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ORIGINAL RESEARCH

Influence of Low-Density Lipoprotein Cholesterol Levels on NSAID-Associated Cardiovascular Risks After Myocardial Infarction: A Population-Based Cohort Study

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Aim: To examine whether low-density lipoprotein cholesterol (LDL-C) levels influence the cardiovascular risk associated with non-aspirin non-steroidal anti-inflammatory drug (NSAID) use after myocardial infarction (MI).

Methods: Using Danish health registries, we conducted a population-based cohort study of all adult patients with first-time MI during 2010–2020 with an LDL-C value before discharge. Based on the latest LDL-C value, we categorized patients into a low and a high LDL-C group (<3.0 vs ≥3.0 mmol/L). We used time varying Cox regression to compute hazard ratios (HRs) with 95% confidence intervals of the association between NSAID use and a major adverse cardiovascular event (MACE: recurrent MI, ischemic stroke, and all-cause death).

Results: We followed 50,573 patients for a median of 3.1 years. While exposed, 521 patients experienced a MACE: 312 in the low LDL-C group and 209 in the high LDL-C group. The HRs for MACE comparing NSAID use with non-use were 1.21 (1.11–1.32) overall, 1.19 (1.06–1.33) in the low LDL-C group, and 1.23 (1.07–1.41) in the high LDL-group. The HRs for recurrent MI and ischemic stroke were comparable between the LDL-C subgroups. The HRs for all-cause death were 1.22 (1.07–1.39) in the low LDL-C group and 1.54 (1.30–1.83) in the high LDL-C group. Changing the cut-off value for LDL-C to 1.8 and 1.4 mmol/L showed consistent results.

Conclusion: In patients with MI, LDL-C levels did not influence the increased risk of MACE associated with NSAID use, but might influence the association between NSAID use and all-cause death.

Keywords: cardiovascular disease, non-steroidal anti-inflammatory drugs, cholesterol, low-density lipoprotein cholesterol, myocardial infarction, effect modification

Introduction

Non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain, fever, and inflammation.[1] In Denmark, about 15% of the population fill at least one NSAID prescription annually.[2] In patients with acute myocardial infarction (MI), NSAID use has been associated with increased risk of recurrent MI,[3–6] ischemic stroke,[7] atrial fibrillation,[3,8] and death.[3,4,6] Consequently, it is recommended that NSAIDs should be used with caution in patients with MI, as they are already at high risk of cardiovascular disease.[9–11] Nevertheless, approximately 9% of Danish patients with first-time MI fill an NSAID prescription within a year.[10] Frequent NSAID use in patients with MI might be explained by the improved survival of MI patients, and hence as they get older stand a higher chance of acquiring conditions associated with chronic pain.[12,13] Therefore, as NSAID use already confers an increased cardiovascular risk, it is crucial to guide NSAID use in patients with, or at high risk of, cardiovascular disease.[3,4,11]

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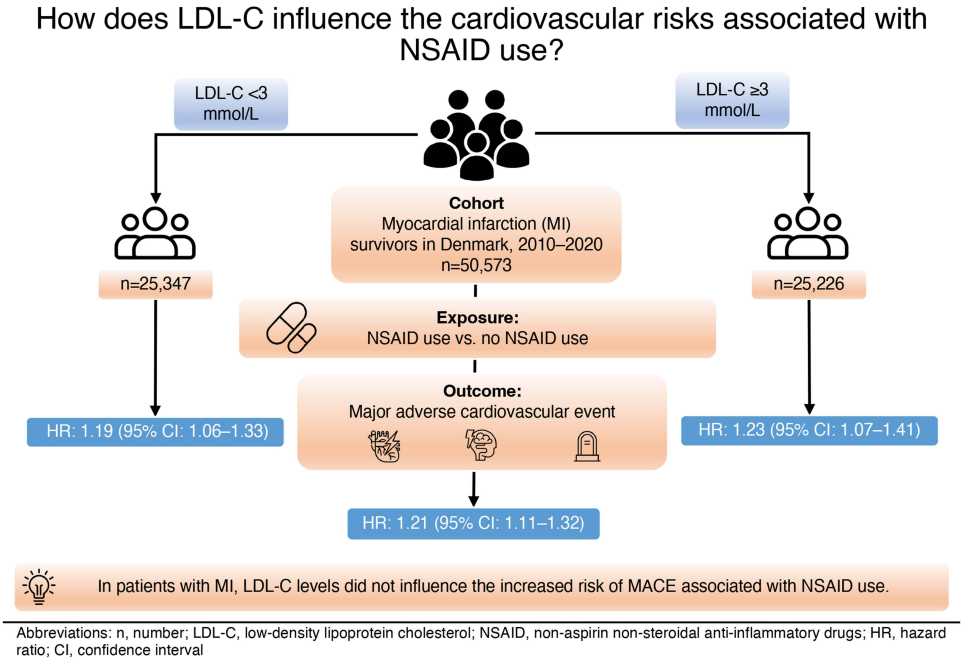
Graphical Abstract



A well-established risk factor for cardiovascular disease is high levels of low-density lipoprotein cholesterol (LDL-C).[9,14,15] The European Society of Cardiology warns against the use of NSAIDs in high-risk individuals including those with dyslipidemia.[16] However, no studies have investigated whether patients' LDL-C levels influence the association between NSAID use and cardiovascular events. Therefore, we investigated the association between NSAID use and cardiovascular events within strata of LDL-C levels among patients with first-time MI.

Methods

Setting

The Danish healthcare system provides universal tax-supported healthcare to all Danish citizens and legal residents, guaranteeing free access to general practitioners and hospitals, as well as partial reimbursement for the costs of prescription drugs, including NSAIDs.[17] The unique Civil Personal Register number, assigned to all Danish citizens at birth and to residents upon immigration, allows individual-level linkage among Danish registries and ensures almost complete follow-up with accurate censoring at death or emigration.[18]

Study Cohort

We used the Danish National Patient Registry (DNPR) to identify all adult (≥18 years of age) patients with a first-time primary and secondary inpatient MI diagnosis from 1 January 2010 until 31 December 2020. The DNPR has registered non-psychiatric inpatient contacts since 1977 and psychiatric inpatient, outpatient clinic, and emergency contacts since 1995.[19] For each patient contact, one primary and optional secondary discharge diagnoses are assigned according to the International Classification of Diseases (ICD) eighth revision until the end of 1993 and 10th revision thereafter.[19]

We included only patients who were alive at discharge, who had at least one LDL-C value recorded at any time before discharge, and who had no prior hospital diagnosis of ischemic stroke. We obtained the LDL-C values from the Clinical Laboratory Information System Research Database at Aarhus University and the Register of Laboratory Results for

Research.[20,21] The former contains laboratory data since 2000 from the North and the Central Denmark Region. The latter contains laboratory data from the other Danish regions and has been nationwide since 2015.[20,21]

Non-Aspirin Non-Steroidal Anti-Inflammatory Drug Use

We used the Danish National Prescription Registry (NPR) to identify all filled NSAID prescriptions using the Anatomical Therapeutic Chemical (ATC) classification code. The Registry has kept detailed records of every prescription filled at community pharmacies in Denmark since 1995.[17] During the study period, all NSAIDs were available by prescription only, apart from small low-dose ibuprofen packages (200 mg of 20 tablets).[2] Because the NPR does not contain information on defined daily dose or treatment duration, we defined NSAID use as two tablets per day.[17] Thus, a patient who filled a prescription for 30 naproxen tablets was considered exposed during the next 15 days (30/2=15). If a new prescription for any NSAID was filled within 14 days after the end of an exposure period (ie, a 14-day grace period), we extended the exposure period by the length of the new prescription. If a new prescription was filled more than 14 days after the end of an exposure period, the next exposure period started on the date of the new prescription.[22]

Blood Cholesterol Levels

We used the most recent LDL-C value any time before hospital discharge to stratify patients into a low LDL-C group (<3.0 mmol/L or <116 mg/dL) and a high LDL-C group (≥3.0 mmol/L). The value for stratification was set at 3.0 mmol/L based on treatment targets for patients at low risk, as most of the patients were not classified as being at high risk or at very high risk before their MI and consequently not yet in treatment for any target LDL-C levels.[23]

Outcomes

The primary outcome was a major adverse cardiovascular event (MACE), defined as a composite of recurrent MI, ischemic stroke, and all-cause death. The secondary outcomes consisted of the individual components of MACE, as well as congestive heart failure, and atrial fibrillation or flutter. We used the DNPR to identify all cardiovascular events.[19] Recurrent MI was defined from primary inpatient diagnoses occurring more than 28 days after the incident event.[24] Ischemic stroke and congestive heart failure were defined from any primary and secondary inpatient diagnoses. Atrial fibrillation or flutter was defined from any primary and secondary inpatient and outpatient diagnoses.[19] The registration of the diagnosis codes used in this study has been validated with positive predictive values of 88% for recurrent MI, 97% for ischemic stroke, 76% for congestive heart failure, and 95% for atrial fibrillation of flutter.[19,25] All-cause death was ascertained from the Danish Civil Registration System and are known to be complete and accurate.[18]

Covariates

The covariates were identified based on their known associations with NSAID use and myocardial infarction. They included continuous age at time of first-time MI, and categorical sex, comorbidity burden, and drug use.[9,10] We used all information from the DNPR in the 10 years preceding first-time MI to assign baseline comorbidities to the patients.[19] We used the Danish Comorbidity Index for Acute Myocardial Infarction (DANCAMI) to categorize comorbidity burden into none (score: 0), low (score: 1–3), moderate (score: 4–5), and severe (score: ≥6).[26] The individual comorbidities included in DANCAMI are provided in Supplemental Table 1. We also adjusted for the comorbidities inflammatory and degenerative rheumatic disease as they are not included in DANCAMI. We used information from the NPR in the year preceding first-time MI to assign baseline drug use to the patients.[17] We adjusted for the drugs shown in Table 1.

Statistical Analyses

We reported continuous variables as counts with percentages and categorical variables as medians with interquartile ranges (IQR). We calculated incidence rates per 100 person-years for the outcomes. We used a Cox proportional-hazards regression to compute hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) of the association between NSAID use and the outcomes, adjusting for the covariates described above. Proportional hazards among the NSAID exposure categories could not be verified as NSAID use was modelled in a time-varying manner.

Table 1 Characteristics of Patients with First-Time Myocardial Infarction at the Time of Hospital Discharge, Denmark, 2010–2020

	All patients n (%)	LDL-C <3.0 mmol/L n (%)	LDL-C ≥3.0 mmol/L n (%)
Total	50,573 (100)	25,347 (100)	25,226 (100)
Sex, male	33,459 (66)	16,571 (65)	16,888 (67)
Age, median (IQR)	68 (58–77)	71 (61–79)	65 (55–74)
Calendar year of MI			
2010–2011	4175 (8.3)	2110 (8.3)	2065 (8.2)
2012–2014	11,333 (22)	5667 (22)	5666 (23)
2015–2017	18,072 (36)	9174 (36)	8898 (35)
2018–2020	16,993 (34)	8396 (33)	8597 (34)
Comorbidity burden*			
No (score: 0)	14,039 (28)	4719 (19)	9320 (37)
Low (score: 1–3)	18,366 (36)	8952 (35)	9414 (37)
Moderate (score: 4–5)	6182 (12)	3522 (14)	2660 (11)
Severe (score: ≥6)	11,986 (24)	8154 (32)	3832 (15)
Other comorbidities			
Inflammatory rheumatic disease	3228 (6.4)	1883 (7.4)	1345 (5.3)
Degenerative rheumatic disease	14,026 (28)	7565 (30)	6461 (26)
Drug use			
ACE inhibitors	8038 (16)	5254 (21)	2784 (11)
ARBs	7277 (14)	4432 (18)	2845 (11)
Diuretics	12,511 (25)	8123 (32)	4388 (17)
Beta-blockers	11,161 (22)	7542 (30)	3619 (14)
Calcium channel blockers	12,142 (24)	7640 (30)	4502 (18)
Statins	15,489 (31)	12,278 (48)	3211 (13)
Nitrates	4817 (10)	3411 (14)	1406 (5.6)
Anticoagulants	3962 (7.8)	2703 (11)	1259 (5.0)
Antiplatelet drugs	13,411 (27)	9645 (38)	3766 (15)
Systemic glucocorticoids	4425 (8.7)	2601 (10)	1824 (7.2)

Notes: *Categorized according to the Danish Comorbidity Index for Acute Myocardial Infarction (DANCAMI).
Abbreviations: n, number; IQR, interquartile range; MI, myocardial infarction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol.

Follow-up started on the date of hospital discharge and ended on the date of an outcome, emigration, or 31 December 2020, whichever occurred first. To avoid immortal time bias, each person was considered not to be using NSAIDs from hospital discharge until a potential first redemption of a prescription for an NSAID. We performed the analyses on the whole cohort and, to examine whether LDL-C modified the association between NSAID use and the outcomes, also in strata of low and high baseline LDL-C values (<3.0 vs ≥3.0 mmol/L). For MACE, we repeated the analyses after changing the cut-off value to 1.8 mmol/L (70 mg/dL) and 1.4 mmol/L (55 mg/dL) as these values are used around the world. For the two secondary outcomes, congestive heart failure and atrial fibrillation or flutter, we restricted the cohort to patients without a history of the specific outcome.

As many patients start statin treatment after MI, we repeated the analyses in one-year MI survivors with at least one LDL-C value recorded in the year following their MI. In this cohort, we started follow-up one year after first-time MI, and we stratified patients into a low (<1.4 mmol/L) and a high (≥1.4 mmol/L) LDL-C group based on the most recent LDL-C value before one year after discharge. We used 1.4 mmol/L as cut-off based on guidelines for patients at very high risk for cardiovascular disease.[23] All statistical calculations were performed on the remote servers of Statistics Denmark using the statistical software program R, version (4.0.2). All ATC and ICD-10 codes used in the study are provided in Supplemental Table 2.

Subgroup and Sensitivity Analyses

We performed two subgroup analyses, one in which we stratified by sex, and another in which we stratified by prior cancer diagnosis, in order to minimize the risk of death due to causes associated with cancer.

We also performed three sensitivity analyses: first, in which we changed the exposure definition from two to three tablets per day to examine the impact of the exposure definition on the results; second, in which we restricted the cohort to MI patients with an LDL-C value in the 90 days before hospital discharge (rather than at any time before hospital discharge) to account for possible changes in LDL-C values that may have occurred the period up to hospital discharge; and third, among one-year survivors, in which we changed the LDL-C cut-off value from 1.4 mmol/L to 1.8 and 3.0 mmol/L to account for different treatment targets.

Results

Patient Characteristics

From 2010 to 2020, we observed 78,130 patients alive at discharge after a first-time MI, among whom 50,573 (65%) had an LDL-C value recorded before discharge and no prior events of ischemic stroke, and thus constituted the study cohort (Supplemental Figure 1). Of these patients, 25,347 (50%) had a baseline LDL-C value <3.0 mmol/L and 25,226 (50%) had a baseline LDL-C value ≥3.0 mmol/L (Table 1). Of all patients, 32,143 (64%) had recorded LDL-C values under hospitalization. Men accounted for 66% overall, 65% of the low LDL-C group, and 67% of the high LDL-C group. The median age was 68 years overall, 71 years in the low LDL-C group, and 65 years in the high LDL-C group. Compared with patients in the high LDL-C group, patients in the low LDL-C group had a higher comorbidity burden (32% vs 15% had a severe comorbidity burden) and used more co-medication (Table 1). Around 31% of the patients used statins before their MI overall, 48% in the low LDL-C group, and 13% in the high LDL-C group. One year after MI, 85% had redeemed at least one prescription of statins overall, 82% in the low LDL-C group, and 89% in the high LDL-C group.

The total follow-up was 175,937 years, corresponding to a median follow-up of 3.1 years per patient (IQR: 1.0–5.3). During follow-up, 12,636 (25%) patients filled at least one NSAID prescription. Types of redeemed NSAID prescriptions were distributed as follows: 72% was ibuprofen, 10% was diclofenac, 7% was naproxen, and 11% was other NSAIDs. On average, the lengths of the exposure periods were 32 days overall, 30 days in the low LDL-C group, and 34 days in the high LDL-C group. The lower and upper quartile as well as the medians were 0 days. For persons who redeemed at least one prescription, the average lengths of exposure periods were 120 days overall, 116 days in the low LDL-C group, and 125 days in the high LDL-C group.

NSAID-Associated Risks After Myocardial Infarction

During follow-up, a total of 16,086 patients (32%) experienced a MACE: 9542 (38%) among patients in the low LDL-C group and 6544 (26%) among patients in the high LDL-C group (Table 2). The baseline incidence rates of MACE per 100 person-years were 9.1 overall, 11.6 in the low LDL-C group, and 7.0 in the high LDL-C group (Table 2).

While exposed, 521 patients experienced a MACE: 312 among patients in the low LDL-C group and 209 among patients in the high LDL-C group (Figure 1). After adjustment, the HRs for MACE comparing NSAID use with non-use were 1.21 (95% CI: 1.11–1.32) overall, 1.19 (95% CI: 1.06–1.33) in the low LDL-C group, and 1.23 (95% CI: 1.07–1.41) in the high LDL-group (Figure 1). Changing the cut-off value to 1.8 mmol/L and 1.4 mmol/L showed consistent results (Figure 1).

For the secondary outcomes, use of any NSAID was associated with increased rates of atrial fibrillation or flutter (HR: 1.25, 95% CI: 1.05–1.48) and all-cause death (HR: 1.33, 95% CI: 1.20–1.48). There were no substantial differences in the HRs between the low and high LDL-C groups for MI recurrence, ischemic stroke, congestive heart failure, or atrial fibrillation or flutter. In contrast, any NSAID use was associated with a higher rate for all-cause death in the high LDL-C group (HR: 1.54, 95% CI: 1.30–1.83) than in the low LDL-C group (HR: 1.22, 95% CI: 1.07–1.39) (Figure 2).

NSAID-Associated Risks in One-Year Survivors

Supplemental Table 3 presents the baseline characteristics of one-year survivors. In these patients, the rate for MACE was not substantially increased with any NSAID use compared with non-use in all one-year survivors (HR: 1.05, 95%

Table 2 Number and Incidence Rates of Cardiovascular Outcomes After Myocardial Infarction According to LDL-C Levels

	All patients (n=50,573)		LDL-C <3.0 mmol/L (n=25,347)		LDL-C ≥3.0 mmol/L (n=25,226)	
	Events, n (%)	Rate* (95% CI)	Events, n (%)	Rate* (95% CI)	Events, n (%)	Rate* (95% CI)
Primary outcome						
MACE[†]	16,086 (32)	9.1 (9.0–9.3)	9542 (38)	12 (11–12)	6544 (26)	7.0 (6.8–7.2)
Secondary outcomes						
Recurrent MI	5649 (11)	3.1 (3.1–3.2)	2773 (11)	3.3 (3.2–3.4)	2876 (11)	3.0 (2.9–3.1)
Ischemic stroke	1831 (3.6)	1.0 (0.9–1.0)	1022 (4.0)	1.2 (1.1–1.2)	809 (3.2)	0.8 (0.8–0.9)
All-cause death	10,588 (21)	5.5 (5.4–5.6)	6992 (28)	7.8 (7.6–8.0)	3596 (14)	3.5 (3.4–3.7)
Congestive heart failure[a]	5698 (12)	3.5 (3.4–3.6)	251 (14)	4.3 (4.2–4.5)	2447 (11)	2.8 (2.7–2.9)
Atrial fibrillation or flutter[b]	4112 (8.8)	2.4 (2.4–2.5)	2403 (10)	3.1 (3.0–3.2)	1709 (7.2)	1.9 (1.8–2.0)

Notes: *Number of events per 100 person-years with 95% confidence intervals (CIs). [†]A composite of recurrent myocardial infarction, ischemic stroke, and all-cause death. [a]After excluding patients with prior events of congestive heart failure: 45,752 patients in the total cohort, 22,840 with LDL-C <3.0 mmol/L, and 22,912 with LDL-C ≥3.0 mmol/L. [b]After excluding patients with prior events of atrial fibrillation of flutter: 46,994 patients in the total cohort, 23,168 with LDL-C <3.0 mmol/L, and 23,826 with LDL-C ≥3.0 mmol/L.
Abbreviations: n, number; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval, MACE, major adverse cardiovascular events; MI, myocardial infarction.

CI: 0.90–1.23), in the low LDL-C group (HR: 1.18, 95% CI: 0.87–1.61), or in the high LDL-C group (HR: 1.00, 95% CI: 0.84–1.21) (Supplemental Table 4).

NSAID use was associated with a decreased rate for all the secondary outcomes except death. For death, NSAID use was associated with a 1.41-fold increased rate among all one-year survivors (HR: 1.41, 95% CI: 1.18–1.69). This association was present in the low LDL-C group (HR: 1.69, 95% CI: 1.20–2.38) and in the high LDL-C group (HR: 1.33, 95% CI: 1.08–1.64) (Supplemental Table 4). Most outcomes occurred in the first year after first-time MI (68% of MACE), as supported from the low number of outcomes among one-year survivors (Supplemental Table 4).

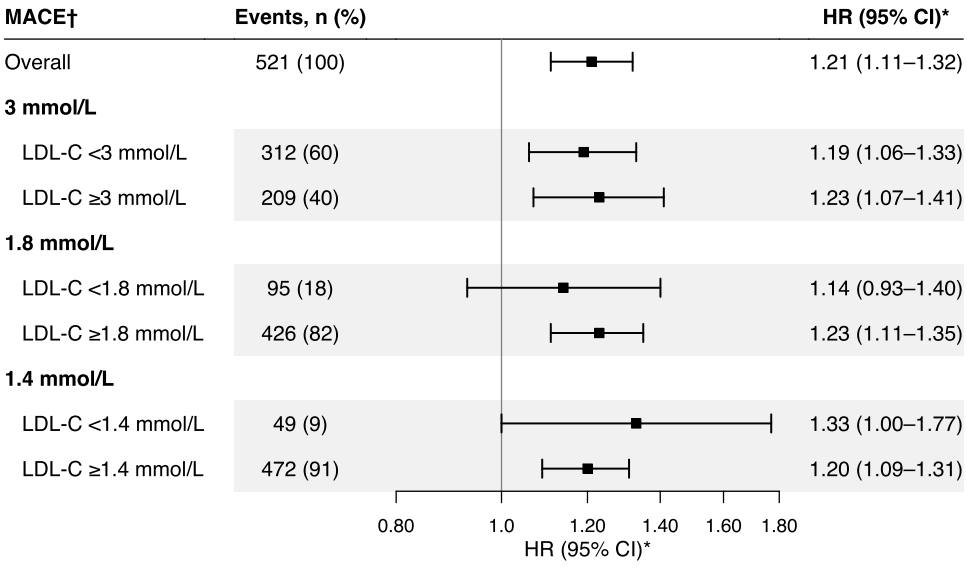


Figure 1 Primary cardiovascular outcome associated with NSAID use vs non-use in myocardial infarction survivors, by baseline LDL-C levels. *Adjusted for age, sex, categorical DANCAMI score, inflammatory rheumatic disease, degenerative rheumatic disease, and concomitant medications. [†]A composite of recurrent myocardial infarction, ischemic stroke, and all-cause death. [a]6,953 patients with LDL-C <1.8 mmol/L and 43,620 patients with LDL-C ≥1.8 mmol/L. [b]2,944 patients with LDL-C <1.4 mmol/L and 47,629 patients with LDL-C ≥1.4 mmol/L.
Abbreviations: n, number; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

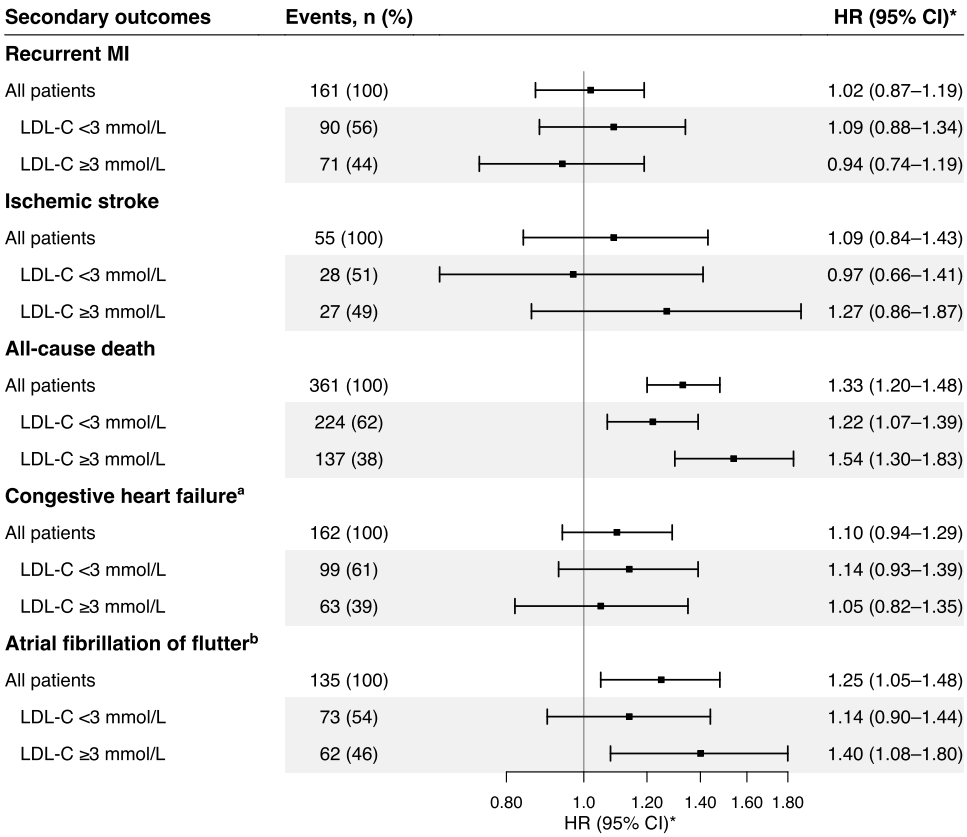


Figure 2 Secondary cardiovascular outcomes associated with NSAID use vs non-use in myocardial infarction survivors, by baseline LDL-C levels. *Adjusted for age, sex, categorical DANCAMI score, inflammatory rheumatic disease, degenerative rheumatic disease, and concomitant medications. [a]After excluding patients with prior events of congestive heart failure: 45,752 patients in the total cohort, 22,840 with LDL-C <3.0 mmol/L, and 22,912 with LDL-C ≥3.0 mmol/L. [b]After excluding patients with prior events of atrial fibrillation of flutter: 46,994 patients in the total cohort, 23,168 with LDL-C <3.0 mmol/L, and 23,826 with LDL-C ≥3.0 mmol/L.
Abbreviations: n, number; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

Subgroup and Sensitivity Analyses

Stratifying by sex showed no substantial difference in the HRs for MACE between the two LDL-C groups, though the rates were slightly higher among females (HR: 1.33, 95% CI: 1.16–1.52) than males (HR: 1.13, 95% CI: 1.01–1.27) (Supplemental Table 5). Stratifying by prior cancer diagnosis also did not show any substantial difference in the HRs for MACE or death in the two LDL-C groups, though the rates were slightly higher among patients with a cancer diagnosis (HR: 1.29, 95% CI: 1.06–1.57) than patients without a cancer diagnosis (HR: 1.19, 95% CI: 1.08–1.31) (Supplemental Table 6).

The results were consistent after changing the definition of NSAID use from two to three tablets per day (Supplemental Table 7), after restricting the cohort to patients with LDL-C value in the 90 days before MI (Supplemental Table 8), and after changing the cut-off value in one-year survivors to 1.8 mmol/L and 3.0 mmol/L (Supplemental Table 9).

Discussion

In patients with first-time MI, NSAID use was associated with an increased cardiovascular event rate compared with non-use. However, this increased rate was not influenced by LDL-C levels overall. As one exception, NSAID use was associated with larger risk of all-cause death in patients with high LDL-C than in patients with low LDL-C.

Previous Literature

NSAIDs and Cardiovascular Risks in Myocardial Infarction Survivors

Taking follow-up time into consideration (3.1 years), the proportion of MI patients who had filled at least one NSAID prescription in our study (25%) is consistent with previous research (9% per year).[10]

Similar to our results, earlier studies have found increased cardiovascular risk associated with NSAID use in patients with previous MI.[4,8,27] In a case-control study, the odds ratio for atrial fibrillation or flutter ranged from 1.17 (95% CI: 1.10–1.24) for non-selective NSAIDs to 1.71 (95% CI: 1.56–1.88) for cyclooxygenase-2 inhibitors.[28] A study among patients with stable atherothrombotic disease found the HR for heart failure to be 1.18 (95% CI: 1.03–1.34) and the HR for MACE (cardiovascular death, myocardial infarction, and stroke) to be 1.16 (95% CI: 1.03–1.30).[7] A Danish study among patients with first-time MI, comparing ibuprofen use with non-use, found an HR for death of 1.50 (95% CI: 1.36–1.67) and an HR for MI recurrence of 1.25 (95% CI: 1.07–1.46).[4] The comparatively lower estimates of some secondary outcomes in the current study might be explained by established recommendations against NSAID use in patients at high cardiovascular risk.[16] Despite differences in study designs, our results point in the same direction, ie, an increased cardiovascular risk associated with NSAID use.

Contrary to our results among one-year survivors, another study among patients with first-time MI found an association between NSAID use after one year and risks of coronary death or MI recurrence.[29] This difference could be explained by the fact that one-year survivors in our study constituted a "fitter" cohort who are more resilient to NSAID use (ie, depletion of susceptibles).[30]

NSAIDs and Cardiovascular Risks According to LDL-C Levels

To our knowledge, no previous literature has examined the influence of cholesterol levels on the association between NSAID use and cardiovascular events. However, few studies have examined the influence of various other risk factors on the association.[31–33] The first study, among respondents to the Danish National Health Surveys of 2010, 2013, or 2017, found no notable difference in the association between NSAID use and MACE (myocardial infarction, ischemic stroke, heart failure, and all-cause death) within subgroups defined by lifestyle (body mass index, smoking status, alcohol consumption, and physical activity level) and socioeconomic position (marital status, education, income, and employment).[31] The second study, conducted among patients who underwent first-time coronary computed tomography angiography on indication of angina pectoris, found no substantial difference in HRs for MACE between patients with no coronary artery disease (1.33, 95% CI 1.06–1.68) and patients with non-obstructive coronary artery disease (1.48, 95% CI 1.06–2.07).[32] The study population, consisting of Danish patients with angina pectoris, was somewhat comparable to ours.[32] The third study found no substantial relative risk differences between patients with low-risk profile (no prior vascular ischemic events) and patients with high-risk profile (prior vascular ischemic events) for neither ibuprofen (1.15 vs 1.32), naproxen (1.29 vs 1.23), nor diclofenac (1.19 vs 1.14).[33] Even though the studies did not have the exact same definition of MACE and the exposure period as we had, the results were consistent with our results. Thus, our study adds to the existing literature that NSAIDs have an increased cardiovascular risk independent of low- or high-risk profile.

Limitations

Because we only had LDL-C information from the North and the Central Denmark Region until 2015, all hospitalized patients with MI before 2015 outside these regions were not included in our study (35%).[20] This should not weaken the external validity of the results as there is found to be a high degree of homogeneity regarding demographic characteristics, healthcare utilization, and medication use between all Danish regions.[34,35]

As we lacked information on over-the-counter ibuprofen sales and in-hospital NSAID use, patients could potentially have been classified incorrectly as non-users. Ibuprofen was the only NSAID available over-the-counter during the study period, and over-the-counter ibuprofen sales only accounts for around 30% of total ibuprofen sales in Denmark.[2] However, the impact of such misclassification has, in Denmark, been shown to be too small to substantially bias effect estimates of the association between NSAID use and cardiovascular risk.[36] Another concern is our lack of information on patient adherence, which cannot be accounted for using the registry data.[17] However, the comparable results observed after changing the exposure definition support the robustness of our findings. No information was missing on outcomes, comorbidities, or medication use.

We did not have exact information on some cardiovascular risk factors such as blood pressure, body mass index, or smoking habits, but did adjust for hospital diagnosed hypertension, various antihypertensive medications, obesity, and chronic pulmonary disease (Supplemental Table 2). Also, as comparisons were made within a cohort of patients with first-time MI, the

baseline characteristics are likely more similar than if compared with the general population. Furthermore, our study might be prone to confounding by contraindication as general practitioners are likely to prescribe NSAIDs more often to healthier patients, in order to adhere to current recommendations. This would result in lower effect estimates, as observed for some of the secondary outcomes.[10,16] Also, some residual confounding may be present due to adjustment for patient characteristics only at baseline, instead of the period including the year following first-time MI.

We obtained LDL-C values before hospital discharge following a first-time MI. As almost 85% of patients filled a statin prescription in the year following their MI, patients in the high LDL-C group could be misclassified as their LDL-C decreases. Accounting for that in our analysis among one-year survivors did not show any markable difference in risk of MACE between the low and high LDL-C groups.

Due to the low number of outcomes, the estimates for one-year survivors were imprecise and should be interpreted with caution. As well, the paucity of outcomes meant that we could not perform the analyses for individual NSAIDs.

Conclusions

In patients with first-time MI, any NSAID use was associated with increased risk of MACE. The LDL-C level did not influence the association between NSAID use and MACE but might influence the association between NSAID use and all-cause death. Thus, healthcare providers should be mindful of the increased cardiovascular risk associated with NSAID use in patients with previous MI, regardless of LDL-C values.

Data Sharing Statement

Not allowed. No new data were generated in support of this research.

Ethical Approval

The use of data from the national registers was approved by the Danish Data Protection Agency through institutional registration (record number 2016-051-000001, Aarhus University record number 2016-051-000001-810). Ethical approval is not required for registry-based studies in Denmark.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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