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ORIGINAL RESEARCH

Description of Cardiovascular Event Rates in Patients Initiating Chronic Opioid Therapy for Noncancer Pain in Observational Cohort Studies in the US, UK, and Germany

Robert LoCasale · David M. Kern · Pierre Chevalier · Siting Zhou · Soheil Chavoshi · Mark Sostek

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ABSTRACT

Introduction: Previous observational studies in the US suggest that opioid analgesic use increases the risk of cardiovascular (CV) events. The current study provides additional background event rates for five prespecified CV outcomes of interest in patients from three countries.

Methods: Three observational cohort studies were conducted in patients from the US ($N = 17{,}604$), the UK ($N = 9{,}823$), and Germany ($N = 9{,}412$). Patients were new opioid users who had undergone ≥6 months of chronic, continuous therapy. De-identified data were collated from electronic healthcare databases in the respective countries. Demographics, clinical characteristics, and opioid use were examined. Overall rates, prevalence rates in patients with established CV disease, and incidence rates in patients without established CV disease were determined for myocardial infarction (MI), stroke, transient ischemic attack, unstable angina, and congestive heart failure (CHF).

Results: Cardiovascular disease at baseline was more prevalent in US and German patients. Back pain and depression were prevalent preexisting comorbidities. The majority of patients were using various weak opioids (based on receptor affinities), CV medications, and antidepressants. Overall rates by individual CV outcome per 1,000 patient-years by country were greatest for CHF (US 37.2, 95% CI 24.1–40.5), unstable angina (UK 8.2, 95% CI 7.0–9.6), and stroke (Germany 5.3, 95% CI 4.1–6.7). Overall rates for MI were: US, 10.7 (95% CI 9.1–12.5), UK, 6.7 (95% CI 5.6–8.0), and Germany, 2.7 (95% CI 1.9–3.7). Overall rates for each CV outcome, prevalence rates in patients with preexisting CV disease, and incidence rates in patients without established CV disease differed by country. Rates were higher in patients with preexisting CV disease.

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R. LoCasale (✉) · S. Chavoshi · M. Sostek
AstraZeneca, Wilmington, DE, USA
e-mail: robert.locasale@astrazeneca.com

D. M. Kern · S. Zhou
HealthCore, Inc., Wilmington, DE, USA

P. Chevalier
IMS Health, Vilvoorde, Belgium

Conclusions: CV risk for new opioid users with ≥6 months of therapy was increased in patients with established CV disease compared with those without established CV disease, and the risk for specific outcomes differed by country. Assessment of CV safety events of new therapies introduced to chronic opioid users should consider sample size and population heterogeneity in the design of an observational study.

Keywords: Cardiovascular; Chronic opioid user; Electronic healthcare database; Opioid receptor antagonist; Safety; Tolerability

INTRODUCTION

Health authority concerns exist regarding the use of peripherally acting μ-opioid receptor antagonists in development for the treatment of opioid-induced constipation (OIC), and a class effect of increased risk of major cardiovascular (CV) events [1]. To better understand the risk of CV events in opioid users with OIC, a greater understanding of the effects of opioid therapy alone is necessary. Appropriate steps for gaining insight into attributable risk for drug safety are to first establish background risk of the event(s) in question. Unfortunately, it is difficult to accurately capture information regarding OIC in electronic healthcare databases, which are typically efficient sources for establishing background risk. However, patients receiving chronic opioid treatment (the source population for OIC) can be reliably identified within the data sources and would be an appropriate surrogate reference population, given that OIC can occur in any patient chronically exposed to opioids [2–4].

Several lines of evidence have shown that opioid therapy is associated with an increased risk for the development of CV events [5–7]. Analysis of data from a cohort of Medicare beneficiaries in the US found an increased risk of CV events, defined as myocardial infarction (MI), stroke, heart failure, revascularization, and out-of-hospital cardiac death, in a population of older adults using the opioid analgesic codeine for 180 days compared with users of oxycodone, propoxyphene, and tramadol, using hydrocodone as the reference exposure [5]. In an older population of Medicare beneficiaries who were diagnosed with osteoarthritis or rheumatoid arthritis, rates for composite CV events, as well as individual CV events (MI, heart failure, stroke, coronary revascularization, out-of-hospital cardiac death), were higher in opioid users compared with patients using nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors [8]. In another claims-based cohort study of US patients, increased incidence rates for the specific events of MI and MI/coronary revascularization were reported in patients receiving chronic high doses of opioids when compared with patients receiving opioid doses of 0 to <1,350 mg (average daily dose of <15 mg) for 90 days, with risk increasing as the level of opioid exposure increased [6]. Additional evidence of the CV effects of opioids was provided in a case–control study by Li et al. [7], who identified a 1.3-fold increased risk of MI in current opioid users compared with nonusers in the UK. Cumulative opioid use (>10 prescriptions) was also associated with an increased risk of MI, as was use of morphine, meperidine, or polytherapy (simultaneous use of multiple opioids) [7].

Despite the presumed link between chronic opioid use and CV events, only a few studies have systematically evaluated the incidence or prevalence of CV events in chronic opioid users [5–7]. The current report expands on the

existing literature by providing CV event rates derived from three highly utilized electronic healthcare databases in the US, the UK, and Germany. The objectives of this evaluation were to determine the overall rates, prevalence rates in patients with established CV disease, and incidence rates in patients without established CV disease for new occurrences of several CV events of interest, and to compare the prevalence rates in patients with established CV disease to the incidence rates in patients without established CV disease. These events included MI, stroke, transient ischemic attack (TIA), unstable angina, and congestive heart failure (CHF).

METHODS

Data Sources

Patients in the US were identified from the HealthCore Integrated Research Database (HIRD), an administrative claims database of commercially insured individuals. Within the total database, approximately 27.6 million patients had medical and pharmacy coverage. Approximately 11.3 million patients had active medical and pharmacy coverage in available health plans. Data for UK patients were obtained from Clinical Practice Research Datalink (CPRD), a system of computerized medical records of general practitioners with approximately 52 million patients. For the purposes of this study, only patients covered by the CPRD-Hospital Episode Statistics merged data were included, which accounted for 45% of the practices in CPRD (approximately 23 million patients). The IMS® Disease Analyzer Germany database of primary care records, representing approximately 13 million patients, was used to access data for German patients.

None of the databases used as sources contained any personal identifiers. An institutional review board was not required for this study. For the UK study, a required ethics review was obtained by CPRD's Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency.

Study Design and Patients

Three observational cohort studies were conducted, each spanning a 5-year period (Fig. 1). Demographics, clinical characteristics, opioid use, and CV events were examined in patients who had newly initiated opioid therapy and who were using opioids for $\geq$6 months. Data were collated for US patients from January 1, 2007, through December 31, 2011; for UK patients from November 1, 2006, through October 31, 2011; and for patients in Germany from January 1, 2007, through December 31, 2011.

For patients with $\geq$6 months of opioid exposure, the index date was defined as the date that was exactly 183 days after the original date of the first prescription/dispensing for an opioid medication during the study intake period. Therefore, the pre-index period included both the 12-month period before opioid initiation and the first 6 months that a patient was exposed to opioids, for a total of 18 months (Fig. 1). The post-index period began at the index date and continued until the end of the follow-up period. In the US study, the follow-up period was defined as the date of the end of the study period, the end of health plan eligibility, or the end of continuous opioid exposure plus 30 days, whichever came first. In the two European studies, the follow-up period was defined as the date of the end of the study period, the date at which the patient transferred to another practice (UK) or the date for "last

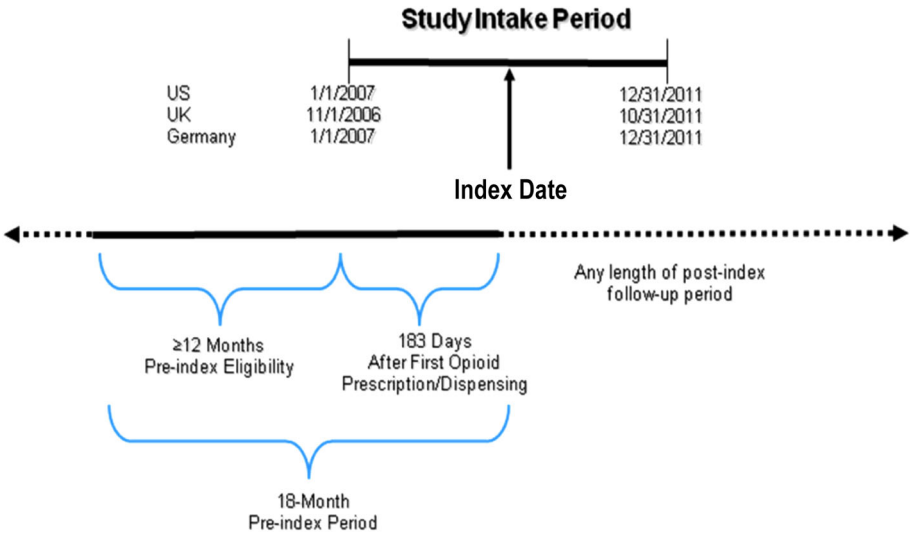

Fig. 1 Study design

contact with subject" (Germany), or at the end of continuous opioid exposure plus 30 days, whichever came first. In the US study, the average follow-up time for the 17,604 patients with ≥6 months' use of opioid was 9.8 months [standard deviation (SD) 11.0 months; median 5.3 months]. In the UK study, the average follow-up time for the 9,823 patients with ≥6 months use of opioid was 673 days (SD 596 days; median 456 days). In the German study, the average follow-up time for the 9,412 patients with ≥6 months' use of opioid was 457 days (SD 493 days; median 260 days).

In all three studies, patients were required to be new users of opioids, with ≥1 opioid prescription written or dispensed during study intake, ≥18 months of continuous healthcare coverage before the index date, and to be ≥18 years of age with >183 days of continuous opioid use at index. Patients who had filled an opioid prescription or who were diagnosed with cancer within 12 months before opioid initiation were excluded. Baseline demographic characteristics were assessed at opioid initiation; clinical characteristics were determined from data collected during the 18-month pre-index eligibility period.

Exposure to Opioid Medications

The opioid medications examined are listed in Table 1. Opioid use at opioid initiation was characterized by type, oral morphine equivalent, strength based on binding affinity for the μ-opioid receptor (weak versus strong), dose, and duration of exposure. Weak opioids include hydrocodone, propoxyphene, codeine, dihydrocodeine, tramadol, tapentadol, and tilidine, and are used for mild to moderate pain. Strong opioids include fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, and meperidine, and are used for moderate to severe pain.

Of the 5.8 million US patients who had ≥1 prescription fill during the intake period, 17,604 had ≥6 months of new continuous opioid therapy and satisfied all other inclusion and exclusion criteria. For UK patients, 99,837 patients were new opioid users with ≥1 prescription fill during the intake period; 46,043

Table 1 Conversion factors for oral morphine equivalents

Analgesic	Route	Dose (mg)	Conversion factor	Oral morphine equivalent
Morphine	Oral	15	1	15
	Parenteral	5	3	15
Codeine	Oral	100	0.15	15
	Parenteral	60	0.25	15
Dihydrocodeine	Oral	100	0.15	15
	Parenteral	60	0.25	15
Fentanyl	Intravenous	0.1	150	15
	Transdermal	0.6	25	90
Hydrocodone	Oral	10	1.5	15
Hydromorphone	Oral	4	3.75	15
	Parenteral	1.5	10	15
Meperidine[a]	Oral	150	0.1	15
	Parenteral	50	0.3	15
Methadone	Oral	5	3	15
	Parenteral	5	3	15
Oxycodone	Oral	10	1.5	15
Oxymorphone	Oral	5	3	15
	Parenteral	1	15	15
Propoxyphene[b]	Oral	100	0.15	15
Tapentadol	Oral	60	0.25	15
Tilidine[c]	Oral	75	0.2	15
	Parenteral	75	0.2	15
Tramadol	Oral	67.5	0.222222	15

[a] Includes pethidine (UK, Germany)
[b] Includes dextropropoxyphene (UK, Germany)
[c] Prescribed in Germany only

patients were eligible, and of these 9,823 were chronic users. In Germany, 9,412 of the 149,808 eligible patients were chronic opioid users.

Outcomes and Analyses

In all three studies, the presence of five major CV events of interest was assessed during the 12 months before opioid initiation plus the first 6 months of opioid exposure, and again during the post-index date follow-up period. These primary outcome variables were MI, stroke, TIA, unstable angina, and CHF (Table 2).

Overall, incidence, and prevalence rates per 1,000 patient-years were calculated separately for each CV event of interest as the number of

Table 2 Definitions for cardiovascular outcomes

Outcome	Definition
MI	Inpatient hospitalization with acute MI diagnosis[a]
Stroke	Inpatient hospitalization with stroke diagnosis[a]
TIA	Inpatient hospitalization with any diagnosis for a TIA[a,b]
	First diagnosis of TIA (with or without hospitalization)[c]
Unstable angina	Inpatient hospitalization with unstable angina diagnosis[a]
CHF	Inpatient hospitalization with CHF diagnosis[a]

CHF congestive heart failure, *MI* myocardial infarction, *TIA* transient ischemic attack

[a] Not required to be the primary diagnosis; for Germany and the UK, diagnoses coded in primary care were also taken into account

[b] US

[c] UK and Germany

patients having at least 1 event divided by the total number of person-years of observation, where observation ends at the time of first event or end of follow-up. The mid-*P* test based on Miettinen's modification was used to calculate the 95% confidence interval (CI) for the CV event rates. Event rates for all CV outcomes occurring during the post-index follow-up period were assessed for the overall population of each study, as well as prevalence rates in the subgroups of patients with prior CV disease versus incidence rates in those with no prior CV disease. Descriptive analyses are presented for all results, and no formal comparative statistical analyses were performed.

RESULTS

Baseline Characteristics and Opioid Treatment Patterns

Baseline demographic and clinical characteristics for all patients enrolled in the US ($N = 17,604$), UK ($N = 9,823$), and Germany ($N = 9,412$) are summarized in Table 3. The US patient population was younger than that in the UK and Germany. Specifically, the largest subgroup of US patients was 45–54 years of age, whereas most patients were aged ≥65 years in the UK and Germany. Gender representation was approximately equal in the US, whereas a greater proportion (more than two-thirds) of the UK and German populations were female.

United States

In the US study population, CV disease as a prespecified comorbidity was present in 64.0% of patients during the pre-index period (Table 3). The most frequently reported prespecified CV event of interest was CHF (4.4%); other CV events of interest were present in <2% of the population, with MI present in 1.5% and stroke in 1.7% of patients. Hypertension was reported in 53.3% of patients. Pain conditions were present in 90.6% of patients, the majority with arthritis, arthropathies, and musculoskeletal pain (excluding rheumatoid arthritis and osteoarthritis, 73.1%), followed by low back pain (50.2%). Other prespecified comorbidities prevalent with opioid use included psychological conditions (37.4%) and endocrine, nutritional and metabolic disorders (33.2%). Hypertension

Table 3 Demographic characteristics at opioid initiation and clinical characteristics during the pre-index period[a]

Characteristic	Country		
	US (*N* = 17,604)	UK (*N* = 9,823)	Germany (*N* = 9,412)
Age, years, mean (SD)	53.8 (16.4)	64.2 (15.8)	73.6 (15.0)
Age, years, *n* (%)			
18–24	486 (2.8)	50 (0.51)	4 (0)
25–34	1,669 (9.5)	342 (3.5)	75 (0.8)
35–44	2,824 (16.0)	879 (9.0)	256 (2.7)
45–54	4,636 (26.3)	1,385 (14.1)	859 (9.1)
55–64	4,047 (23.0)	2,012 (20.5)	1,414 (15.0)
65+	3,942 (22.4)	5,155 (52.5)	6,804 (72.3)
Sex, *n* (%)			
Male	8,967 (50.9)	3,067 (31.2)	3,081 (32.7)
Female	8,637 (49.1)	6,756 (68.8)	6,331 (67.3)
Presence of comorbid disease, *n* (%)			
MI	267 (1.5)	69 (0.7)	228 (2.4)
Stroke	301 (1.7)	97 (1.0)	629 (6.7)
TIA	172 (1.0)	92 (0.9)	201 (2.1)
Unstable angina	244 (1.4)	176 (1.8)	393 (4.2)
CHF	776 (4.4)	138 (1.4)	104 (1.1)
Comorbidities associated with opioid use, *n* (%)[b]			
Pain conditions	15,943 (90.6)	6,659 (67.8)	7,790 (82.8)
Other arthritis, arthropathies, and musculoskeletal pain	12,871 (73.1)	NA	NA
Low back pain	8,836 (50.2)	NA	NA
Dorsalgia	NA	3,535 (36.0)	4,009 (42.6)
CV disease	11,262 (64.0)[c]	1,187 (12.1)	5,736 (60.9)
Hypertension	9,385 (53.3)	611 (6.2)	5,025 (53.4)
Other ischemic heart disease	NA	NA	1,924 (20.4)
Heart failure	1,329 (7.5)	NA	1,319 (14.0)
Hyperlipidemia	NA	NA	901 (9.6)
Pure hypercholesterolemia	NA	NA	900 (9.6)
Endocrine, nutritional and metabolic diseases	5,844 (33.2)	1,105 (11.3)	3,326 (35.3)
Diabetes mellitus	3,433 (19.5)	909 (9.3)[d]	2,576 (27.4)[d]
Psychological conditions/mood (affective) disorders	6,582 (37.4)	1,350 (13.7)	2,192 (23.3)

Table 3 continued

Characteristic	Country		
	US ($N = 17,604$)	UK ($N = 9,823$)	Germany ($N = 9,412$)
Anxiety	2,952 (16.8)	NA	NA
Major depressive disorders	1,166 (6.6)	1,306 (13.3)	2,038 (21.7)
Substance abuse	3,108 (17.7)	NA	NA
Concomitant medications, *n* (%)[e]			
CV and antihypertensive medications	9,702 (55.1)	6,060 (61.7)	6,266 (66.6)
ACE inhibitors	3,337 (19.0)	2,337 (23.8)	3,685 (39.2)
ARB	1,291 (7.3)	1,001 (10.2)	1,252 (13.3)
Beta blockers	442 (2.5)	1,970 (20.1)	1,941 (20.6)
Calcium channel blockers	2,530 (14.4)	2,561 (26.1)	2,163 (23.0)
Diuretics, thiazide	1,757 (10.0)	2,007 (20.4)	1,602 (17.0)
Diuretics, loop	2,098 (11.9)	2,370 (24.1)	2,874 (30.5)
Statins	4,725 (26.8)	4,072 (41.5)	2,205 (23.4)
Psychological medications			
Antidepressants	7,165 (40.7)	5,322 (54.2)	3,024 (32.1)
SSRIs	4,303 (24.4)	2,337 (23.8)	754 (8.0)
Tricyclics	1,306 (7.4)	3,538 (36.0)	1,926 (20.5)
Antianxiety agents	5,863 (33.3)	3,505 (35.7)	2,569 (27.3)
Antipsychotics	1,595 (9.1)	1,558 (15.9)	658 (7.0)
Proton pump inhibitors	4,353 (24.7)	5,153 (52.5)	4,417 (46.9)
Anticholinergics	527 (3.0)	1,531 (15.6)	1,067 (11.3)
Anticonvulsants	4,869 (27.7)	1,853 (18.9)	1,434 (15.2)
Antihistamines	44 (0.2)	2,461 (25.1)	1,279 (13.6)
Muscle relaxants	5,924 (33.7)	322 (3.3)	1,003 (10.7)

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *CV* cardiovascular, *NA* not available, *SSRI* selective serotonin reuptake inhibitor

[a] Includes the original 12-month pre-index period (i.e., the 12 months before initiating opioids) plus the first 6 months a patient is exposed to opioids, for a total of 18 months

[b] Includes the top 20 most prevalent indications pre-index for UK and Germany

[c] Includes angina pectoris, cardiac arrhythmia, coronary artery disease, heart failure, hypertension, myocardial infarction, revascularization

[d] Unspecified diabetes mellitus, type 2 diabetes without complications

[e] Used by ≥10% of patients

Table 4 Opioid characteristics at opioid initiation date

Characteristic	Country		
	US (*N* = 17,604)	UK (*N* = 9,823)	Germany (*N* = 9,412)
Opioid strength, *n* (%)			
Weak	14,712 (83.6)	8,671 (88.4)	4,894 (52.0)
Strong	3,075 (17.4)	1,142 (11.6)	3,494 (37.1)
Opioid type, *n* (%)			
Weak opioids			
Hydrocodone	8,386 (47.6)	NA[a]	NA[a]
Propoxyphene[b]	1,601 (9.1)	279 (2.8)	–[c]
Codeine	570 (3.2)	3,885 (39.6)	537 (5.7)
Dihydrocodeine	3 (0)	1,946 (19.8)	–
Tramadol	4,320 (24.5)	2,085 (21.2)	2,812 (29.9)
Tapentadol	8 (0)	–[d]	15 (0.2)
Tilidine	–	–[e]	2,465 (26.2)
Strong opioids			
Fentanyl	303 (1.7)	325 (3.3)	1,645 (17.5)
Hydromorphone	106 (0.6)	3 (0)	294 (3.1)
Methadone	198 (1.1)	2 (0)[f]	–
Morphine	219 (1.2)	445 (4.5)	518 (5.5)
Oxycodone	2,371 (13.5)	153 (1.6)	605 (6.4)
Oxymorphone	22 (0.1)	–	–
Meperidine[g]	25 (0.1)	6 (0.1)	7 (0.1)
Route of administration, *n* (%)			
Oral	17,399 (98.8)	8,468 (86.2)	7,247 (78.4)
Injection/intravenous	5 (0)	–	–
Parenteral	–	3 (0)	19 (0.2)
Transdermal	–	303 (3.1)	1,602 (17.0)
Other	303 (1.7)	–	66 (0.7)[h]
Unknown	–	1,049 (10.7)[i]	478 (5.1)[i]

NA not available

[a] Not prescribed in the UK or Germany

[b] Includes dextropropoxyphene (UK, Germany)

[c] Withdrawn from market in 2007, but was still available in the UK in combination with paracetamol (co-proxamol) on a named patient basis, for long-term chronic pain and for patients who had been treated previously

[d] Launched in the UK in mid-year 2011 (Palexia), so too late to appear in the data

[e] Not available in the UK

[f] Mainly used as substitution therapy for other opiates; cases where the use as substitution therapy was documented were not included in the study

[g] Includes pethidine (UK, Germany)

[h] Includes rectal and nasal administration

[i] Includes unidentified administration routes (missing data) or cases where multiple administration routes were combined (e.g., oral and transdermal)

(53.3%) and diabetes (19.5%) were the most prevalent prespecified comorbidities outside of pain conditions. More patients reported substance abuse (17.7%) than anxiety (16.8%) or major depressive disorders (6.6%). Use of CV and antihypertensive medications [55.1%, particularly statins (26.8%)], antidepressants (40.7%), and antianxiety agents (33.3%) was common.

With regard to opioid treatment, weak opioids, as defined by receptor binding affinities, were used by the majority of the US patients (83.6%) at first dispensing (Table 4). The most commonly prescribed opioids (used by >10% of patients) were the weak opioids hydrocodone (47.6%) and tramadol (24.5%), followed by the strong opioid oxycodone (13.5%). Nearly all (98.8%) opioid medications were administered orally.

United Kingdom

In the UK study population, the prespecified comorbidity of CV disease was present in 12.1% of patients during the pre-index period; unstable angina (1.8%) and CHF (1.4%) were the most common prespecified CV events of interest, and hypertension was present in 6.2% of patients (Table 3). A prior pain diagnosis was reported in 67.8% of patients, with dorsalgia being the most common (36.0%). Mood/affective disorders (13.7%) were present and were almost exclusively major depressive disorders (13.3%). Cardiovascular and hypertensive medications (61.7%), antidepressants (54.2%), and proton pump inhibitors (52.5%) were the most frequently used concomitant medications in the UK population.

At first prescription, weak opioids were primarily used in the UK (88.4%), with codeine (39.6%), tramadol (21.2%), and dihydrocodeine (19.8%) the most commonly prescribed medications. The primary route of administration was oral (86.2%), although other routes were occasionally used (Table 4).

Germany

In the German study population, CV disease was present in 60.9% of patients during the pre-index period; stroke (6.7%) and unstable angina (4.2%) were the most frequently reported prespecified CV events of interest (Table 3). Additional prespecified comorbidities in this patient population included pain conditions (82.8%); endocrine, nutritional and metabolic disorders (35.3%); and mood/affective disorders (23.3%). The most common diagnoses in each of the above categories, respectively, were hypertension (53.4%), dorsalgia (42.6%), diabetes (27.4%), and major depressive disorders (21.7%). Cardiovascular and antihypertensive medications (66.6%), primarily angiotensin-converting enzyme inhibitors (39.2%), proton pump inhibitors (46.9%), and antidepressants (32.1%), were commonly used.

Approximately half of German patients were treated with weak opioids at first prescription (Table 4). The most frequently used opioids were tramadol (29.9%) and tilidine (26.2%), as well as the strong opioid fentanyl (17.5%). The primary route of administration was oral (78.4%); however, other routes of delivery, including transdermal (17.0%) and rectal/nasal (0.7%), were employed.

Cardiovascular Event Rates

The overall, incidence, and prevalence rates for new CV events of interest occurring during the post-index follow-up period are presented in Table 5. Higher overall rates for MI, stroke, TIA, unstable angina, and CHF were observed in the US study population than in either the UK or German study populations.

In the overall US study population, CV event rates were highest for CHF (37.2, 95% CI 24.1–40.5) and MI (10.7, 95% CI 9.1–12.5). Prevalence rates were generally 4- to 7-fold higher in patients with established CV disease, compared with patients without CV disease. An exception was CHF, which was 13-fold greater in patients with established CV disease compared to those without CV disease.

Overall CV event rates in the UK study population were greatest for unstable angina (8.2, 95% CI 7.0–9.6) and MI (6.7, 95% CI 5.6–8.0). Prevalence rates for unstable angina and TIA were greater (ninefold and sixfold, respectively) and ranged from 3- to 4-fold higher for other outcomes in patients with established CV disease versus the incidence rates in those without CV disease.

In the German study population, overall CV event rates were highest for stroke (5.3, 95% CI 4.1–6.7) and MI (2.7, 95% CI 1.9–3.7). Prevalence rates in patients with established CV disease for individual outcomes were 1.4- to 3-fold higher than incidence rates in patients without CV disease, with the exception of unstable angina, where rates were similar in patients with or without prior CV disease. In contrast with the observations in the US and UK populations, no single outcome showed a markedly higher rate in patients with established CV disease.

DISCUSSION

Differences were observed in the demographics, clinical characteristics, and patterns of opioid use in the three patient populations, which was attributed in part to the data collection methods unique to the individual databases used in each country. As an example, the US patients tended to be younger than those in the UK and Germany, which is consistent with the database for the US population, which is typical of an administrative claims database and contains mostly privately insured patients aged <65 years. Because the source data only captures supplemental Medicare insurance, US patients aged ≥65 years are underrepresented. In contrast, the UK and German databases comprise office-based electronic medical records and reflect the typical patient populations seen by the individual physicians. A greater proportion of patients in the UK and German populations were female.

The presence of CV comorbidities of interest differed depending on the geographic origin of the respective patient populations. Given the length of time for baseline observations, which should be sufficient to capture chronic conditions or a record of prior major CV events, the limited presence of CV disease diagnoses in the UK at baseline relative to the US and Germany is difficult to explain. However, the inclusion of CV medications compensated for the lack of diagnosis detail, as the assumption was made that if a patient in the UK was on a CV medication, they most likely had a diagnosis of a CV comorbidity. The most frequently reported CV comorbidities were CHF in the US population, unstable angina in the UK population, and stroke in the German population. Cardiovascular disease, hypertension, and diabetes were present in greater percentages of US and German patients. Cardiovascular and antihypertensive medications were the most commonly used concomitant medications across countries, likely because of the presence of risk factors for other CV events, such as diabetes, and the older age of the UK and German populations.

The high proportion of pain diagnoses was expected. Despite this being a chronic opioid use cohort, the proportion of patients with a pain diagnosis was not 100%, suggesting that some

chronic use may be related to postsurgical maintenance therapy or to other diagnoses such as osteoarthritis or diabetic neuropathy. Patterns of opioid use also differed by geographic location (Table 4). Although use of weak opioids predominated in all three countries, there were differences in the specific types of prescribed medication, which may be attributed in part to regulatory approval, product availability, and clinical guideline recommendations for treatment with opioids in each country.

When the rates for new occurrences of CV events of interest following opioid initiation and treatment for ≥6 months were examined, overall rates were higher in the US versus the UK and German study populations. As expected, subgroup analyses of our results showed that an established history of CV disease was associated with a higher prevalence of the CV outcomes of interest compared with patients with no established history of CV disease. In particular, the rates for CHF (in the US) and unstable angina (in the UK) were at least ninefold greater in patients with established CV disease. Part of this difference in the rates for CHF may be attributable to different definitions for CHF in the databases, where the US database used ICD9 codes, the UK database used abridged ICD10 and READ codes, and the German database used ICD10 codes. In addition, the definition of CHF in the US database included ancillary diagnosis codes (see Table 3 footnote). The collection of source data also differed, with US data obtained from a claims database while data from the UK and Germany were from electronic healthcare databases. Notably, incidence rates for CHF were higher in those with prior CV disease, which could be largely attributed to those patients with CHF at baseline. Incidence rates for CHF were also higher in the US and UK datasets, which contained linked hospital data. No consistent pattern of events was observed across the geographic patient populations. Event rates may differ across geographic patient populations because of subtle differences in diagnostic criteria; lifestyle factors, such as diet, exercise, and smoking; and variation in comorbidity and concomitant medication patterns. The finding that CV event rates were higher in the US compared with the UK and Germany for almost all CV endpoints—except for rates of unstable angina and TIA observed in the UK—was particularly interesting given the younger age of the US population (Table 5), although there are no clear or simple explanations for these findings.

The rate of MI in the US population in the current study is slightly higher than that previously reported by Carman et al., who observed incidence rates ranging from 4.88 to 8.16 in opioid users [6]. In another study by Solomon et al. [8], involving an elderly population of Medicare beneficiaries from two states (mean age 80 years), the incidence rates for MI (29, 95% CI 21–38), heart failure (45, 95% CI 36–57), and stroke (18, 95% CI 13–26) in opioid users were comparable with rates observed in patients with established CV disease in the current study. Compared with data for the UK and German populations with established CV disease where patients tended to be older (mean ages of 64 and 74 years, respectively), the rates reported by Solomon were within range for MI and stroke in the UK population but higher compared with the German population [8].

In the US population, overall rates for CHF were sixfold and 23-fold higher than the overall rates in the UK and Germany, respectively. Similarly, prevalence rates in US patients with CV disease were sixfold and 32-fold higher than those in UK or German patients. The incidence rates in US patients without CV disease were also higher (1.6-fold versus UK patients and eightfold versus German patients).

Table 5 Incidence/prevalence rates per 1,000 patient-years for new occurrences of cardiovascular events of interest during the post-index follow-up period in patients receiving opioid therapy for ≥183 days: overall and by presence of established CV disease[a]

Outcome	US[b]			UK[c]			Germany[c]		
	Overall (*N* = 17,604)	With established CVD (*n* = 4,714)	Without established CVD (*n* = 12,890)	Overall (*N* = 9,823)	With established CVD (*n* = 419)	Without established CVD (*n* = 9,404)	Overall (*N* = 9,412)	With established CVD (*n* = 1,273)	Without established CVD (*n* = 8,139)
MI									
N events	153	109	44	126	13	113	32	10	22
Incidence rate (95% CI)	10.7 (9.1–12.5)	30.2 (24.9–36.3)	4.1 (3.0–5.5)	6.7 (5.6–8.0)	19.9 (11.1–33.1)	6.2 (5.2–7.5)	2.7 (1.9–3.7)	6.5 (3.4–11.6)	2.1 (1.4–3.1)
Stroke									
N events	133	89	44	102	10	92	63	11	52
Incidence rate (95% CI)	9.3 (7.8–10.9)	24.7 (19.9–30.2)	4.1 (3.0–5.5)	5.4 (4.4–6.6)	15.1 (7.8–26.8)	5.1 (4.1–6.2)	5.3 (4.1–6.7)	7.2 (3.8–12.4)	5.0 (3.8–6.5)
TIA									
N events	94	55	39	89	16	73	25	6	19
Incidence rate (95% CI)	6.6 (5.3–8.0)	15.2 (11.6–19.6)	3.6 (2.6–4.9)	4.7 (3.8–5.8)	25.0 (14.8–39.6)	4.0 (3.2–5.0)	2.1 (1.4–3.0)	3.9 (1.6–8.1)	1.8 (1.1–2.8)
Unstable angina									
N events	119	80	39	154	35	119	12	1	11
Incidence rate (95% CI)	8.3 (6.9–9.9)	22.2 (17.8–27.5)	3.6 (2.6–4.9)	8.2 (7.0–9.6)	56.3 (39.9–77.3)	6.6 (5.5–7.9)	1.0 (0.5–1.7)	0.7 (0.06–3.0)	1.0 (0.6–1.8)
CHF									
N events	526	425	101	115	14	101	19	6	13

Table 5 continued

Outcome	US[b]			UK[c]			Germany[c]		
	Overall (N = 17,604)	With established CVD (n = 4,714)	Without established CVD (n = 12,890)	Overall (N = 9,823)	With established CVD (n = 419)	Without established CVD (n = 9,404)	Overall (N = 9,412)	With established CVD (n = 1,273)	Without established CVD (n = 8,139)
Incidence rate (95% CI)	37.2 (24.1–40.5)	123.1 (111.8–135.3)	9.4 (7.7–11.4)	6.1 (5.1–7.3)	21.2 (12.2–34.7)	5.6 (4.6–6.7)	1.6 (1.0–2.4)	3.9 (1.6–8.0)	1.2 (0.7–2.1)

CHF congestive heart failure, *CI* confidence interval, *CVD* cardiovascular disease, *MI* myocardial infarction, *TIA* transient ischemic attack

[a] Calculated as the number of patients having at least one event, divided by the total number of person-years of observation, where observation ends at the time of first event or end of follow-up

[b] Number of patients with event

[c] Number of events

Strengths of this study include the expansion of the investigation of CV event rates in opioid users to two European countries, whereas previous studies have only evaluated US populations. Notably, these results provide insight into the background CV event rates in the three countries with highly utilized data sources, suggesting that these background event rates could serve as a threshold for detection of potential CV safety signals with respect to the administration of peripherally acting μ-opioid receptor antagonists. In addition, the examination of CV event rates in patients with and without established CV disease provides a means to better understand the impact of prior CV disease history on the occurrence of CV events after opioid therapy is initiated.

This report has several limitations. Because prescription data were assessed, it is unknown if medication was actually taken by the patients. However, it is reasonable to believe drug was consumed given the continuous prescribing patterns (e.g., the maximum time gap between prescriptions was 30 days) by the treating physicians. One limitation associated with the evaluation of new opioid users is that some patients may have had cumulative, but not continuous, exposure to opioids for >183 days and therefore would not be included in the analysis. In addition, because only new users of opioids were included in the populations studied, patients who were already routine opioid users were not included. In the US dataset, there is bias toward individuals with commercially available insurance related to the source of the data. In the UK dataset, the availability of codeine and dihydrocodeine as over-the-counter medications may have resulted in underestimation of their use. Given that the UK data source comprised the records of general practitioners, diagnoses of prior CV risk factors might be underrecorded when compared

with utilization of medication indicated to treat CV risk factors. These discrepancies would result in the observed lack of concordance between the presence of written prescriptions for a CV risk factor and a diagnosis for its indication (eg., hypertension). Subsequently, this may lead to underestimation or overestimation of CV event rates within the CV disease strata, but would not affect the overall incidence rate. It is important to note that the current study considered risk factors for CV disease separately, given that some medications may be used for primary prevention and that the presence of a risk factor may not equate to the presence of CV disease. Lastly, given the heterogeneity in treatment, summary level CV event rates may differ (increased or decreased) from those in particular patient subgroups (e.g., gender, age, and race).

CONCLUSION

In summary, the current study determined the level of risk for CV events in new users of opioids and provides a background rate for others to use in future research. Rates for specific CV outcomes in new users of opioids were higher in patients with established CV disease. Higher rates for each event were observed in the US study population than in either the UK or German study populations. In accordance with database selection guidance as described in the Guidelines for Good Database Selection and Use [9], careful evaluation of each data source is necessary to account for sample size and potential treatment effect heterogeneity when designing observational studies for the CV safety of new products.

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Conflict of interest. Robert LoCasale is an employee of AstraZeneca Pharmaceuticals, LP. David M. Kern is employed by HealthCore Inc., which received funding from AstraZeneca Pharmaceuticals, LP for this study. Pierre Chevalier is employed by IMS Health, which received funding from AstraZeneca Pharmaceuticals, LP for this study. Siting Zhou is employed by HealthCore Inc., which received funding from AstraZeneca Pharmaceuticals, LP for this study. Soheil Chavoshi is an employee and shareholder of AstraZeneca Pharmaceuticals, LP. Mark Sostek is an employee and shareholder of AstraZeneca Pharmaceuticals, LP.

Compliance with ethics guidelines. None of the databases used as sources contained any personal identifiers. An institutional review board was not required for this study. For the UK study, a required ethics review was obtained by CPRD's Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency.

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