JACC: ADVANCES VOL. 3, NO. 10, 2024

ORIGINAL RESEARCH

Ongoing Opioid Treatment and Symptoms of Myocardial Infarction in Calls to the Emergency Medical Services

Anne Storgaard Nørskov, MD,[a,b] Amalie Lykkemark Møller, PhD,[c,d] Christian Torp-Pedersen, MD, DMSc,[a,c] Helena Domínguez, MD, PhD,[b,e] Stig Nikolaj Blomberg, PhD,[f] Helle Collatz Christensen, MD, PhD,[g] Kristian Kragholm, MD, PhD,[h] Eva Prescott, MD, DMSc,[b] Jacob Lønborg, MD, DMSc,[i] Andrim Halili, MD,[a,b] Fredrik Folke, MD, PhD,[f,j] Casper Niels Bang, MD, PhD[b]

ABSTRACT

BACKGROUND Ongoing opioid treatment can potentially modify symptoms of myocardial infarction (MI) and cause a lack of recognition and treatment delay.

OBJECTIVES The purpose of this study was to examine MI symptoms and the time to hospitalization for patients in ongoing opioid treatment compared to patients without ongoing opioid treatment.

METHODS We evaluated calls to the Copenhagen Emergency Medical Services in Denmark from 2014 to 2018. Calls were included when followed by hospitalization and a diagnosis of MI. Symptoms of MI and the time from call to hospitalization in patients in ongoing opioid treatment initiated prior to the onset of MI were compared to a control group of MI patients without opioid treatment.

RESULTS In total, 6,633 calls were included; 552 calls from patients in opioid treatment and 6,081 calls from controls. Patients in opioid treatment were older and had more comorbidities than controls. Chest pain was less prevalent in MI patients in opioid treatment compared to controls (adjOR: 0.70; 95% CI: 0.57-0.85). The median time from the call to hospitalization was longer in patients in opioid treatment than in controls (50 vs 47 minutes; $P = 0.006$).

CONCLUSIONS In calls to the Emergency Medical Services, opioid treatment initiated prior to the onset of MI was associated with less frequent chest pain in MI. Therefore, awareness of ongoing opioid treatment may improve telephone triage of patients with MI, as symptom presentation in opioid-treated patients may differ and potentially challenge and delay the emergency response. (JACC Adv. 2024;3:101268) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, Copenhagen University Hospital - North Zealand, Hillerød, Denmark; [b]Department of Cardiology, Copenhagen University Hospital-Bispebjerg and Frederiksberg, Copenhagen, Denmark; [c]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [d]Cancer Surveillance and Pharmacoepidemiology, Danish Cancer Society Research Center, Copenhagen, Denmark; [e]Department of Biomedicine, University of Copenhagen, Copenhagen, Denmark; [f]Copenhagen University Hospital - Emergency Medical Services Copenhagen, Copenhagen, Denmark; [g]Prehospital Center, Copenhagen University Hospital, Næstved, Denmark; [h]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [i]Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, University Hospital, Copenhagen, Denmark; and the [j]Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Gentofte, Denmark.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 29, 2023; revised manuscript received August 12, 2024, accepted August 15, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101268

ABBREVIATIONS AND ACRONYMS

ICD-10 = International Classification of Diseases-10th revision

MI = myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

STEMI = ST-segment elevation myocardial infarction

Symptoms of acute cardiovascular disease are essential for the early identification of the disease and the subsequent initiation of life-saving treatment.[1] It is not investigated if ongoing opioid treatment initiated prior to the onset of acute cardiovascular disease affects the symptom presentation of acute cardiovascular disease.

Worldwide, opioids are used for a broad range of chronic and acute disorders,[2] and in some Western countries prescribed at a level that contributes to the "*opioid crisis.*"[3,4] Since the mid-1990s more than 500,000 deaths in the United States have been attributed to opioids, with a steep rise in overdose deaths in the last few years.[5]

Globally, more than seven million people are diagnosed with acute coronary syndrome each year including myocardial infarction (MI).[6] Symptom presentation contributes to the clinical assessment of MI.[7] Chest pain is prevalent in several cardiovascular diseases[8] and is considered the cardinal manifestation of MI.[6,9] However, patients may present with atypical MI symptoms.[6,10-13] In a large study of calls to the Emergency Medical Services, atypical symptoms were reported as the primary symptoms of MI in 24% of all calls.[13]

In patients with MI, the first prehospital contact is often a telephone consultation,[14] eg, with the Emergency Medical Services. Hence, healthcare personnel play a critical role in identifying symptoms of MI to ensure the correct visitation of calls. If ongoing opioid treatment masks chest pain in patients with MI, this could challenge early recognition of MI and potentially delay treatment initiation. No study has previously investigated whether patients in ongoing opioid treatment less frequently report chest pain as the primary symptom of MI in calls to the Emergency Medical Services.

We hypothesize that ongoing opioid treatment initiated prior to the onset of MI attenuates chest pain in the acute setting of MI and is associated with increased time to hospitalization.

The present study aims to investigate if symptoms of MI registered in calls to the Emergency Medical Services differ between patients in ongoing opioid treatment and patients without ongoing opioid treatment. Furthermore, the study aims to investigate if the time from the call to hospitalization is longer in MI patients in ongoing opioid treatment compared to patients without ongoing opioid treatment.

METHODS

ETHICAL APPROVAL. Informed consent and approval from The Danish National Committee on Health Research Ethics are not required for register-based studies in Denmark. This project was approved by the Danish Patient Safety Authority and the data responsible institute, The Capital Region of Denmark with the approval number P-2019-191, in accordance with the General Data Protection Regulation.

STUDY DESIGN. In this registry-based study, calls to the Copenhagen Emergency Medical Services were identified. Subsequently, hospital admission with the primary diagnosis of MI was linked to the calls to investigate the MI symptom presentation in calls, see the flow diagram in **Figure 1**. This study was performed at the Department of Cardiology, Copenhagen University Hospital-North Zealand, Denmark.

DATA SOURCES. The study was based on data from Danish registries. Baseline characteristics were registered in the Civil Registration System, Population Education Register, Income Statistics Register, and National Patient Registry.[15-18] Opioid treatment was registered in the National Prescription Registry.[19] Symptom presentation of MI was registered in calls to the Copenhagen Emergency Medical Services combining data from the emergency number and the out-of-hours service.[20] Death was registered in the Civil Registration System.[15]

POPULATION. The population consisted of calls to the Copenhagen Emergency Medical Services followed by hospitalization with a primary diagnosis of MI.

Patients were eligible when hospitalized within 24 hours after a call to the Emergency Medical Services. Analyses were based on the first call prior to hospitalization.

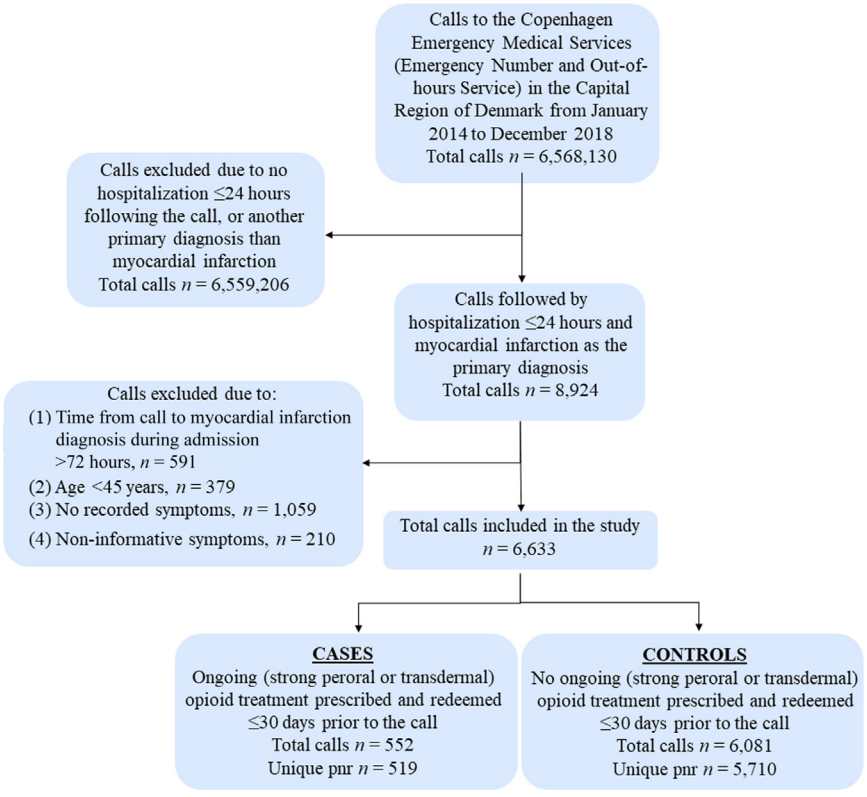
We compared MI patients who were in ongoing opioid treatment initiated prior to the onset of MI to a control group of MI patients without ongoing opioid treatment.

Patients were eligible above 45 years of age, as MI is rare below this age and young patients may differ in clinical presentation and pathophysiology, which influence the perception of symptoms.

Comorbidities were included if diagnosed within 10 years before the call.

CALLS TO THE EMERGENCY MEDICAL SERVICES. This study included calls to the Copenhagen Emergency Services of the Capital Region of Denmark

FIGURE 1 Flow Diagram



*pnr is the anynomous identification number.

between 2014 and 2018. This service covered calls to the emergency number (1-1-2, equivalent to 9-1-1) and the out-of-hours service (1813, a nonurgent medical helpline) with 1.8 million citizens in the region.[21] In the algorithm with prespecified symptoms, healthcare personnel (physicians, paramedics, and nurses) at the Emergency Medical Services registered one primary symptom most appropriate to the history of the patient, complaints, and/or purpose of the call. The healthcare personnel had the possibility to add subcomplaints in the algorithm and a short text, but only registration of a primary symptom was required. The registered symptom impacted the dispatcher's emergency response in the algorithm. To ensure consistency, only the primary symptom was included in the analyses.

The person calling the Emergency Medical Services was most often the patient, but the call could be mediated by a relative, general practitioner, bystander, etc. In Denmark, patients are expected to call the Emergency Medical Services to be triaged. However, some patients choose to self-transport to the emergency department without calling.[23]

The emergency number and the out-of-hours service used one identical software system, but the services differed in the protocols used; the Danish Index[22] was used at the emergency number and a locally developed electronic decision support system was used at the out-of-hours service.[20]

Throughout the study, calls to the Emergency Medical Services (both emergency number and out-out-hours service) will be referred to as "*calls*."

SYMPTOM PRESENTATION. The primary outcome was symptom presentation of MI registered as the primary symptom in the calls. The primary outcome was chest pain vs non-chest pain symptoms. Non-chest pain symptoms were further stratified into the following categories: 1) breathing problems; 2) other cardiac symptoms (eg, palpitations, pain when breathing, pacemaker problems, and abnormal blood pressure); 3) central nervous system symptoms; 4) unconscious; 5) abdominal, back, or urinary

symptoms; and 6) other atypical symptoms. Missing data on symptom presentation were grouped into 1) noninformative symptoms (2% of all calls, including 1% of calls from patients in ongoing opioid treatment and 2% of calls from the controls) and 2) no recorded symptoms (11% of all calls, including 9% of calls from patients in ongoing opioid treatment and 11% of calls from the controls) and excluded from the study. See Supplemental Table 1 for the list of symptom registration and description.

EXPOSURE. The exposure was ongoing opioid treatment defined as opioid treatment initiated prior to the onset of MI, where an opioid prescription was redeemed within 30 days prior to the call and will be referred to as "*ongoing opioid treatment*" throughout the study. Patients not in ongoing opioid treatment will be referred to as "*controls.*" Strong opioids (morphine, nicomorphine, oxycodone, pethidine, fentanyl, ketogan, methadone, tramadol, tapentadol, buprenorphine, and the combination of oxycodone and naloxone) administered through peroral and transdermal route were included, and the use was not restricted to certain conditions, see Supplemental Table 2 for the list of opioids included. Patients receiving weak opioids (eg, codeine) were included in the control group. Sensitivity analyses were performed to test the association between chest pain in MI and opioid treatment stratified by different durations of treatment and morphine equivalent dosages.[24-27] Average dosages and lengths of the opioid treatment were estimated based on the redeemed opioid prescriptions in relation to assumed minimum, maximum, and standard dosages. Information on the indication of opioid treatment was not available in the National Prescription Registry.

DEFINITION OF MI. MI was defined by the primary diagnosis of I21 in the 10th revision of the International Classification of Diseases (ICD-10), see the ICD-10 codes in the Supplemental Table 3. We included ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI). MI diagnoses were included when assigned to the patient within 72 hours after the call. Type 2 MI and unstable angina pectoris were not included, see Supplemental Table 3.

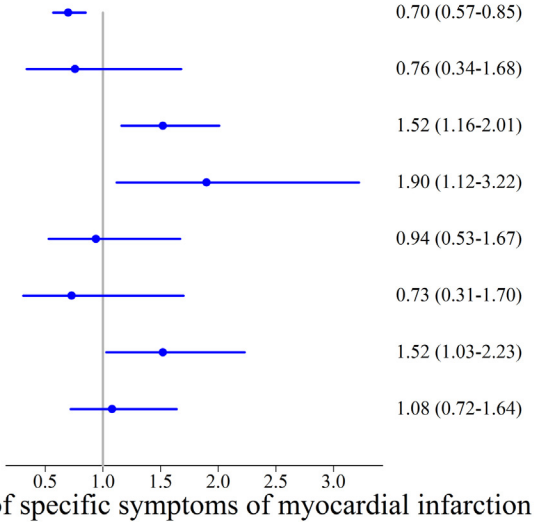
STATISTICAL ANALYSES. The exposure was ongoing opioid treatment at the time of the call. The main outcome was the primary symptom registered in calls up to 24 hours before admission with MI as the primary diagnosis. Descriptive statistics used means and standard deviations or medians and quartiles (reported as 1st and 3rd quartile) for continuous and percentages for discrete variables. Comparisons used *t*-test and chi-squared test. All regression analyses were multivariable and adjusted for the following covariates: sex, age, comorbidity status (including chronic ischemic heart disease, diabetes, atrial fibrillation, hypertension, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, cancer, and peripheral vascular disease), call type (emergency number and out-of-hours service), MI type (STEMI and NSTEMI), educational level, income level, and if living at a nursing home. Simple imputation was performed for missing data. The main outcome was presented in symptom categories in a forest plot (**Figure 2**) by logistic regression analyses. Further stratification was performed by sex and age in treemap charts (**Figure 3**), baseline information in forest plots (**Figure 4**, Supplemental Figure S1), call type in treemap charts (**Figure 5**), and diabetes in treemap charts (Supplemental Figure 3). Chest pain presentation stratified by duration of opioid treatment (above or below 30 days) and dosage (above or below 20 mg/day) was analyzed by logistic regression in a forest plot (Supplemental Figure 2). Thirty-day mortality was analyzed by logistic regression. Assignment of an acute ambulance was analyzed by logistic regression. Time from call to hospitalization according to opioid use was tested by comparing time above the median of the study population as a dichotomous outcome. Additionally, the median time difference was analyzed by multiple linear regression with log-transformation of the time from call to hospitalization. A sensitivity analysis of the inverse probability of treatment weighting was conducted. Propensity scores assessed the probability of receiving ongoing opioid treatment given the above listed covariates. Weights of the inverse probability of treatment weighting were calculated as the inverse of the propensity scores in a logistic regression model with chest pain as the outcome. Interaction analyses were examined by likelihood ratio tests. Statistical programming was carried out in R software (version 4.2.1).[28]

RESULTS

STUDY POPULATION. The study included 6,633 calls from patients hospitalized with MI as the primary diagnosis, including 552 calls from patients in ongoing opioid treatment, and 6,081 calls from the controls, see the flow diagram in **Figure 1**. Patients in ongoing opioid treatment were older than controls (mean age 73 vs 69 years), were more often females (52% vs 34%), had poorer educational attainment, and a higher burden of comorbidities, see detailed baseline characteristics in **Table 1**.

FIGURE 2 Symptoms of Myocardial Infarction According to Opioid Use

Symptoms of myocardial infarction	Frequency of symptoms in patients in ongoing opioid treatment (N=552) vs. controls (N=6,081)	p-value	Odds ratio (95% CI)
Chest pain	363 (65.8%) vs. 4,655 (76.5%)	<0.001	0.70 (0.57-0.85)
Other cardiac symptoms	7 (1.3%) vs. 126 (2.1%)	0.496	0.76 (0.34-1.68)
Breathing problems	81 (14.7%) vs. 427 (7.0%)	0.003	1.52 (1.16-2.01)
Abdominal, back, or urinary symptoms	18 (3.3%) vs. 116 (1.9%)	0.018	1.90 (1.12-3.22)
Central nervous system symptoms	14 (2.5%) vs. 151 (2.5%)	0.835	0.94 (0.53-1.67)
Unconscious	6 (1.1%) vs. 105 (1.7%)	0.464	0.73 (0.31-1.70)
Other atypical symptoms	35 (6.3%) vs. 237 (3.9%)	0.034	1.52 (1.03-2.23)
Unclear problem	28 (5.1%) vs. 264 (4.3%)	0.700	1.08 (0.72-1.64)



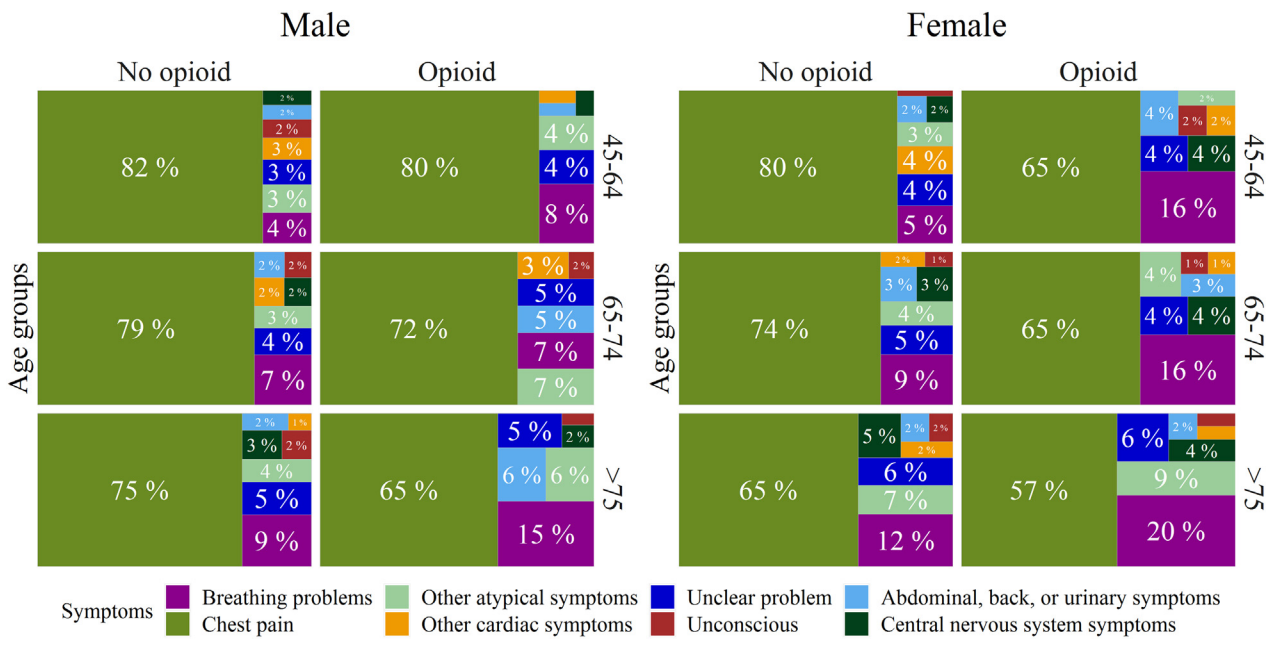
Forest plot with estimation of adjusted odds of primary symptoms of myocardial infarction stratified by opioid use. Total calls (out-of-hours service and emergency number) $N = 6,633$. Calls From patients in ongoing opioid treatment $n = 552$. Calls from the controls $n = 6,081$. Adjusted odds ratios are analyzed by multivariable regression comparing calls from patients in ongoing opioid treatment to controls. Odds ratio <1 indicates lower odds of the specific primary symptom of myocardial infarction in patients in ongoing opioid treatment compared to controls.

SYMPTOMS OF MI. In Figure 2, a forest plot illustrates the adjusted odds of different symptom presentations of MI registered in calls according to opioid use in multivariable regression analyses. The adjusted odds of presenting with chest pain were lower for MI patients in ongoing opioid treatment compared to the controls. Conversely, ongoing opioid treatment was associated with more frequent non-chest pain symptoms of MI, particularly breathing problems, abdominal, back, or urinary symptoms, and other atypical symptoms. In Figure 3, treemap charts with MI symptoms stratified by opioid use, sex, and age are visualized. The absolute frequencies of non-chest pain symptoms were increased in females and by increasing age, particularly in patients in ongoing opioid treatment.

In Figure 4, a forest plot illustrates the adjusted odds of chest pain in MI registered in calls comparing patients in ongoing opioid treatment to controls across subgroups in multivariable regression analyses. As seen in Figure 4, chest pain was less frequent in patients in ongoing opioid treatment compared to controls across demographic information, call type (emergency number and out-of-hours service), and comorbidities, except patients with diabetes, atrial fibrillation, and if living at a nursing home. In Figure 5, treemap charts with MI symptoms are visualized and stratified by call type (emergency number and out-of-hours service), opioid use, sex, and age. The frequency of chest pain in MI seemed lowest in calls to the out-of-hours service among females aged >75 years in ongoing opioid treatment.

EMERGENCY RESPONSE. The median time elapsed from call to hospitalization was 3 minutes longer for MI patients in ongoing opioid treatment compared to controls (50 [IQR: 41-63] vs 47 [IQR: 37-60] minutes) and significant in a multivariable regression analysis (OR: 1.28; 95% CI: 1.06-1.53; $P = 0.009$). In patients with chest pain, the median time was longer in patients in ongoing opioid treatment (47 [IQR: 37;57] vs 45 [IQR: 36-56] minutes), though not statistically significant in a multivariable regression analysis (OR: 1.12; 95% CI: 0.90-1.40; $P = 0.322$). In patients with non-chest pain symptoms, the median time from call to hospitalization was longer in patients in ongoing opioid treatment (61 [IQR: 49-83] vs 55 [IQR: 42-75] minutes) and significant in a multivariable regression analysis (OR: 1.57; 95% CI: 1.13-2.18; $P = 0.007$). Similarly, by multiple linear regression with log-transformation of time from call to hospitalization,

FIGURE 3 Symptoms of Myocardial Infarction by Opioid Use, Sex, and Age



Treemap charts with symptoms of myocardial infarction in calls to the Emergency Medical Services (combined emergency number and out-of-hours service). Total calls $N = 6{,}633$. The charts are stratified by opioid use, sex, and age. The size of the colored areas is proportional to the numbers addressed as frequencies.

the median time was significantly longer in patients in ongoing opioid treatment than controls when analyzing all calls ($P = 0.001$) and patients with non-chest pain symptoms ($P = 0.029$), though not in patients with chest pain ($P = 0.382$).

There were nonsignificantly fewer acute ambulances assigned to patients in ongoing opioid treatment compared to controls in a multivariable regression analysis (74% vs 79%; OR: 0.81; 95% CI: 0.65-1.01; $P = 0.061$).

MI CLASSIFICATION. Chest pain in MI was less frequently registered in calls from patients in ongoing opioid treatment compared to controls in the setting of both STEMI (69% vs 80%) and NSTEMI (65% vs 75%), see **Figure 4**. The adjusted odds of chest pain in MI for patients in ongoing opioid treatment vs controls were not significantly different between STEMI and NSTEMI, see **Figure 4**.

THIRTY-DAY MORTALITY. The 30-day mortality was significantly increased in MI patients in ongoing opioid treatment compared to controls in a multivariable regression analysis (10% vs 5%; OR: 1.54; 95% CI: 1.11-2.14; $P = 0.010$). This difference was independent of the primary symptom (chest pain vs non-chest pain symptoms, P for interaction = 0.873).

PATIENTS CALLING MORE THAN ONCE. Patients in ongoing opioid treatment had more calls than the controls to the Emergency Medical Services that led to hospitalization with a primary diagnosis of MI (9% vs 6% of patients had more than one call). In the recurrent incidences of MI, chest pain in MI remained less frequent in patients in ongoing treatment compared to controls (81% vs 85% of the calls). Similarly, in repeated calls within 24 hours prior to hospitalization, patients in ongoing opioid treatment had less frequent chest pain than controls (52% vs 59% of the calls).

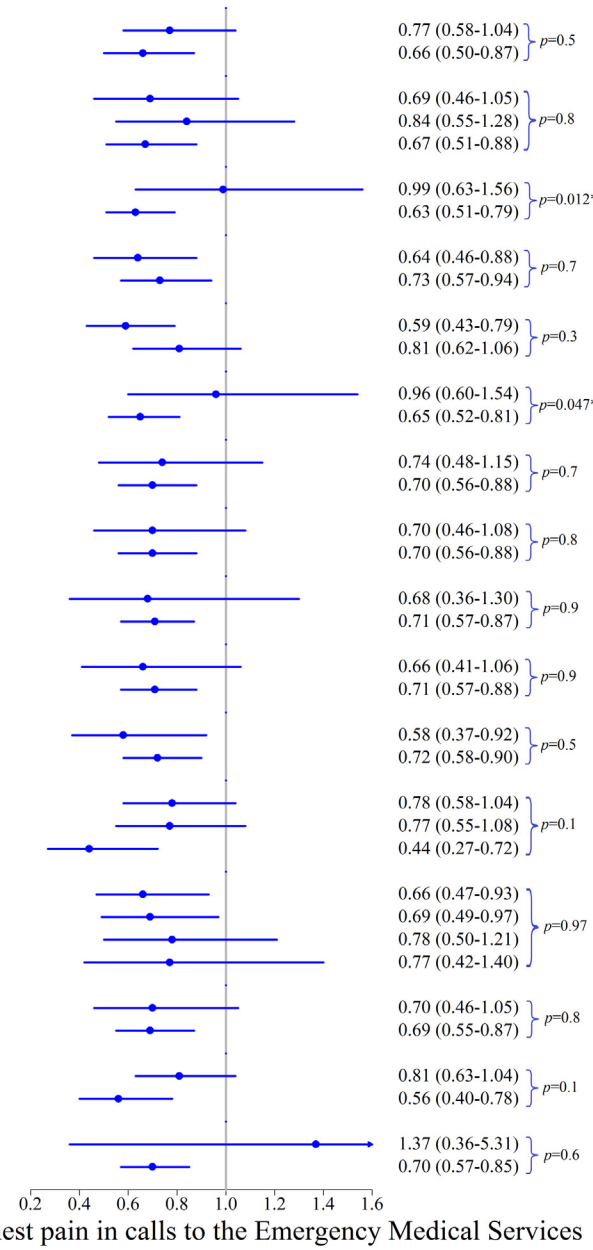
SENSITIVITY ANALYSES. No clinically significant difference was observed in the adjusted odds of chest pain in MI in patients in ongoing opioid treatment and controls when comparing prescription time prior to the call (opioid treatment initiated 14 days, 30 days, or 60 days prior to the call or estimated as any duration of opioid use at the call time).

In the inverse probability of treatment weighting analysis, ongoing opioid treatment remained associated with a significant decrease in the adjusted odds of chest pain in MI (OR: 0.70; 95% CI: 0.64-0.76; $P < 0.001$).

In Supplemental Table 1, the adjusted odds of chest pain stratified by comorbidities and demographic information are listed with different reference groups.

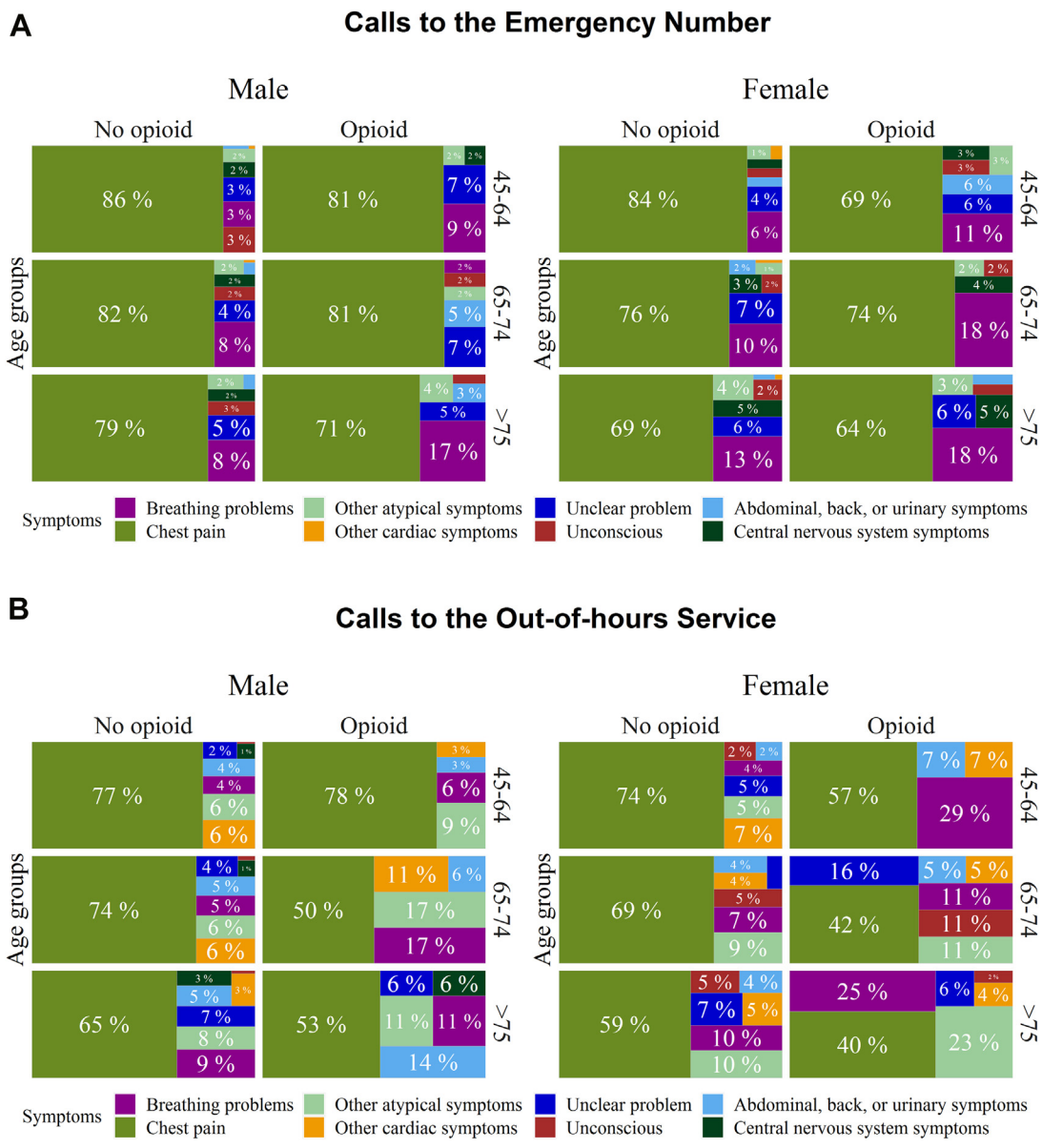
FIGURE 4 Chest Pain in Myocardial Infarction by Opioid Use and Baseline Information

Variables	Frequency of chest pain in myocardial infarction in patients in ongoing opioid treatment vs. controls	Odds ratio (95% CI)	
Sex			
Male	190/265 (71.7%) vs. 3,197/4,035 (79.2%)	0.77 (0.58-1.04)	p=0.5
Female	173/287 (60.3%) vs. 1,458/2,046 (71.3%)	0.66 (0.50-0.87)	
Age groups			
45-64 years	104/139 (74.8%) vs. 1,896/2,323 (81.6%)	0.69 (0.46-1.05)	p=0.8
65-74 years	89/130 (68.5%) vs. 1,228/1,586 (77.4%)	0.84 (0.55-1.28)	
>75 years	170/283 (60.1%) vs. 1,531/2,172 (70.5%)	0.67 (0.51-0.88)	
Diabetes			
Yes	88/123 (71.5%) vs. 696/971 (71.7%)	0.99 (0.63-1.56)	p=0.012*
No	275/429 (64.1%) vs. 3,959/5,110 (77.5%)	0.63 (0.51-0.79)	
Chronic ischemic heart disease			
Yes	179/243 (73.7%) vs. 1,545/1,872 (82.5%)	0.64 (0.46-0.88)	p=0.7
No	184/309 (59.5%) vs. 3,110/4,209 (73.9%)	0.73 (0.57-0.94)	
Hypertension			
Yes	144/225 (64.0%) vs. 1,647/2,174 (75.8%)	0.59 (0.43-0.79)	p=0.3
No	219/327 (67.0%) vs. 3,008/3,907 (77.0%)	0.81 (0.62-1.06)	
Atrial fibrillation			
Yes	89/122 (73.0%) vs. 509/680 (74.9%)	0.96 (0.60-1.54)	p=0.047*
No	274/430 (63.7%) vs. 4,146/5,401 (76.8%)	0.65 (0.52-0.81)	
Heart failure			
Yes	85/128 (66.4%) vs. 562/775 (74.4%)	0.74 (0.48-1.15)	p=0.7
No	278/424 (65.6%) vs. 4,093/5,326 (76.8%)	0.70 (0.56-0.88)	
Chronic obstructive pulmonary disease			
Yes	77/134 (57.5%) vs. 344/538 (63.9%)	0.70 (0.46-1.08)	p=0.8
No	286/418 (68.4%) vs. 4,311/5,543 (77.8%)	0.70 (0.56-0.88)	
Chronic kidney disease			
Yes	44/65 (67.7%) vs. 258/345 (74.8%)	0.68 (0.36-1.30)	p=0.9
No	319/487 (65.5%) vs. 4,397/5,736 (76.7%)	0.71 (0.57-0.87)	
Peripheral vascular disease			
Yes	71/108 (65.7%) vs. 421/571 (73.7%)	0.66 (0.41-1.06)	p=0.9
No	292/444 (65.8%) vs. 4,234/5,510 (76.8%)	0.71 (0.57-0.88)	
Cancer			
Yes	69/111 (62.2%) vs. 557/743 (75.0%)	0.58 (0.37-0.92)	p=0.5
No	294/441 (66.7%) vs. 4,098/5,338 (76.8%)	0.72 (0.58-0.90)	
Educational level			
Basic	179/278 (64.4%) vs. 1,583/2,161 (73.3%)	0.78 (0.58-1.04)	p=0.1
Intermediate	131/187 (70.1%) vs. 2,006/2,588 (77.5%)	0.77 (0.55-1.08)	
Advanced	53/87 (60.9%) vs. 1,066/1,332 (80.0%)	0.44 (0.27-0.72)	
Income level			
Low	111/180 (61.7%) vs. 1,120/1,554 (72.1%)	0.66 (0.47-0.93)	p=0.97
Low-intermediate	124/193 (64.2%) vs. 1,068/1,440 (74.2%)	0.69 (0.49-0.97)	
Intermediate-high	84/117 (71.8%) vs. 1,193/1,516 (78.7%)	0.78 (0.50-1.21)	
High	44/62 (71.0%) vs. 1,274/1,571 (81.1%)	0.77 (0.42-1.40)	
Myocardial infarction type			
ST-elevation myocardial infarction	93/134 (69.4%) vs. 1,675/2,089 (80.2%)	0.70 (0.46-1.05)	p=0.8
non-ST-elevation myocardial infarction	270/418 (64.6%) vs. 2,980/3,992 (74.6%)	0.69 (0.55-0.87)	
Call type			
Emergency number	273/381 (71.7%) vs. 3,125/3,911 (79.9%)	0.81 (0.63-1.04)	p=0.1
Out-of-hours service	90/171 (52.6%) vs. 1,530/2,170 (70.5%)	0.56 (0.40-0.78)	
Living at a nursing home			
Yes	11/18 (61.1%) vs. 48/82 (58.5%)	1.37 (0.36-5.31)	p=0.6
No	352/534 (65.9%) vs. 4,607/5,999 (76.8%)	0.70 (0.57-0.85)	



Forest plot with estimation of adjusted odds of chest pain in myocardial infarction stratified by opioid use and demographic information. Total calls (out-of-hours service and emergency number) $N = 6{,}633$. Calls from patients in ongoing opioid treatment $n = 552$. Calls from the controls $n = 6{,}081$. Adjusted odds ratios are analyzed by multivariable regression comparing calls from patients in ongoing opioid treatment to the controls. *P* indicates the interaction analysis by likelihood ratio test. *Indicates statistical significance. Odds ratio <1 indicates lower odds of chest pain in myocardial infarction in patients in ongoing opioid treatment compared to the controls.

FIGURE 5 Symptoms of Myocardial Infarction in Calls to the Emergency Number and Out-of-Hours Service



Treemap charts with symptoms of myocardial infarction in calls to the emergency number (A) and out-of-hours service (B). Calls to the emergency number $n = 3{,}911$. Calls to the out-of-hours service $n = 2{,}170$. The charts are stratified by call type, opioid use, sex, and age. The size of the colored areas is proportional to the numbers addressed as frequencies.

In Supplemental Figure 2, a forest plot illustrates the adjusted odds of chest pain in MI stratified by dosage and duration of ongoing opioid treatment compared to controls. No clinically significant difference was found in duration or dosage on the adjusted odds of chest pain.

In **Figure 4**, interaction analyses are performed. Diabetes and atrial fibrillation were significant on the adjusted odds of chest pain in MI in patients in ongoing opioid treatment compared to controls (*P* for interaction, respectively, 0.012 and 0.047), though nonsignificant by Bonferroni correction. See Supplemental Figure 3 for analyses on diabetes.

DISCUSSION

MAIN FINDINGS. In our registry-based study of 6,633 calls to the Copenhagen Emergency Medical Services,

TABLE 1 Baseline Characteristics According to Opioid Use

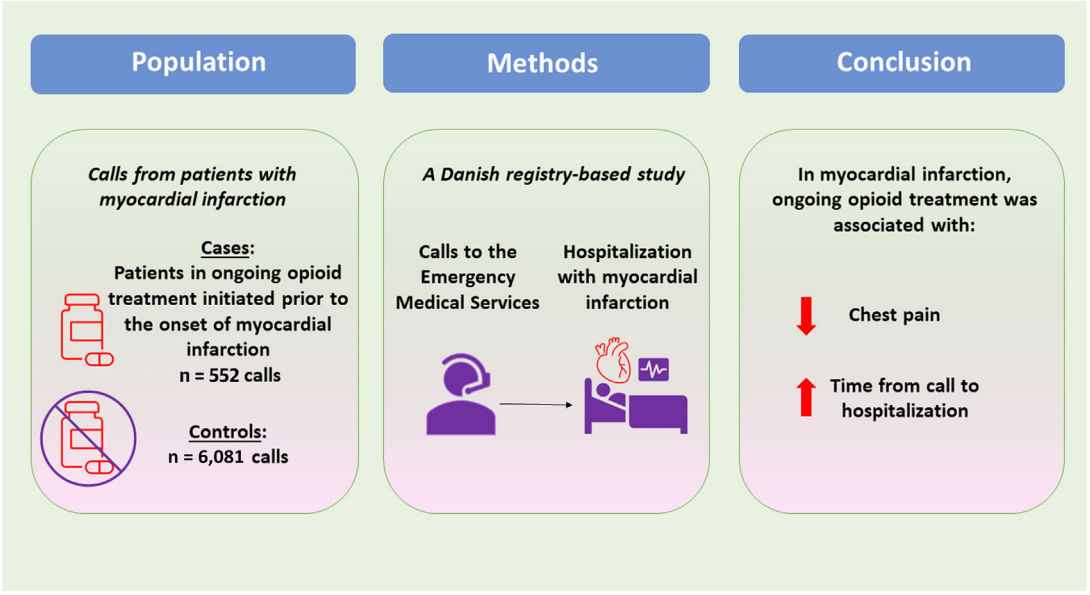
	Total Calls (N = 6,633)	Calls From Patients in Ongoing Opioid Treatment (n = 552)	Calls From Controls (n = 6,081)	*P* Value
Call type				0.030
Out-of-hours service (Medical Helpline 1813)	2,341 (35.3)	171 (31.0)	2,170 (35.7)	
Emergency number (1-1-2)	4,292 (64.7)	381 (69.0)	3,911 (64.3)	
Unique individuals (*n*, % of calls)	6,186 (93.3)	519 (94.0)	5,710 (93.9)	
Female	2,333 (35.2)	287 (52.0)	2,046 (33.6)	<0.001
Age, y	69 ± 12.8	73 ± 12.6	69 ± 12.6	<0.001
Age groups				<0.001
45-64 y	2,462 (37.1)	139 (25.2)	2,323 (38.2)	
65-74 y	1,716 (25.9)	130 (23.6)	1,586 (26.1)	
≥75 y	2,455 (37.0)	283 (51.3)	2,172 (35.7)	
Educational level[a]				<0.001
Basic	2,100 (33.4)	254 (48.1)	1,846 (32.0)	
Intermediate	2,775 (44.1)	187 (35.4)	2,588 (44.9)	
Advanced	1,419 (22.5)	87 (16.5)	1,332 (23.1)	
Income level[b]				<0.001
Low	1,633 (25.0)	174 (31.9)	1,459 (24.4)	
Low-intermediate	1,633 (25.0)	193 (35.3)	1,440 (24.1)	
Intermediate-high	1,630 (25.0)	116 (21.2)	1,514 (25.3)	
High	1,636 (25.0)	63 (11.5)	1,573 (26.3)	
Comorbidity[c]				
Chronic ischemic heart disease	2,115 (31.9)	243 (44.0)	1,872 (30.8)	<0.001
Atrial fibrillation	802 (12.1)	122 (22.1)	680 (11.2)	<0.001
Heart failure	833 (13.3)	128 (23.2)	755 (12.4)	<0.001
Peripheral vascular disease	679 (10.2)	108 (19.6)	571 (9.4)	<0.001
Hypertension	2,399 (36.2)	225 (40.8)	2,174 (35.8)	0.021
Diabetes	1,094 (16.5)	123 (22.3)	971 (16.0)	<0.001
Chronic kidney disease	410 (6.2)	65 (11.8)	345 (5.7)	<0.001
Chronic obstructive pulmonary disease	672 (10.1)	134 (24.3)	538 (8.8)	<0.001
Cancer	854 (12.9)	111 (20.1)	743 (12.2)	<0.001
Charlson comorbidity index[d]	2 (1-4)	3 (2-7)	2 (1-4)	<0.001
Myocardial infarction type				<0.001
ST-elevation myocardial infarction (STEMI)	2,223 (33.5)	134 (24.3)	2,089 (34.4)	
Non-ST-elevation myocardial infarction (NSTEMI)	4,410 (66.5)	418 (75.7)	3,992 (65.6)	
Troponin ratio at hospitalization[d]				
1st troponin	3 (1-13)	4 (1-15)	3 (1-13)	0.616
2nd troponin	26 (4-121)	14 (3-69)	27 (4-126)	0.009
3rd troponin	50 (8-203)	23 (4-114)	54 (8-211)	0.002
Time from call to 1st troponin (hours)	3.6 (10.3)	5.3 (13.3)	3.4 (10.0)	<0.001
Living at a nursing home	100 (1.5)	18 (3.3)	82 (1.3)	<0.001

Values are n (%), mean (±SD), or median (IQR). [a]Educational levels categorized according to the International Standard Classification of Education (ISCED)[36]: ISCED-code ≤2: *basic*, ISCED-code 3 to 4: *intermediate*, and ISCED-code ≥5: *advanced*. [b]Income level defined as the equivalised income accounting for redistribution within the family and analyzed by stratification into quartiles of the total population (*low*, *low-intermediate*, *intermediate-high*, *high*). [c]Comorbidity diagnoses given within 10 years prior to the call, defined by the diagnosis and/or diagnosis-specific medication. Cancer excludes non-melanoma skin cancer. [d]Troponin: calculated as a ratio of the measured troponin divided by the threshold level, respectively, troponin T = 14 ng/L and troponin I = 25 ng/L.

we found an association between ongoing opioid treatment and less frequent complaints of chest pain in MI compared to controls. Furthermore, ongoing opioid treatment was associated with more frequent non-chest pain symptoms. Lastly, the time from the call to hospitalization was slightly longer for patients in ongoing opioid treatment compared to controls (please see the **Central Illustration**).

SYMPTOM PRESENTATION OF MI. Chest pain is the cardinal symptom of MI.[6] However, patients may present with other symptoms, such as dyspnea, palpitations, nausea, vomiting, syncope, or pain in the neck, stomach, left arm, shoulder, and jaw.[6] Several factors might influence chest pain in MI, for example, diabetes,[12] increasing age,[6] and female sex[10,11] are associated with less chest pain. A recent meta-

CENTRAL ILLUSTRATION **Ongoing Opioid Treatment and Symptoms of Myocardial Infarction Registered in Calls to the Emergency Medical Services**



Nørskov AS, et al. JACC Adv. 2024;3(10):101268.

analysis suggested that sex differences in chest pain in acute coronary syndrome may be due to different interpretations and symptom descriptions, rather than actual major differences in the symptoms of acute coronary syndrome.[29]

Our study showed that chest pain was less frequent in calls from patients in ongoing opioid treatment than controls, with nonsignificantly less chest pain in females, by increasing age, and in calls to the out-of-hours service. We observed more frequent non-chest pain symptoms, particularly breathing problems. This could be attributed to opioid-induced pain-relief with breathing problems as a prominent symptom of acute heart failure secondary to MI. Additionally, the higher burden of comorbidities in patients in ongoing opioid treatment may have impacted the clinical presentation of MI.

TIME FROM CALL TO HOSPITALIZATION. Limiting the time from symptom onset to the initiation of treatment is crucial in preventing myocardial damage in MI.[30] A Danish study found a median time of 113 minutes from call to the Emergency Medical Services to primary percutaneous coronary intervention in a total of 14,534 patients.[31] However, sparse evidence is available on time from call to hospitalization. We found a median time difference of 3 minutes from the call to hospitalization in MI patients in ongoing opioid treatment compared with controls (50 vs 47 minutes), and slightly longer for patients with non-chest pain symptoms (61 vs 55 minutes). These are slightly longer and statistically significant delays for patients in ongoing opioid treatment. However, 3- and 6-minute median time differences are considered with minor clinically significant implications.[8,9] Additionally, we found nonsignificantly lower allocation of acute ambulances in patients in ongoing opioid treatment compared to controls. We hypothesize that this may be due to the higher frequency of non-chest pain symptoms of MI in patients in ongoing opioid treatment than in controls.

To examine the variety of MI symptoms, we included patients admitted until 24 hours after the call, as some patients presented with symptoms that did not lead to immediate admission. Instead, some patients were referred to a consultation at the emergency doctor service. Hence, admission could be postponed and potentially challenge the time for successful revascularization. However, most patients were admitted within a few hours after the call.

PERSPECTIVES. The acute management of MI should be based on an evaluation of risk factors, clinical presentation, electrocardiogram, biomarkers, other diagnostic tools, and patient preferences.[32] Chest pain is considered a symptom of relevance for acute

cardiovascular diseases but is also associated with a high degree of over-triage.[33] Hence, it is a challenge to minimize over-triage with inappropriate ambulance transport and admission at the emergency department. However, it is crucial in the telephone triage not to overlook conditions that need an emergency response and acute admission.

Our results can be generalized to MI patients above the age of 45. The lower frequency of chest pain in patients in ongoing opioid treatment may have challenged the clinicians in the identification of MI symptoms, the decision of a proper emergency response, and potentially induced a risk of overlooking MI, which may have contributed to the slightly longer time to hospitalization and increased 30-day mortality. This may also be explained by the unmeasured frailty of opioid-treated patients. Nevertheless, increased awareness of ongoing opioid treatment is needed, as our results indicate less frequent chest pain in MI in calls. Hence, the findings are of clinical relevance to ensure correct emergency response.

Further quantitative and qualitative studies are suggested to be conducted in other clinical settings, eg, the emergency room, to establish the level of impact of ongoing opioid treatment on chest pain in MI.

STRENGTHS. This is the first study to evaluate MI symptoms in patients in ongoing opioid treatment calling the Emergency Medical Services. The large sample size of 6,633 calls was a strength of the study.

We linked the personal identification numbers to Danish registries, which are comprehensive and well-validated. Hence, we were able to identify patients in ongoing opioid treatment as a subgroup with more frequent non-chest pain symptoms of MI.

STUDY LIMITATIONS. The analysis of MI symptoms was limited by the symptom registration in calls, eg, patients may have presented with non-registered symptoms. Furthermore, the symptom registration included only the primary symptom most appropriate to the history of the patient and/or the purpose of the call to identify a proper emergency response. This induces a risk of misclassification of the primary symptom. However, we do not expect this to be a source of bias with systematic differences between patients in ongoing opioid treatment and controls.

The study is limited by the missing information on the indication of the opioid treatment.

There is a possibility of misclassification by the ICD-10 codes as some patients may have suffered from type 2 MI while assigned the ICD-10 code for type 1 MI.

The 30-day mortality analysis was potentially challenged by confounding by indication, as patients in ongoing opioid treatment had a higher burden of comorbidities.

Though we adjusted for comorbidities in our analyses, the complexity of underlying diseases and drugs prescribed for other conditions may have affected the symptom presentation.

Ongoing opioid treatment was defined by the redemption of an opioid prescription. Whether the patients took the opioids as prescribed could not be confirmed in the registries. Hence, there is a risk of misclassification.

There is a risk of selection bias, as some MI patients may not be included in the study if they were not referred to the hospital after calling the Emergency Medical Services or if they did not call the Emergency Medical Services (eg, due to silent MI or self-transport directly to the emergency department).

As our study is registry-based, the results ought to be interpreted as associations and trends, rather than causality of the impact of ongoing opioid treatment on MI symptoms.

CONCLUSIONS

Ongoing opioid treatment was associated with less frequent chest pain complaints in MI in patients calling the Copenhagen Emergency Medical Services. Furthermore, ongoing opioid treatment was associated with more frequent non-chest pain symptoms, particularly breathing problems, abdominal, back, or urinary symptoms, and other atypical symptoms. Finally, MI patients in ongoing opioid treatment had slightly increased time from call to hospitalization. These findings underline the need for a clinical focus on patients in ongoing opioid treatment, as symptom presentation in these patients may differ and potentially challenge the emergency response.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by The Danish Heart Foundation (grant number 18-R122-A8403). Dr Torp-Pedersen has received grants from Novo Nordisk and Bayer. Dr Bang is employed at Novo Nordisk, Denmark. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Anne Storgaard Nørskov, Department of Cardiology, Copenhagen University Hospital-Bispebjerg and Frederiksberg, Nordre Fasanvej 57, DK-2000 Frederiksberg, Denmark. E-mail: anne.storgaard.noerskov@regionh.dk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Non-chest pain symptoms of MI challenge the identification of MI and are more frequent in women, elderly, and patients with diabetes. Also, patients in ongoing opioid therapy initiated before the onset of acute coronary ischemia are observed to have more frequent complaints of non-chest pain symptoms of MI, such as dyspnea, abdominal, back, or urinary symptoms, when directly examined in telephone calls to the Emergency Medical Services.

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: Healthcare personnel in the Emergency Medical Services play a critical role in early recognition of MI symptoms in telephone calls to ensure correct visitation and subsequent initiation of life-saving treatment. Increased awareness of symptom presentation in patients in ongoing opioid treatment is needed in the telephone triage, as chest pain in MI may be masked in these patients and induce a risk of treatment delay.

TRANSLATIONAL OUTLOOK 1: As this is a registry-based study of symptoms registered in calls to the Emergency Medical Services, further quantitative and qualitative studies are suggested to be conducted in other clinical settings, eg, the emergency department, to establish the level of impact of ongoing opioid treatment on chest pain presentation in MI.

TRANSLATIONAL OUTLOOK 2: As opioids are widely used worldwide and symptom presentation is a crucial tool in diagnostics, additional studies are suggested to be conducted on the impact of opioids on pain perception in other pain-dominated diseases, as opioid use may challenge diagnostics due to its pain-relieving effect.

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KEY WORDS **chest pain, coronary ischemia, emergency number, opioid therapy, out-of-hours service, symptom**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**