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Clinical paper

Pharmacotherapy and hospital admissions before out-of-hospital cardiac arrest: A nationwide study☆

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ABSTRACT

Background: For out-of-hospital cardiac arrest (OHCA) to be predicted and prevented, it is imperative the healthcare system has access to those vulnerable before the event occurs. We aimed to determine the extent of contact to the healthcare system before OHCA.
Methods: All patients in Denmark with a registered OHCA June 1, 2001–December 31, 2005 were matched on age and sex with 10 random controls from the entire Danish population. We estimated the association with OHCA by conditional logistic regression analyses, and we determined the proportion of patients in contact with the healthcare system before OHCA from hospital admissions or claimed prescriptions.
Results: We identified 12,089 patients with an OHCA. Of these, 62% (7548) and 85% (10,312) were in contact with the healthcare system up to 30 days and 1 year before OHCA, respectively. Association with OHCA up to 30 days before the event pertained to myocardial infarction (odds ratio (OR) = 6.4, 95% confidence interval (CI): 4.7–8.6)); heart failure (OR = 5.1, CI: 4.1–6.3); ischemic heart disease (OR = 1.9, CI: 1.6–2.4); and cardiac dysrhythmia (OR = 1.8, CI: 1.4–2.2). Concomitant pharmacotherapy up to 30 days before OHCA with the strongest association was: corticosteroids (systemic) (OR = 2.7, CI: 2.5–3.0), bronchial dilators (OR = 2.5, CI: 2.3–2.7), anti-psychotic medication (OR = 2.1, CI: 1.9–2.3), and digoxin (OR = 2.1, CI: 2.0–2.3). Similar results were found for associations up to 1 year before OHCA.
Conclusion: Contrary to general belief, the majority of OHCA patients are in contact with the healthcare system shortly before OHCA.

1. Introduction

Sudden cardiac death (SCD) is the single most important cause of death in the industrialized world with an estimated annual incidence of 295,000 treated out-of-hospital cardiac arrests (OHCA) in the US alone.[1] Despite substantial public and political awareness, SCD remains a major clinical and public health problem with a need for clinical strategies for primary and secondary prevention.[2] Thus, identifying risk factors predisposing SCD is of great importance in order to identify particular high-risk subgroups within the general population.[3]

Studies have found that the majority of SCD individuals are from the general population; consequently, these persons are largely unknown to the treating physician as SCD may be the first cardiac event.[4] However, these findings were made on a background of registered patient morbidity only and did not include other indicators of healthcare contact. Thus, the aim of this study was to assess hospital admissions and to characterize ongoing concomitant pharmacotherapy in a nationwide OHCA population that would add to the epidemiological knowledge of SCD.

2. Methods

A unique and permanent personal civil registration number is assigned to all residents in Denmark, enabling individual-level

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linkage of information between nationwide registers. The Danish Register of Medicinal Product Statistics (national prescription register) holds information on all dispensed drug prescriptions from Danish pharmacies since 1995. Dispensed drugs are classified according to the Anatomical Therapeutic Chemical (ATC) system. Pharmacies in Denmark must register all dispensed drug prescriptions because of partial reimbursement of drug expenses by the government-financed healthcare system; hence a high validity and accuracy of the register is ensured.[5] We obtained information on hospitalizations and comorbidity from the Danish National Patient Register, which holds all admissions to Danish hospitals since 1978.[6] Every hospital admission is registered with one primary diagnosis and, if appropriate, two or more secondary diagnoses according to the International Classification of Diseases – before 1994 the 8th revision (ICD-8) and after 1994 the 10th revision (ICD-10).

2.1. Study population

Information on OHCA 2001–2005 was obtained from the Danish Cardiac Arrest Register and the Copenhagen Mobile Emergency Care Unit (MECU). The nationwide Danish Cardiac Arrest Register (comprising all OHCA among Denmark's 5.41 million inhabitants) was established June 1, 2001. The register holds information on date, time, and occurrence of all OHCA where an ambulance was dispatched and information about whether the individual received cardiopulmonary resuscitation or defibrillation (from bystanders or ambulance personnel).[7] Coverage and detailed information on the Copenhagen MECU have been described previously.[8,9] In brief, physician staffed ambulances systematically records all data from all registered OHCAs from the central part of Copenhagen.

To assess differences in comorbidity, hospital admissions and pharmacotherapy among OHCA patients and the general population, every OHCA patient was matched on age and sex with 10 controls from the Danish population who on January 1, 2001 were ≥14 years of age as done previously.[10] The controls were assigned the same date of OHCA as the case they were matched upon.

2.2. Comorbidity, hospital admissions, and pharmacotherapy

To investigate the time relation of contact to the healthcare system and OHCA, we studied patient contact in two overlapping periods: up to 30 days before OHCA, and up to 1 year before OHCA. We defined patient comorbidity as hospital admission up to 10 years before date of OHCA. Patients with diabetes were identified as individuals who claimed at least one prescription of glucose-lowering medication (ATC: A10; oral or insulin). Information on hospital admissions was obtained from the Danish National Patient Register as primary or secondary diagnosis for the following ICD-10 codes: peripheral vascular disease (I70, I74), cerebral vascular disease (I60–69), ischemic heart disease (I20–I25), arrhythmias (I47–49), myocardial infarction (MI) (I21, I22), heart failure (I42, I50, I110, J81), peptic ulcer (K25–K28), trauma (S00–S99, T00–T35), psychiatric illness (including substance abuse) (F00–F99), liver disease (K70–K77, B150, B160, B190), malignancy (C00–C97), and chronic obstructive pulmonary disease (COPD) (J42, J44). We identified patients with cardiovascular disease (CVD) by the following hospital admissions: I00–I45, I47–I99.

The National Prescription Register provided information on concomitant pharmacotherapy according to the following ATC codes: antidepressants (N06A), sedatives and anxiolytics (N05B, N05C), anti-psychotic agents (N05A), analgesics (including morphine) (N02), bronchial dilators (R02), corticosteroids (systemic) (H02A), antithrombotic agents (B01), cholesterol-lowering agents (C10), anti-angina medication (C01D) angiotensin converting enzyme inhibitors or angiotensin-2 receptor blockers (C09), betablockers (C07), diuretics (C03), and digoxin (C01A).

We divided patients into prioritized groups according to hospital admissions and concomitant pharmacotherapy before OHCA to assess the type and number of patients in contact with the healthcare system. Those with diabetes or those admitted to a hospital with CVD were grouped as "cardiovascular-specific hospital admissions" and had the highest priority. Patients not included in this group but with one of the following hospital admissions: peptic ulcer, trauma, psychiatric illnesses, liver disease, malignancy, or COPD were grouped as "non-cardiovascular-specific hospital admissions" and were prioritized second highest. Those with no hospital admissions but with at least one claimed prescription for the following: cholesterol-lowering agents, anti-thrombotic agents, anti-angina medication, calcium inhibitors, betablockers, angiotensin converting enzyme inhibitors and angiotensin-II-receptor blockers, digoxin, and diuretics were grouped together as "cardiovascular-specific pharmacotherapy" and prioritized third highest. Patients who claimed a prescription for one of the following: antidepressants, anxiolytics and sedatives, anti-psychotics, analgesics (incl. morphine), bronchial dilators or corticosteroids, but with no hospital admissions and no claimed prescription for cardiovascular specific pharmacotherapy were grouped as "non-cardiovascular-specific pharmacotherapy" and prioritized the lowest. Those not assigned to any prioritized group did not have any apparent contact with the healthcare system shortly before OHCA.

2.3. Statistics

Comparison of categorical variables was done with a chi-square test. Differences between continuous variables were tested with Kruskall–Wallis test (non-parametric). Conditional multivariable logistic regression analyses were done to determine which covariates were associated with OHCA. Two models were applied. In the first model we adjusted for concomitant pharmacotherapy listed in Table 1 (Fig. 1). In the second model we adjusted for the types of hospital admissions listed in Table 1 (Fig. 2). Association is given as odds ratios (OR). Model assumptions of no interaction and linearity of continuous variables were fulfilled unless otherwise specified. The reference group was identified using the "greedy macro match algorithm".[11] For all analyses a two-sided p-value <0.05 was considered statistically significant. All analyses were done using SAS, version 9.1 (SAS institute Inc., Cary, NC, USA).

2.4. Ethics

The study was approved by the Danish Data Protection Agency (No. 2008-41-2685). No ethical approval is required for retrospective register-based studies in Denmark.

3. Results

The Danish Cardiac Arrest Register and the Copenhagen MECU yielded 13,701 OHCA in 2001–2005; of these 1414 (10.3%) OHCA were excluded because of no personal civil registration number (non-residents in Denmark, tourists etc.) or because of a misreported civil registration number. Also excluded were 198 (1.5%) OHCA patients who were <14 years of age on January 1, 2001. Thus, the final OHCA study population comprised 12,089 individuals. The randomly selected age-and-sex matched control population comprised 120,890 individuals.

Of the 12,089 OHCA patients, 20.8% (2516) were known with underlying comorbidity of ischemic heart disease, 17.6% (2125) with heart failure, and 11.8% (1421) with previous MI. OHCA was

Table 1
Hospital admissions and concomitant pharmacotherapy for out-of-hospital cardiac arrest patients and the control population matched on age and gender.

	OHCA population		Control population	
N	12,089		120,890	
Men (%)	7923 (65.5)		79,230 (65.5)	
Age (years) (IQR)	70.0 (59–79)		70.0 (59–79)	
Men's age (years) (IQR)	69.0 (58–78)		69.0 (58–78)	
Women's age (years) (IQR)	73.0 (61–82)		73.0 (61–82)	
	30 days*	1 year*	30 days*	1 year*
Hospital admissions before event				
Peripheral vascular disease (%)	34 (0.3)	235 (1.9)	119 (0.1)	751 (0.6)
Cerebral vascular disease (%)	88 (0.7)	482 (4.0)	239 (0.2)	1897 (1.6)
Ischemic heart disease (%)	262 (2.2)	1101 (9.1)	440 (0.4)	3351 (2.8)
Myocardial infarction (%)	133 (1.1)	470 (3.9)	94 (0.1)	865 (0.7)
Cardiac dysrhythmia (%)	193 (1.6)	854 (7.1)	369 (0.3)	2628 (2.2)
Heart failure (%)	252 (2.1)	1073 (8.9)	208 (0.2)	1609 (1.3)
Diabetes (%)	684 (5.7)	1389 (11.5)	3417 (2.8)	6381 (5.3)
Peptic ulcer (%)	33 (0.3)	260 (2.2)	98 (0.1)	951 (0.8)
Trauma (%)	222 (1.8)	1446 (12.0)	992 (0.8)	9554 (7.9)
Psychiatric illness (%)	148 (1.2)	693 (5.7)	183 (0.2)	1512 (1.3)
Liver disease mild/severe (%)	22 (0.2)	104 (0.9)	27 (0.02)	160 (0.1)
Malignancy (%)	349 (2.9)	853 (7.1)	443 (0.4)	2520 (2.1)
COPD (%)	320 (2.7)	1081 (8.9)	275 (0.2)	1744 (1.4)
Concomitant pharmacotherapy				
Antidepressants (%)	1048 (8.7)	2282 (18.9)	5047 (4.2)	11,874 (9.8)
Sedatives and anxiolytics (%)	1906 (15.8)	4034 (33.8)	8820 (7.3)	24,562 (20.3)
Anti-psychotic medication (%)	590 (4.9)	1209 (10.0)	1953 (1.6)	4248 (3.5)
Analgesics (incl. morphine) (%)	2333 (19.3)	5020 (41.5)	11,258 (9.5)	30,425 (25.2)
Bronchial dilators (%)	1677 (13.9)	2640 (21.8)	5358 (4.4)	11,244 (9.3)
Corticosteroids (systemic) (%)	716 (5.9)	1782 (14.7)	1567 (1.3)	7081 (5.9)
Antithrombotic agents (%)	1258 (10.4)	3686 (30.5)	7496 (6.2)	21,450 (17.7)
Cholesterol lowering drugs (%)	531 (4.4)	1432 (11.9)	3504 (2.9)	9243 (7.7)
Calcium inhibitors (%)	702 (5.8)	2120 (17.5)	5145 (4.3)	14,308 (11.8)
Beta-blockers (%)	923 (7.6)	2535 (21.0)	5583 (4.6)	15,539 (12.9)
ACEi and ARB (%)	1318 (10.9)	3351 (27.7)	7621 (6.3)	18,814 (15.6)
Diuretics (%)	2193 (18.1)	5593 (46.3)	9628 (8.0)	30,219 (25.0)
Digoxin (%)	784 (6.5)	1721 (14.2)	2517 (2.1)	5566 (4.6)
Anti-angina medication (%)	662 (5.5)	1620 (13.4)	2141 (1.8)	6804 (5.6)

Dichotomous variables are given in numbers and percentages. Continuous variables are given in medians and IQR, inter-quartile range; COPD, chronic obstructive pulmonary disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

* In all instances p value for difference between case and control groups was $p < 0.0001$.

more frequent in men and with increasing age, except in individuals older than 90 years (data not shown).

Information on hospital admissions and concomitant pharmacotherapy for the OHCA population and the age-and-sex matched control population is shown in Table 1. Fig. 1 shows the overall odds from the adjusted conditional logistic regression analyses for concomitant pharmacotherapy associated with OHCA. Corticosteroids (systemic), bronchial dilators, digoxin, anti-angina medication and anti-psychotic agents, had the strongest association with OHCA 30 days before the event. The association with OHCA 1 year before the event was the strongest for anti-psychotic medication, digoxin, bronchial dilators, diuretics, and corticosteroids (systemic). Fig. 2 shows the overall odds from the adjusted conditional logistic regression analyses for being admitted to hospital before OHCA.

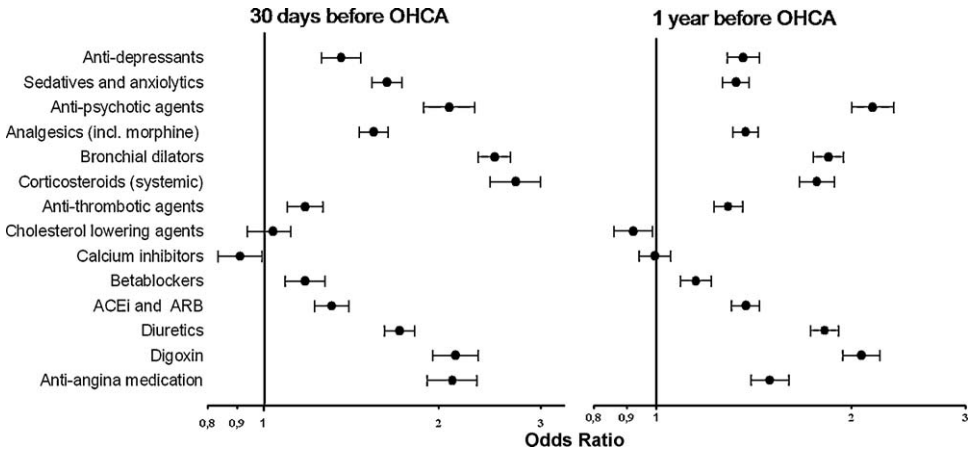

Fig. 1. Odds Ratios for concomitant pharmacotherapy associated with out-of-hospital cardiac arrest.
Odds ratios derived from conditional logistic regression analysis. Individuals who did not experience an OHCA were used as reference group. Error bars illustrate 95% confidence interval. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

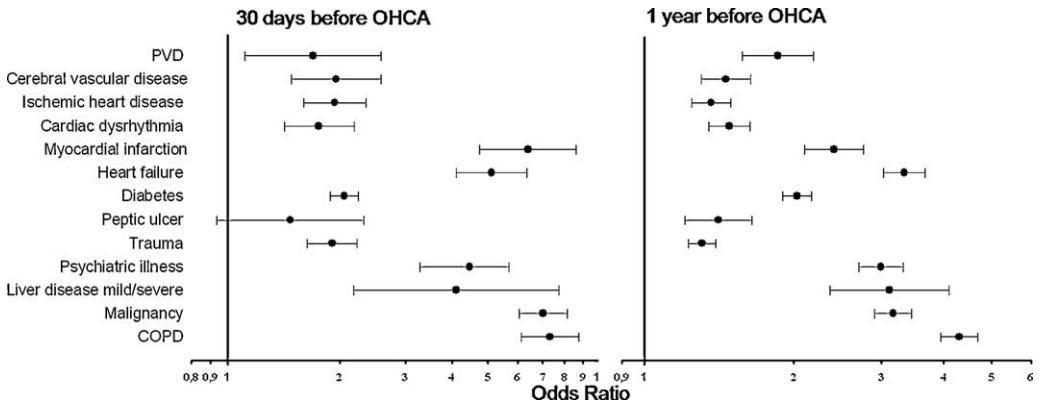

Fig. 2. Odds ratios for hospital admissions associated with out-of-hospital cardiac arrest. Odds ratios derived from conditional logistic regression analysis. Individuals who did not experience an OHCA were used as reference group. Error bars illustrate 95% confidence interval. PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease.

Hospital admissions for MI, heart failure, liver disease, COPD, malignancy and psychiatric illness were all strongly associated with OHCA up to 30 days before the event. The hospital admissions with the strongest association with OHCA up to 1 year before the event were COPD, heart failure, malignancy, liver disease, psychiatric illness and MI. Additional models including prescription information as well as hospital admissions were performed additionally and yielded similar results. Because of the high correlation between some medications and diseases these models were not selected for presentation.

Fig. 3 illustrates the proportion of OHCA patients with a hospital admission and/or a claimed prescription before OHCA according to the prioritized groupings: (1) cardiovascular-specific hospital admission; (2) non-cardiovascular-specific hospital admissions; (3) cardiovascular-specific pharmacotherapy; or (4) non-cardiovascular-specific pharmacotherapy. Of the 12,089 individuals with OHCA, 62% (7548) were either admitted to hospital or had a claimed prescription up to 30 days before the event. Further, 85% (10,312) had a hospital admission or a claimed prescription up to 1 year before the event (Fig. 3). The discriminative power of the model was good with a c-statistics value of 0.72 and 0.67 with information on concomitant pharmacotherapy and hospital admissions included in the model 1 year and 30 days before OHCA, respectively.

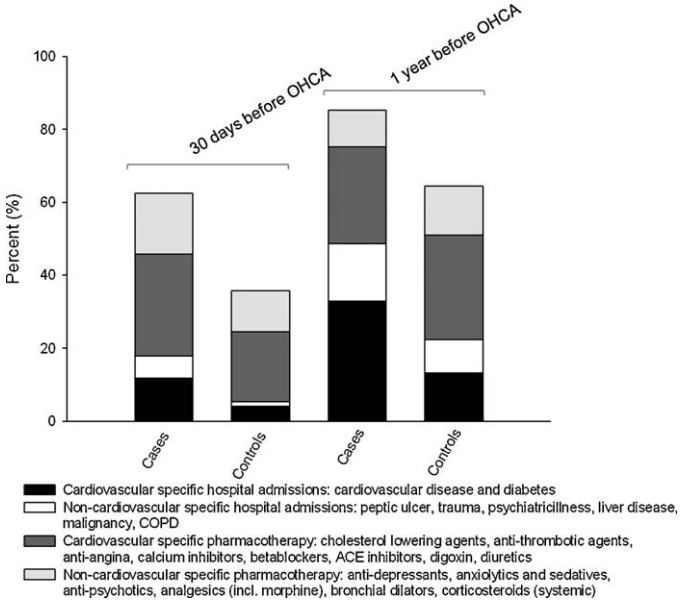

Fig. 3. Pharmacotherapy and hospital admissions 30 days and 1 year before out-of-hospital cardiac arrest. Stacked bar chart with following priorities: (1) cardiovascular specific hospital admissions; (2) non-cardiovascular-specific hospital admissions; (3) cardiovascular specific pharmacotherapy; (4) non-cardiovascular-specific pharmacotherapy.

Tables 2 and 3 show detailed information on hospital admissions and concomitant pharmacotherapy among the OHCA individuals according to prioritized groupings shown in Fig. 3.

4. Discussion

The major finding in this nationwide population-based study was that 62% (7548) and 85% (10,312) of all individuals with OHCA between 2001 and 2005 were either admitted to hospital or claimed a prescription for a limited number of drugs shortly before the OHCA. Thus our findings suggest that the majority of OHCA individuals are in contact with the healthcare system shortly before OHCA.

Studies have demonstrated the difficulty associated with identifying and predicting which individuals are susceptible to SCD because there is a opposite relationship between the number of risk factors applied and the number of SCD incidents.[4] Thus, most SCD individuals are comprised within the general population. The general population has less apparent risk factors predisposing SCD; hence the SCD individuals cannot be identified as high-risk individuals before their death[12] Unlike the findings made by Myerburg et al.,[4] who included all patient history predisposing SCD, we focused primarily on short-term patient history before the event. We also included information on patients in treatment with a limited number of prescription drugs in the year before the event. The prescription drugs included in this study were drugs with an assumed effect on the cardiovascular or respiratory system, or drugs that have previously been associated with sudden death. Importantly, without the information on concomitant pharmacotherapy, we would have been able to identify only 18 and 49% of patients who were admitted to hospital up to 30 days and 1 year before OHCA, respectively. Thus, the additional information on claimed prescriptions before OHCA enabled us to identify more patients who were in contact with the healthcare system before the event. This is new information on the aetiology of OHCA patients and could prove useful in the design of future preventive strategies (Fig. 3).

Over the years many tests for predicting and identifying patients at risk of SCD have been developed focusing on coronary perfusion, pump function, arrhythmias, structural abnormalities etc. Unfortunately, most tests, alone or in combination, have a high negative predictive value and a low positive predictive value.[13] Thus, it is

Table 2
Concomitant pharmacotherapy and hospital admissions for out-of-hospital cardiac arrest individuals according to the prioritized groups: cardiovascular-specific hospital admissions and non-cardiovascular specific hospital admissions 30 days and 1 year before arrest.

	Cardiovascular-specific hospital admissions[a]		Non-cardiovascular-specific hospital admissions[b]	
	30 days	1 year	30 days	1 year
N	1432	3961	732	1919
Men (%)	979 (68.4)	2604 (65.8)	404 (55.2)	1158 (60.3)
Age (years) (IQR)	72.0 (63–80)	73.0 (64–81)	69.0 (58–78)	67.0 (53–78)
Men's age (years) (IQR)	71.0 (62–79)	72.0 (63–80)	68.0 (56–76)	65.0 (50–76)
Women's age (years) (IQR)	74.0 (65–82)	75.0 (66–83)	71.0 (60–80)	70.0 (58–80)
Hospital admissions				
Peripheral vascular disease (%)	34 (2.4)	235 (5.9)	–	–
Cerebral vascular disease (%)	88 (6.2)	482 (12.2)	–	–
Ischemic heart disease (%)	262 (18.3)	1101 (27.8)	–	–
Myocardial infarction (%)	133 (9.3)	470 (11.9)	–	–
Cardiac dysrhythmia (%)	193 (13.5)	854 (21.6)	–	–
Heart failure (%)	252 (17.6)	1073 (27.1)	–	–
Diabetes (%)	684 (47.8)	1389 (35.1)	–	–
Peptic ulcer (%)	16 (1.1)	156 (3.9)	17 (2.3)	104 (5.4)
Trauma (%)	27 (1.9)	546 (13.8)	195 (26.6)	900 (46.9)
Psychiatric illness (%)	41 (2.9)	327 (8.3)	107 (14.6)	366 (19.1)
Liver disease mild/severe (%)	4 (0.3)	51 (1.3)	18 (2.5)	53 (2.8)
Malignancy (%)	64 (4.5)	358 (9.0)	285 (38.9)	495 (25.8)
COPD (%)	135 (9.4)	669 (16.9)	185 (25.3)	412 (21.5)
Concomitant pharmacotherapy				
Antidepressants (%)	151 (10.5)	865 (21.8)	87 (11.9)	543 (28.3)
Sedatives and anxiolytics (%)	263 (18.4)	1576 (39.8)	213 (29.1)	909 (47.4)
Anti-psychotic medication (%)	63 (4.4)	376 (9.5)	63 (8.6)	334 (17.4)
Analgesics (incl. morphine) (%)	388 (27.1)	2280 (57.6)	278 (38.0)	1021 (53.2)
Bronchial dilators (%)	221 (15.4)	1048 (26.5)	214 (29.2)	656 (34.2)
Corticosteroids (systemic) (%)	85 (5.9)	753 (19.0)	156 (21.3)	535 (27.9)
Antithrombotic agents (%)	329 (23.0)	2137 (54.0)	44 (6.0)	291 (15.2)
Cholesterol lowering drugs (%)	189 (13.2)	890 (22.5)	11 (1.5)	74 (3.9)
Calcium inhibitors (%)	132 (9.2)	1079 (27.2)	32 (4.4)	187 (9.7)
Beta-blockers (%)	267 (18.7)	1435 (36.2)	25 (3.4)	179 (9.3)
ACEi and ARB (%)	363 (25.4)	1956 (49.4)	37 (5.1)	232 (12.1)
Diuretics (%)	504 (35.2)	2825 (71.3)	139 (19.0)	768 (40.0)
Digoxin (%)	206 (14.4)	1134 (28.6)	31 (4.2)	119 (6.2)
Anti-angina medication (%)	196 (13.7)	1001 (25.3)	18 (2.5)	110 (5.7)

[a] Cardiovascular-specific hospital admissions: cerebral vascular disease, ischemic heart disease, previous myocardial infarction, cardiac dysrhythmia, heart failure and diabetes.
[b] Non-cardiovascular-specific hospital admissions: peptic ulcer, trauma, psychiatric illness, liver disease, malignancy, COPD: chronic obstructive pulmonary disease.

easier to identify patients at low risk of SCD than to accurately predict patients likely to die suddenly. In this study, we were able to demonstrate how the majority of OHCA individuals were patients with an established contact to the healthcare system shortly before event. The perfect test for predicting SCD does not exist. However, if it did, it would be paramount to be able to identify the population relevant for the test. With this in mind, the specificity of a future test needs to be high, as illustrated in Fig. 3 where approximately 35 and 65% of the control population are either hospitalized or in treatment with a limited number of drugs up to 30 days and 1 year before OHCA, respectively. Nevertheless, the main aim of the study was not to develop a method with a high specificity, but to identify healthcare contacts for patients with OHCA.

OHCA individuals are more than twice as likely to have diabetes both 30 days and 1 year before OHCA (Fig. 2). Our findings are in accordance with current knowledge on the established strong causal link between diabetes, CVD and sudden cardiac arrest.[14,15] Additionally, the majority of our study population comprised elderly men, which could partly explain the elevated risk of diabetes. Men are more likely than women to develop lifestyle diseases such as diabetes, which may ultimately lead to CVD.[16]

Hospital admissions for a range of cardiovascular risk markers including peripheral vascular disease, cerebral vascular disease, ischemic heart disease and cardiac dysrhythmia demonstrated a slight increase in the association with OHCA, whereas hospital admissions for MI or heart failure had a very strong association with OHCA (Fig. 2). Notably, we found that the likelihood of having an OHCA after a recent hospitalization for MI diminished over time (Fig. 2). These results are concordant with the findings made in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) on the time-related risk reduction of sudden death after previous MI.[17]

The mechanism and presentation of SCD in patients with heart failure is complex as patients with heart failure may have previous MI, primary dilated cardiomyopathy, and other CVD.[14] Heart failure is a well-known major risk factor for both non-sudden and sudden death.[18] Our study supports these findings (Fig. 2). Interestingly, results from a sub-analysis in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) study and another large meta-analyses found that a greater proportion of patients with less severe compared with more severe heart failure experienced sudden death.[19,20] Thus, patients with a hospitalization for heart failure are inevitably at risk of an OHCA regardless of heart failure severity.

Studies have found a threefold increase in risk of ischemic heart disease, stroke and SCD, independently of current smoking habits, in patients with COPD.[21] Further, cardiovascular death accounts for approximately 50% of all deaths in patients with COPD.[22] From all hospital admissions investigated, COPD had the strongest association with OHCA (Fig. 2). Notably, mortality and morbidity rates with COPD are increasing worldwide, and it is estimated

Table 3
Concomitant pharmacotherapy 30 days and 1 year before out-of-hospital cardiac arrest according to the prioritized groups: cardiovascular specific pharmacotherapy, and other pharmacotherapy in patients with no hospital admissions up to 1 year before arrest.

	Cardiovascular-specific pharmacotherapy[a]		Other pharmacotherapy[b]	
	30 days	1 year	30 days	1 year
N	3364	3217	2020	1215
Men (%)	2171 (64.5)	2057 (63.9)	1091 (54.0)	725 (59.7)
Age (years) (IQR)	75.0 (66–82)	74.0 (65–81)	69.0 (56–78)	63.0 (50–75)
Men's age (years) (IQR)	74.0 (66–81)	72.0 (64–80)	68.0 (54–78)	62.0 (49–73)
Women's age (years) (IQR)	77.0 (68–84)	77.0 (67–84)	70.0 (57–79)	64.0 (52–77)
Concomitant pharmacotherapy				
Antidepressants (%)	369 (11.0)	538 (16.7)	441 (21.8)	336 (27.7)
Sedatives and anxiolytics (%)	647 (19.2)	980 (30.5)	783 (38.8)	569 (46.8)
Anti-psychotic medication (%)	157 (4.7)	249 (7.7)	307 (15.2)	250 (20.6)
Analgesics (incl. morphine) (%)	901 (26.8)	1278 (39.7)	766 (37.9)	441 (36.3)
Bronchial dilators (%)	568 (16.9)	583 (18.1)	674 (33.4)	353 (29.1)
Corticosteroids (systemic) (%)	239 (7.1)	313 (9.7)	236 (11.7)	181 (14.9)
Antithrombotic agents (%)	885 (26.3)	1258 (39.1)	–	–
Cholesterol lowering drugs (%)	331 (9.8)	468 (14.6)	–	–
Calcium inhibitors (%)	538 (16.0)	854 (26.6)	–	–
Beta-blockers (%)	631 (18.8)	921 (28.6)	–	–
ACEi and ARB (%)	918 (27.3)	1163 (36.2)	–	–
Diuretics (%)	1550 (46.1)	2001 (62.2)	–	–
Digoxin (%)	547 (16.3)	468 (14.6)	–	–
Anti-angina medication (%)	448 (13.3)	509 (15.8)	–	–

[a] Cardiovascular specific pharmacotherapy: antithrombotic agents, cholesterol lowering drugs, calcium inhibitors, betablockers, diuretics, digoxin, anti-angina medication, ACEi: angiotensin converting enzyme inhibitor and ARB: angiotensin receptor blocker.
[b] Other pharmacotherapy: antidepressants, sedatives and anxiolytics, analgesics (incl. morphine), bronchial dilators and corticosteroids (systemic).

that approximately 5% or more of the adult American population is affected by COPD.[23,24] The very high association between a hospital admission for COPD and OHCA could also explain the increased odds of being in treatment with systemic corticosteroids and bronchial dilators, the cornerstones of COPD treatment, before OHCA (Fig. 1).[25]

We found an increased likelihood of being hospitalized with a psychiatric illness among OHCA patients (Fig. 2). This finding could in part be accredited findings stating that patients with a psychiatric illness often carry an increased somatic risk of sudden death due to CVD, mood disorders, and other somatic diseases.[26] In addition, these patients have behavioural risk factors, including substance abuse, poor self-care and health-related behaviour, smoking and other effects of mental illnesses predisposing SCD. We also found increased likelihood of being on antipsychotic treatment before OHCA (Figs. 1 and 2). Anti-psychotic agents (including typical and atypical anti-psychotic agents) pose a risk of inducing SCD[27–29] and their use should be carefully weighed.

4.1. Strengths and limitations

The main strength of this study is the unique combination of all OHCA on a nationwide level with national registers holding information on comorbidity, hospitalizations and concomitant pharmacotherapy for all individuals. The study population comprised citizens both in and out of the labour market, independent of sex, socioeconomic status, age, race, and participation in specific health and insurance programs. Thus the risk of selection bias was minimized. The Danish healthcare system partially reimburses drug expenses; therefore, Danish pharmacies must register all dispensed prescriptions, ensuring complete nationwide registration.

The main limitation of the study is inherent in its observational nature, being based on administrative registries and not including clinical data. In our conditional multivariable logistic regression analyses, we used claimed prescriptions up to 30 days and 1 year before OHCA as a proxy for being in treatment with specific medication. We cannot determine with certainty whether patients actually took the drug. Nonetheless, as there is partial patient co-payment of drug expenses, we assumed that if patients claimed a prescription there was a high probability that they actually took the medication. In addition, although we tried to eliminate potential confounders, we acknowledge that our findings may be biased by unidentified confounders. We also acknowledge the possibility that the accessibility and exposure to the healthcare system in Denmark may differ to that of other countries.

5. Conclusion

In this study we were able to demonstrate that 62% and 85% of 12,089 patients with OHCA registered 2001–2005 were in contact with the healthcare system 30 days and 1 year before OHCA, respectively. The fact that he majority of OHCA patients are in contact with the healthcare system shortly before OHCA could prove useful when deciding where to focus clinical strategies for primary and secondary prevention of OHCA.

Conflicts of interest

None declared.

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to study design, interpretation of the data, intellectual discussion and revision of the manuscript. All authors have read and approved the final version of the manuscript before submission.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics – 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480–6.
2. Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol 2001;12:369–81.
3. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998;98:2334–51.
4. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. Circulation 1992;85:I2–10.
5. Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. Dan Med Bull 1997;44:445–8.
6. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46:263–8.
7. Working group of the Danish Cardiac Arrest Registry. Status report. http://www.kliniskedatabaser.dk/doks/Endelig_rapport_til_ARF_DanskHjertestopregisteraarsrapport2005-331.doc; 2005 [accessed 01.20.10].
8. Horsted TI, Rasmussen LS, Meyhoff CS, Nielsen SL. Long-term prognosis after out-of-hospital cardiac arrest. Resuscitation 2007;72:214–8.
9. Folke F, Lippert FK, Nielsen SL, et al. Location of cardiac arrest in a city center: strategic placement of automated external defibrillators in public locations. Circulation 2009;120:510–7.
10. Fosbol E, Gislason G, Jacobsen S, et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. Clin Pharmacol Ther 2008.
11. Greedy macro match algorithm by Lori S. Parsons. http://www2.sas.com/proceedings/sugi26/p214-26.pdf; 2001 [accessed 01.11.09].
12. Demirovic J, Myerburg RJ. Epidemiology of sudden coronary death: an overview. Prog Cardiovasc Dis 1994;37:39–48.
13. Wellens HJ, de Vreede J, Gorgels AP. Sudden cardiac death. How to reduce the number of victims? Eur Heart J 1995;16:7–9.
14. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task force on sudden cardiac death of the European Society of Cardiology. Eur Heart J 2001;22:1374–450.
15. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898–918.
16. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999;100:1134–46.
17. Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med 2005;352:2581–8.
18. Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest – the relevance of heart failure. The Maastricht Circulatory Arrest Registry. Eur Heart J 2003;24:1204–9.
19. Kjekshus J. Arrhythmias and mortality in congestive heart failure. Am J Cardiol 1990;65:42I–8I.
20. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.
21. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc Am Thorac Soc 2005;2:8–11.
22. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Symptoms of chronic bronchitis and the risk of coronary disease. Lancet 1996;348:567–72.
23. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance – United States, 1971–2000. MMWR Surveill Summ 2002;51:1–16.
24. Chen JC, Mannino DM. Worldwide epidemiology of chronic obstructive pulmonary disease. Curr Opin Pulm Med 1999;5:93–9.
25. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532–55.
26. Zarate Jr CA, Patel J. Sudden cardiac death and antipsychotic drugs: do we know enough? Arch Gen Psychiatry 2001;58:1168–71.
27. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. BMJ 2002;325:1070.
28. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry 2001;58:1161–7.
29. 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;360:225–35.