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Anti-inflammatory treatment and risk of depression in 91,842 patients with acute coronary syndrome and 91,860 individuals without acute coronary syndrome in Denmark☆

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ABSTRACT

Background: We examined if treatment with acetylsalicylic acid (ASA), non-steroid anti-inflammatory drugs (NSAID), or statins after acute coronary syndrome (ACS) are associated with decreased risk of depression.
Method: This register-based cohort study included all individuals with a first-time hospital admissions with an ACS diagnosis registered between January 2001 to December 2009 (N = 91,842) and a comparable reference population without ACS (N = 91,860). Information of ASA, NSAID, and statin use were retrieved from a national prescription register. The study population was followed for hospitalization with depression or receiving prescription of antidepressant medication for up to one year after ACS or study entry (early depression) or one to twelve years after ACS or study entry (late depression).
Results: ASA use after ACS was associated with decreased risk of early depression with hazard ratios (HR) of 0.89 (95% confidence interval 0.85–0.93) but not with late depression 0.96 (0.90–1.01). The corresponding HRs for statin were 0.90 (0.86–0.94) and 0.86 (0.82–0.90). In the non-ACS population, statin use was not associated with neither early nor late depression (HRs 1.04 (0.96–1.12) and 1.00 (0.95–1.06)), while ASA was associated with increased risk of late (HR 1.09 (1.04–1.14)) but not early depression (HR 1.03 (0.97–1.09)). In both populations, NSAID use was associated with increased risk of late but not early depression.
Conclusion: Use of ASA or statins were associated with decreased risk of depression in ACS patients but not in individuals without ACS, while use of NSAID was associated with increased risk of late depression in both populations.

1. Introduction

Acute coronary syndrome (ACS) includes unstable angina and acute myocardial infarction which are conditions characterized by decreased blood flow in the coronary arteries leading to cardiac ischemia. ACS is very common worldwide [1]. Similar to other studies, we have recently shown that patients with ACS had 1.5 times higher risk of developing depression compared to a matched background population [2].

The association between ACS and depression is not fully understood, but accumulated low-grade inflammation is proposed as a possible link [3]. Thus, acute myocardial infarction is followed by a rapid increase in inflammatory markers [4], which might induce a neuro-inflammatory process that could trigger depression. This has together with the increased level of inflammation in depression led to the hypothesis that anti-inflammatory medication may reduce symptoms of depression [5]. Acetylsalicylic acid (ASA) and statins are medications recommended as standard therapy following ACS [6] and due to their anti-inflammatory properties, these medications could affect the incidence of post-ACS depression [5]. Previous studies indicate that ASA and statin use may be associated with decreased risk of depression in both healthy individuals [7–9], and ACS patients [10,11]. However, results are conflicting [12–14]. Furthermore, non-steroid anti-inflammatory drugs (NSAIDs) are reported to reduce symptoms of depression [15–17], but also with inconsistent findings [9,18].

The aim of this paper is to examine the hypothesis that ASA, NSAID, and statin use is associated with decreased risk of early depression (occurring within the first year after ACS event) as well as late depression

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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(depression occurring after the first year of ACS event) in both ACS patients and a non-ACS population.

2. Methods

2.1. Study population

This register-based cohort study included all first time hospitalizations (and outpatient's visits since 1995) of ACS in individuals over 15 years of age registered from January 1st 2001 to December 31th 2009 in the Danish National Patient Registry by the following International Classification of Diseases (ICD)-10 codes: I20.0 *Unstable angina pectoris*, I21.0-I21.3 *ST-elevation myocardial infarction* (*STEMI*), 121.4 *Non-STEMI* and I21.9 *Acute myocardial infarction*. Patients with an ACS diagnosis from 1995 to 2001 were excluded in the analysis. Using information from the Danish Civil Registration System, a comparable reference population without ACS was established by 1:1 matching on gender, age, and municipality on time of ACS diagnosis. The study was evaluated and approved by the Danish Data Protection Agency.

2.2. Depression outcomes

Diagnoses of depression were obtained from the National Patient Register and the Danish Cause of Death Register using ICD10 diagnoses F31.3–33;34.1, and purchases of antidepressant medication (which can only be purchased by prescription) was obtained from the Danish Prescription Register using Anatomical Therapeutic Classification (ATC) codes N06A from study entry to censoring or end of follow-up (December 31th 2012). A depression diagnosed within the first month after entry date was assumed to reflect ongoing depression and therefore we defined *early depression* as hospitalization with depression or purchase of antidepressants between one month and one year after study entry. *Late depression* was hospitalization with depression or purchase of antidepressants from one year and up to 12 years after study entry. In the analyses of late depression, having early depression was included in the covariable previous depression and were thus adjusted for.

2.3. Anti-inflammatory medication

All prescriptions of ASA, NSAID, or statin from study entry to end of follow-up were obtained from the Danish Prescription Register using ATC codes B01AC06, B01AC56, N02BA01, and N02BA51 for ASA, M01A for NSAID and C10AA for statins. For all individuals, the first prescription dating from five years preceding ACS or study entry until the end of the first month or at the end of the first year were obtained.

2.4. Covariables

Information on education, cohabitation status and ethnicity was obtained from the Integrated Database for Labor Market Research. Education was categorized as basic education (7–9 grade of obligatory schooling), medium education (high school degree/vocational), higher education (more than high school degree), or unknown. Cohabitation status was categorized as single or living with a partner. Ethnicity was coded as Danish, immigrant, descendent of immigrants, or unknown. From the National Patient Registry and the Danish Prescription Register, we included information on hospitalization or medication for somatic or psychiatric diseases five years preceding inclusion date. The following co-morbid diseases were considered: connective tissue disease, inflammatory disease, infectious disease, chronic obstructive pulmonary disease (COPD), obesity, hypertension, diabetes mellitus, anxiety, alcoholism, and previous depression. The latter defined by a diagnosis of depression or use of antidepressant medication from 5 years preceding study entry. From the Danish Prescription Register, we also included information on prescription of warfarin, clopidogrel, or betablockers after study entry. The ICD-10 and ATC codes used to define the covariables in the ACS and reference population are shown in Supplemental Table 1. The covariables were chosen based on a previous analysis of diseases or patient characteristics associated with depression following ACS [19], and inflammatory components of the diseases. Use of other cardiac medication in the prevention of ACS was included as use may reflect both use of ASA and statin. Lithium was included due to its use for bipolar depression. Anxiety and diabetes (neuropathic pain in diabetes) were included as these diseases may also be treated with antidepressant medication.

2.5. Statistical analyses

Stata version 13.1 (StataCorp, College Station, TX) was used for all statistical analyses. Data was analyzed separately for ACS patients and the reference population. Missing data (14% for education) were included as a fixed number. Baseline characteristics were estimated the date of ACS event or the corresponding date for the non-ACS population. We used *t*-tests or Wilcoxon rank-sum tests to test the difference between continuous parametric and nonparametric variables and chi2-tests to test the difference between binary variables (Table 1).

We first analyzed whether ASA, NSAID, or statin use at the end of the first month after study entry was associated with decreased risk of early depression in ACS patients and the non-ACS population. We used Cox proportional hazards regressions with follow-up time as the underlying time scale. Individuals were entered one month after study entry and censored at depression, death, emigration, or end of follow-up (1 year after study entry). A total of 7318 ACS-patients and 305 non-ACS individuals died or emigrated before the end of the first month and were excluded from the analyses. All analyses were mutually adjusted for age, gender, and all covariables mentioned in the covariable section. The proportional hazards assumption was tested graphically by plotting –log(−log(survival)) vs. log(follow-up time) and no violations were found. Furthermore, we stratified individuals based on their combined use of ASA, NSAID, and statins and tested whether the single or combined use of any of these medications were associated with risk of early depression in both populations.

Second, we analyzed whether ASA, NSAID, statin use or the combined use of these medications at the end of the first year after study entry was associated with decreased risk of late depression in ACS patients and the non-ACS population. All analyses were performed similarly to the analyses for early depression. Individuals were entered one year after study entry and censored at depression, death, emigration, or end of follow-up (December 31th 2012). A total of 14,805 ACS-patients and 3448 non-ACS individuals died or emigrated before the end of the first year and were excluded from the analyses. A total of 10,380 ACS-patients and 6520 non-ACS individuals had early depression and were included in the variable previous depression.

Since depression after acute coronary syndrome is associated with increased mortality [2], we also performed Fine Gray competing risk regression models to account for the competing risk of death or emigration (that individuals died/emigrated before they could develop depression).

Table 1
Population characteristics of 183,702 patients with acute coronary syndrome (ACS) and a non-ACS population.

	ACS patients	Non-ACS population	P-difference[c]
Basic characteristics at baseline			
Number, N (%)	91,842 (50)	91,860 (50)	
Age, median (IQR), years	68 (57–78)	68 (57–78)	0,12
Women, N (%)	35,581 (39)	35,421 (39)	0,42
Single, N (%)	40,111 (44)	38,957 (42)	<0.01
Only primary school, N (%)	37,689 (41[a])	33,085 (36[b])	<0.01
Danish ethnicity, N (%)	86,076 (94)	87,206 (95)	<0.01
Somatic comorbidity at baseline			
Connective tissue disease, N (%)	5800 (6)	3868 (4)	<0.01
Inflammatory disorder, N (%)	44,084 (48)	33,800 (37)	<0.01
Infection, N (%)	71,479 (78)	64,248 (70)	<0.01
Chronic obstructive pulmonary disease, N (%)	19,856 (22)	14,031 (15)	<0.01
Obesity, N (%)	4203 (5)	2762 (3)	<0.01
Hypertension, N (%)	53,367 (58)	38,540 (42)	<0.01
Diabetes Mellitus, N (%)	12,029 (13)	6145 (7)	<0.01
Psychiatric comorbidity at baseline			
Anxiety	34,278 (37)	27,485 (30)	<0.01
Alcoholism	3220 (4)	2426 (3)	<0.01
Previous depression before 1 month after entry, N (%)	13,638 (15)	10,512 (11)	<0.01
Previous depression before 1 year after entry, N (%)	21,426 (23)	14,906 (16)	<0.01
Medication use after study entry			
Warfarin, N (%)	13,143 (14)	8786 (10)	<0.01
Clopidogrel, N (%)	52,064 (57)	5963 (6)	<0.01
Betablockers, N (%)	69,534 (76)	24,077 (26)	<0.01
Outcome measures: depression status			
Early depression, N (%)	10,380 (11)	6520 (7)	<0.01
Late depression, N (%)	12,886 (14)	13,334 (15)	<0.01

IQR = interquartile range.
[a] 13,088 (14%) had missing information.
[b] 12,302 (13%) had missing information.
[c] Chi-square test.

3. Results

We followed 91,842 ACS patients and 91,860 subjects from the non-ACS population. During the first year 11% of ACS patients and 7% in the non-ACS population developed depression. When the study populations were followed (median 6.0 years (0.0–12.0 years)) 14% of ACS patients and 15% of the non-ACS individuals developed late depression.