioids. The present study findings concurred with this sex difference, with the rates of CVD events in female opioid users being significantly higher compared with non-users in all models of the multi-variable analyses.[28]

A major study strength is the large sample of community-dwelling participants, who, after robust screening at baseline, had no prior CVD events. The data were also obtained from a contemporary randomized trial in a large older population with age and sex distributions comparable with population norms.[69] The ASPREE trial was subject to rigorous quality control, and all endpoints were formally adjudicated by experts blinded to treatment allocation.[22–25,70]

Study limitations

Due to the observational design of the present study, causal relations between opioid use and the incidence of CV events cannot be established. Opioid use was defined as documented use either at baseline and/or AV1; however, the specific opioids were not included as overall duration and cumulative dose of opioid use cannot be ascertained. Ideally, a dose–response analysis would have been included to help strengthen the association for causality. Prescribed opioid use at subsequent annual visits was not included, and the measurement of incident CVD events was measured after AV1 to account for immortal-time bias. Furthermore, some participants may have started or discontinued opioids after AV1, which may impact results. In the sub-analysis of patients who started opioid use at AV1 (n = 342), 300 had been diagnosed with cancer prior to AV1. However, the diagnosis of cancer prior to AV1 has been adjusted for in Model 4. Despite thorough attempts to control for extensive confounders in the multi-variate analysis, there are still unmeasured confounders. For example, we did not assess the effect of chronic pain per se on CV outcomes. As such, residual confounding bias cannot be ruled out.

Conclusions

Amongst community-dwelling adults ≥65 years of age, opioid use, especially in women, may be associated with a higher incidence of CV events, stroke, heart failure hospitalization, and all-cause mortality. The study's observational design limits causal inferences but strikes a cautionary note for all medical practitioners to limit the prescription of opioids in the setting of non-cancer pain. Further research needs to be undertaken to fill the knowledge gaps surrounding the use of opioids in older individuals.

Conflict of interest

The remaining authors have nothing to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Concomitant Medication exposure.
Table S2. CVD among propensity matched samples.
Table S2. Association between opioid use and individual components of CVD events occurring after AV1.

References

1. International WHO. Cardiovascular diseases (CVDs) 2021. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (17 May 2021).
2. Ogungbe O, Akil L, Ahmad HA. Exploring unconventional risk-factors for cardiovascular diseases: Has opioid therapy been overlooked? *Int J Environ Res Public Health*. 2019; **16**: 2564.
3. Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. *Ann Intern Med*. 2011; **155**: 325–328.
4. McCabe SE, West BT, Boyd CJ. Medical use, medical misuse, and nonmedical use of prescription opioids: Results from a longitudinal study. *Pain*. 2013; **154**: 708–713.
5. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. 2010; **363**: 1981–1985.
6. Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, Schneeweiss S. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med*. 2010; **170**: 1979–1986.
7. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *J Intern Med*. 2013; **273**: 511–526.
8. Rawal H, Patel BM. Opioids in cardiovascular disease: Therapeutic options. *J Cardiovasc Pharmacol Ther*. 2018; **23**: 279–291.
9. Tanaka K, Kersten JR, Riess ML. Opioid-induced cardioprotection. *Curr Pharm Des*. 2014; **20**: 5696–5705.
10. Aghadavoudi O, Eizadi-Mood N, Najarzadegan MR. Comparing cardiovascular factors in opium abusers and non-users candidate for coronary artery bypass graft surgery. *Adv Biomed Res*. 2015; **4**: 12.
11. Marmor M, Penn A, Widmer K, Levin RI, Maslansky R. Coronary artery disease and opioid use. *Am J Cardiol*. 2004; **93**: 1295–1297.
12. Abdi A, Basgut B. An evidence-based review of pain management in acute myocardial infarction. *Journal of Cardiology and Clinical Research*. 2016; **4**: 1067.
13. Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV Jr, Gibler WB, Peterson ED, CRUSADE Investigators. Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the CRUSADE quality improvement initiative. *Am Heart J*. 2005; **149**: 1043–1049.
14. Sites BD, Beach ML, Davis MA. Increases in the use of prescription opioid analgesics and the lack of improvement in disability metrics among users. *Reg Anesth Pain Med*. 2014; **39**: 6–12.
15. Hoots BE, Xu L, Kariisa M, Wilson NO, Rudd RA, Scholl L, Schieber L, Seth P. CDC National Centre for Injury Prevention and Control 2018 annual surveillance report of drug-related risks and outcomes. 2018.
16. Ferrell BA. Managing pain and discomfort in older adults near the end of life. Annals of Long-Term Care. The American Geriatrics Society Annual Scientific Meeting; May 14, 2003; Baltimore, MD. 2003.
17. Pergolizzi J, Boger RH, Budd K, Dahan A, Erdine S, Hans G, Kress HG, Langford R, Likar R, Raffa RB, Sacerdote P. Opioids and the management of chronic severe pain in the elderly: Consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008; **8**: 287–313.
18. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart WF. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*. 2010; **105**: 1776–1782.
19. Kosten TR, George TP. The neurobiology of opioid dependence: Implications for treatment. *Sci Pract Perspect*. 2002; **1**: 13–20.
20. Results from the 2018 National Survey on Drug Use and Health: Detailed tables. 2021 [cited 2021 20 June]. https://www.samhsa.gov/data/
21. Chhatre S, Cook R, Mallik E, Jayadevappa R. Trends in substance use admissions among older adults. *BMC Health Serv Res*. 2017; **17**: 584.
22. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, Reid CM, Lockery JE, Kirpach B, Storey E, Shah RC, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Johnston CI, Ryan J, Radziszewska B, Jelinek M, Malik M, Eaton CB, Brauer D, Cloud G, Wood EM, Mahady SE, Satterfield S, Grimm R, Murray AM, ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med*. 2018; **379**: 1509–1518.
23. McNeil JJ, Woods RL, Nelson MR, Reid CM, Kirpach B, Wolfe R, Storey E, Shah RC, Lockery JE, Tonkin AM, Newman AB, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Ryan J, Radziszewska B, Grimm R, Murray AM, ASPREE

Investigator Group. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med*. 2018; **379**: 1499–1508.
24. Group AI. Study design of ASPirin in reducing events in the elderly (ASPREE): A randomized, controlled trial. *Contemp Clin Trials*. 2013; **36**: 555–564.
25. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, Kirpach B, Shah RC, Ives DG, Storey E, Ryan J, Tonkin AM, Newman AB, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Radziszewska B, Grimm R, Murray AM, ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med*. 2018; **379**: 1519–1528.
26. ATC Code: Anatomical Therapeutic Chemical Classification System. [cited 2020 August 20]. https://www.atccode.com
27. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. *Pharmacoepidemiol Drug Saf*. 2011; **20**: 754–762.
28. Khodneva Y, Muntner P, Kertesz S, Kissela B, Safford MM. Prescription opioid use and risk of coronary heart disease, stroke, and cardiovascular death among adults from a prospective cohort (REGARDS study). *Pain Med*. 2016; **17**: 444–455.
29. Seltenhammer MH, Marchart K, Paula P, Kordina N, Klupp N, Schneider B, Fitzl C, Risser DU. Micromorphological changes in cardiac tissue of drug-related deaths with emphasis on chronic illicit opioid abuse. *Addiction*. 2013; **108**: 1287–1295.
30. Sobanski P, Krajnik M, Shaqura M, Bloch-Boguslawska E, Schafer M, Mousa SA. The presence of mu-, delta-, and kappa-opioid receptors in human heart tissue. *Heart Vessels*. 2014; **29**: 855–863.
31. Mei B, Wang T, Wang Y, Xia Z, Irwin MG, Wong GT. High dose remifentanil increases myocardial oxidative stress and compromises remifentanil infarct-sparing effects in rats. *Eur J Pharmacol*. 2013; **718**: 484–492.
32. Reece AS. High-sensitivity CRP in opiate addiction: Relative and age-dependent elevations. *Cardiovasc Toxicol*. 2012; **12**: 149–157.
33. Malinin AI, Callahan KP, Serebruany VL. Paradoxical activation of major platelet receptors in the methadone-maintained patients after single pill of aspirin. *Thromb Res*. 2001; **104**: 297–299.
34. Correa D, Farney RJ, Chung F, Prasad A, Lam D, Wong J. Chronic opioid use and central sleep apnea: A review of the prevalence, mechanisms, and perioperative considerations. *Anesth Analg*. 2015; **120**: 1273–1285.
35. Solhjoo S, Punjabi NM, Ivanescu AE, Crainiceanu C, Gaynanova I, Wicken C, Buckenmaier C III, Haigney MC. Methadone destabilizes cardiac repolarization during sleep. *Clin Pharmacol Ther*. 2021; **110**: 1066–1074.
36. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, Giannuzzi P. Prognostic value of nocturnal Cheyne-stokes respiration in chronic heart failure. *Circulation*. 1999; **99**: 1435–1440.
37. Bradley TD, Floras JS. Sleep apnea and heart failure: Part II: Central sleep apnea. *Circulation*. 2003; **107**: 1822–1826.
38. Lavie L. Obstructive sleep apnoea syndrome--an oxidative stress disorder. *Sleep Med Rev*. 2003; **7**: 35–51.
39. Kasasbeh E, Chi DS, Krishnaswamy G. Inflammatory aspects of sleep apnea and their cardiovascular consequences. *South Med J*. 2006; **99**: 58–67 quiz 8–9, 81.
40. Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. *Sleep*. 2003; **26**: 15–19.
41. Fletcher EC. Cardiovascular disease associated with obstructive sleep apnea. *Monaldi Arch Chest Dis*. 2003; **59**: 254–261.
42. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Juni P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis. *BMJ*. 2011; **342**: c7086.
43. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: Nested case-control study. *Lancet*. 2005; **365**: 475–481.
44. Haag MD, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. *Arch Intern Med*. 2008; **168**: 1219–1224.
45. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006; **296**: 1633–1644.
46. Chan AT, Manson JE, Albert CM, Chae CU, Rexrode KM, Curhan GC, Rimm EB, Willett WC, Fuchs CS. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation*. 2006; **113**: 1578–1587.
47. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006; **332**: 1302–1308.
48. Mladenka P, Applova L, Patocka J, Costa VM, Remiao F, Pourova J, Mladěnka A, Karlíčková J, Jahodář L, Vopršalová M, Varner KJ, Štěrba M, TOX-OER and CARDIOTOX Hradec Králové Researchers and Collaborators. Comprehensive review of cardiovascular toxicity of drugs and related agents. *Med Res Rev*. 2018; **38**: 1332–1403.
49. Paratz ED, Cunningham NJ, MacIsaac AI. The cardiac complications of methamphetamines. *Heart Lung Circ*. 2016; **25**: 325–332.
50. Mirijello A, Tarli C, Vassallo GA, Sestito L, Antonelli M, d'Angelo C, Ferrulli A, de Cosmo S, Gasbarrini A, Addolorato G. Alcoholic cardiomyopathy: What is known and what is not known. *Eur J Intern Med*. 2017; **43**: 1–5.
51. Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, Francis GS, Lenihan D, Lewis EF, McNamara DM, Pahl E, Vasan RS, Ramasubbu K, Rasmusson K, Towbin JA, Yancy C. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: A scientific statement from the American Heart Association. *Circulation*. 2016; **134**: e579–e646.
52. Specka M, Bonnet U, Heilmann M, Schifano F, Scherbaum N. Longitudinal patterns of benzodiazepine consumption in a German cohort of methadone maintenance treatment patients. *Hum Psychopharmacol*. 2011; **26**: 404–411.
53. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: Molecular mechanisms and clinical considerations. *Clin J Pain*. 2008; **24**: 479–496.
54. Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers: Correlates of drug type and use status. *J Pain Symptom Manage*. 1994; **9**: 462–473.
55. Sato Y, Yoshihisa A, Hotsuki Y, Watanabe K, Kimishima Y, Kiko T, Kanno Y, Yokokawa T, Abe S, Misaka T, Sato T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Nakazato K, Ishida T, Takeishi Y. Associations of benzodiazepine with adverse prognosis in heart failure patients with insomnia. *J Am Heart Assoc*. 2020; **9**: e013982.
56. Zwas DR, Keren A, Amir O, Gotsman I. Treatment of heart failure patients with anxiolytics is associated with adverse outcomes, with and without depression. *J Clin Med*. 2020; **9**.
57. Conrad R, Schilling G, Bausch C, Nadstawek J, Wartenberg HC, Wegener I, Geiser F, Imbierowicz K, Liedtke R. Temperament and character personality profiles and personality disorders in chronic pain patients. *Pain*. 2007; **133**: 197–209.
58. Goubert L, Crombez G, Van Damme S. The role of neuroticism, pain catastrophizing and pain-related fear in vigilance to pain: A structural equations approach. *Pain*. 2004; **107**: 234–241.
59. Knaster P, Karlsson H, Estlander AM, Kalso E. Psychiatric disorders as assessed with SCID in chronic pain patients: The anxiety disorders precede the onset of pain. *Gen Hosp Psychiatry*. 2012; **34**: 46–52.

60. Ramirez-Maestre C, Lopez Martinez AE, Zarazaga RE. Personality characteristics as differential variables of the pain experience. *J Behav Med*. 2004; **27**: 147–165.
61. Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Arch Gen Psychiatry*. 2008; **65**: 1275–1284.
62. Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *JAMA*. 2007; **298**: 1794–1796.
63. Koponen H, Alaraisanen A, Saari K, Pelkonen O, Huikuri H, Raatikainen MJ, Savolainen M, Isohanni M. Schizophrenia and sudden cardiac death: A review. *Nord J Psychiatry*. 2008; **62**: 342–345.
64. Honkola J, Hookana E, Malinen S, Kaikkonen KS, Junttila MJ, Isohanni M, Kortelainen ML, Huikuri HV. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. *Eur Heart J*. 2012; **33**: 745–751.
65. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009; **360**: 225–235.
66. Blazer DG. Depression in late life: Review and commentary. *J Gerontol A Biol Sci Med Sci*. 2003; **58**: 249–265.
67. Lopez AD, Murray CC. The global burden of disease, 1990-2020. *Nat Med*. 1998; **4**: 1241–1243.
68. Clinic M. How opioid addiction occurs 2018. https://www.mayoclinic.org/diseases-conditions/prescription-drug-abuse/in-depth/how-opioid-addiction-occurs/art-20360372 (30 May 2021).
69. Rhodin A, Stridsberg M, Gordh T. Opioid endocrinopathy: A clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clin J Pain*. 2010; **26**: 374–380.
70. McNeil JJ, Woods RL, Nelson MR, Murray AM, Reid CM, Kirpach B, Storey E, Shah RC, Wolfe RS, Tonkin AM, Newman AB, Williamson JD, Lockery JE, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Trevaks RE, Orchard SG, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Grimm RH, ASPREE Investigator Group. Baseline characteristics of participants in the ASPREE (ASPirin in reducing events in the elderly) study. *J Gerontol A Biol Sci Med Sci*. 2017; **72**: 1586–1593.