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Full Length Article

Cardiovascular event rates and trajectories of LDL-cholesterol levels and lipid-lowering therapy in patients with atherosclerotic cardiovascular disease: A population-based cohort study

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ABSTRACT

Background: An understanding of cardiovascular event rates and low-density lipoprotein cholesterol (LDL-C) levels and trajectories in patients with atherosclerotic cardiovascular disease is needed to evaluate treatment goals and adherence to guidelines.

Methods: We conducted a population-based cohort study in the North and Central Denmark Regions. Patients with prevalent atherosclerotic cardiovascular disease (myocardial infarction, non-hemorrhagic stroke, or peripheral artery disease) during 2006–2009 were identified. All patients received lipid-lowering therapy (statins or ezetimibe) and had LDL-C levels ≥1.8 mmol/L at baseline (January 1, 2010). We followed patients for 6 years until a primary composite outcome of cardiovascular death, myocardial infarction, non-hemorrhagic stroke, hospitalization for unstable angina, or coronary revascularization. Additionally, we characterized changes in LDL-C levels and use of statins during follow-up.

Results: The study included 10,772 patients (median age 69.2 years, 60.4% male). The overall event rate for the primary outcome was 62.7 (95% confidence interval: 59.2–66.2) per 1000 person-years. This event rate was higher among men than among women and increased with age and baseline LDL-C levels. Approximately 25% of patients with LDL-C measurements during follow-up achieved LDL-C levels below 1.8 mmol/L. Of the approximately two-thirds of patients using statins at the end of follow-up, nearly all patients (97%) received high-intensity therapy.

Conclusions: In this population of patients with atherosclerotic cardiovascular disease, we found high cardiovascular event rates, which increased with baseline LDL-C levels. Although most patients were on high-intensity statin therapy at end of follow-up, only one-quarter reached the guideline-recommended target LDL-C level ≤ 1.8 mmol/L.

1. Introduction

Atherosclerotic cardiovascular disease currently accounts for the majority of deaths in most parts of the world [1]. Within the realm of cardiovascular disease, coronary heart disease and stroke are the number 1 and number 3 causes of death, accounting for 42% and 35% of global cardiovascular mortality, respectively [1]. Based on data from the National Health and Nutrition Examination Survey (NHANES), a series of surveys conducted in the United States during 2009–2010, an estimated 16.2 million Americans (7.2% of the population) have prevalent atherosclerotic cardiovascular disease [1,2].

Treatment of this disease includes therapies aimed at reducing the level of low-density lipoprotein cholesterol (LDL-C) to prevent recurrent cardiovascular events [3,4]. However, despite the potential for reducing LDL-C levels pharmacologically, EUROASPIRE IV, an observational study conducted across Europe, suggested that 80% of patients with established coronary heart disease do not achieve LDL-C levels < 1.8 mmol/L [5].

It was shown recently that non-statin lipid-lowering therapy, including the cholesterol reuptake inhibitor ezetimibe and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, when added to statin therapy, further reduce the risk of cardiovascular events in populations with established atherosclerotic cardiovascular disease [6–8].

Cardiovascular event rates are often higher among patients with atherosclerotic disease included in population-based registries than among those observed in randomized clinical trials [9]. Thus, to

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evaluate the potential benefit of new preventive therapies, it is essential to examine cardiovascular event rates encountered outside a trial environment, in a routine clinical setting. In addition, it is important to understand the current quality of care in patients with established atherosclerotic cardiovascular disease. Such analyses will allow for identification of high-risk patients who may benefit from newer cholesterol-lowering therapies.

We examined real-world estimates of cardiovascular event rates in a secondary prevention population at very high cardiovascular risk. We also reported patterns of statin use and trajectories of LDL-C levels during 6 years of follow-up in this population.

2. Methods

2.1. Design, setting, and data sources

We conducted a population-based cohort study of patients with prevalent atherosclerotic cardiovascular disease in the North and Central Denmark Regions (population ~1.8 million inhabitants or about one-third of the total Danish population) [10]. The Danish National Health Service provides tax-supported health care, ensuring unfettered access to general practitioners and hospitals for all Danish residents. The unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration permits accurate linkage of all registries at the individual level in Denmark [11].

The Danish Civil Registration System [11] issues central personal registry numbers and uses them to track vital status, with daily electronic updates. The Danish National Patient Registry [12] has collected data on admission and discharge diagnoses, procedures, and surgeries from all non-psychiatric hospitals since 1977 and from emergency room visits and outpatient contacts since 1995. Each hospital contact is recorded in the Danish National Patient Registry with one primary diagnosis and one or more secondary diagnoses, coded according to the *International Classification of Diseases* (ICD), *Eighth Revision* (ICD-8) during 1977–1993 and *Tenth Revision* (ICD-10) thereafter.

We obtained data on cholesterol tests ordered in the hospital inpatient and outpatient settings and by general practitioners from the Clinical Laboratory Information System Research Database using Nomenclature for Properties and Units (NPU) codes [13]. We retrieved information on drug prescriptions from the Aarhus University Prescription Database [14], which covers the entire Central and North Denmark Regions. This Database contains data on all prescriptions dispensed in Danish community pharmacies for reimbursed medicines since 1998, recorded according to Anatomical Therapeutic Chemical Classification system (ATC) codes. The Registry of Causes of Death [15] provided information on specific cardiovascular causes of death. While information on all-cause deaths was available for the entire study period, access to information on specific causes of death, needed to correctly capture cardiovascular deaths, was available only until the end of 2011. All codes used in the study are listed in Table S1.

2.2. Study populations

We identified patients with a diagnosis of myocardial infarction (MI), non-hemorrhagic stroke (NS), or peripheral artery disease (PAD) during the 4-year period prior to the baseline date of January 1, 2010 (Fig. S1). We used both primary and secondary diagnosis codes assigned to patients during inpatient stays or outpatient specialist clinic visits. Eligibility criteria were an LDL-C level of $\geq$1.8 mmol/L for patients' most recent measurement before January 1, 2010 and receipt of statin and/or ezetimibe therapy, defined as at least 1 prescription $\leq$90 days prior to January 1, 2010. Only patients aged 40 years or older at baseline were included in the study.

Patients were required to reside in the Central or North Denmark Regions from their MI/NS/PAD admission date and until January 1, 2010. Patients who left the study Regions during follow-up were censored.

2.3. Outcomes

The primary outcome was a composite of MI, NS, hospitalization for unstable angina, or coronary revascularization (defined as performance of percutaneous coronary intervention (PCI)). The secondary outcome was a composite of MI or stroke. We analyzed the primary and secondary outcomes both with and without cardiovascular deaths, due to restrictions in availability of follow-up data for cardiovascular deaths. Cardiovascular death was defined as death from venous thromboembolism, MI, stroke, heart failure, or arrhythmia, based on immediate/primary causes of death. Outcomes were identified through primary and secondary diagnosis codes recorded during inpatient admissions and outpatient specialist clinic visits.

In addition, we analyzed LDL-C goal attainment during follow-up using LDL-C measurements during each year of follow-up. We categorized patients by clinically relevant LDL-C levels: < 1.8 mmol/L, 1.8–2.5 mmol/L, 2.5–3.5 mmol/L, and ≥ 3.5 mmol/L. We additionally characterized the use of lipid-lowering therapy during follow-up as the proportion of patients using statin and ezetimibe based on prescriptions redeemed within 90 days before the end of each year of follow-up. For statin users, we ascertained the intensity of statin use at baseline and during follow-up by calculating simvastatin-equivalent cumulative doses, using relevant conversion factors for each type of statin (Table S2) followed by categorization of intensity of statin use [low (< 20 mg/day), moderate (20 – < 80 mg/day), and high (≥80 mg/day), Table S3]. In brief, the simvastatin-equivalent cumulative dose was obtained by multiplying number of pills × dose per pill × simvastatin conversion factor for each prescription and then summing across all prescriptions redeemed within 90 days before January 1, 2010 and within 90 days before the end of each year of follow-up and dividing by 90 days to obtain dose/day.

2.4. Patient characteristics

We used the complete inpatient and outpatient clinic medical history available in the Danish National Patient Registry [12] (from 1977 up to December 31, 2009) to ascertain the presence of cardiometabolic disease, including MI, NS, PAD, polyvascular disease (> 1 type of atherosclerotic disease), hypertension, and diabetes. From the Aarhus University Prescription Database, we retrieved information on use of cardiovascular drugs [statins (including intensity of use)], ezetimibe, aspirin, P2Y12 inhibitors, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists). LDL-C levels (most recent measurement prior to baseline) were obtained from the Clinical Laboratory Information System Research Database.

2.5. Statistical analysis

We tabulated characteristics of the study population, including age, sex, follow-up time, region of residence, atherosclerotic inclusion event (MI, NS, or PAD), previous cardiometabolic disease, use of cardiovascular drugs, and LDL-C levels.

Crude event rates were calculated per 1000 person-years for the primary and secondary outcomes. We calculated event rates for the entire cohort and for relevant subgroups by sex, age groups, baseline LDL-C levels, baseline lipid-lowering therapy use, inclusion event (MI, NS, or PAD), presence of polyvascular disease, and diabetes. The cohort was followed starting on January 1, 2010 and patients were censored at death, emigration, 31 December 2015, or occurrence of any prespecified cardiovascular event defined as a primary or secondary outcome, whichever came first.

We used cumulative incidence functions with death as a competing risk to calculate risks during follow-up. We graphically illustrated the

cumulative incidence curves for the primary and secondary outcomes with and without cardiovascular death. Cumulative incidence, accounting for competing risk of death, was estimated in a two-step process [16]. In the first step, we calculated the Kaplan–Meier estimate of overall survival from any event. In this step, both the event of interest as well as the competing risk of death were considered events. In the second step, we calculated the conditional probabilities of experiencing the event of interest. The cumulative incidences of the event of interest were estimated using these probabilities.

The distribution of patients in the pre-defined LDL-C categories during each year of follow-up were calculated as the number of patients in each LDL-C category relative to the total number of patients with LDL-C measurements during that year. Similarly, the distribution of patients receiving low-, moderate-, and high-intensity statin therapy was calculated as the number of patients in each category relative to the total number of patients receiving statin therapy during each year of follow-up.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). According to Danish legislation, informed consent and approval from an ethics committee is not required for registry-based studies. The study was approved by the Danish Data Protection Agency (record number: 1-16-02-1-08).

3. Results

We identified a total of 10,722 individuals (median age 69.2 years, 60.4% male) with prevalent atherosclerotic cardiovascular disease (Table 1). About one-third (36%) were included based on MI, 39% based on NS, and 24% based on PAD. At baseline, only 2% used ezetimibe and 99% used statins. Among statin users, 16% were receiving high-intensity statin therapy. Almost half of patients (43%) had an LDL-C measurement ≥ 2.5 mmol/L and 6% had an LDL-C level ≥ 4.0 mmol/L. The median LDL-C level was 2.55 mmol/L (25th to 75th quartile: 2.00 to 2.80) and thus comparable to the median LDL-C level at baseline in the FOURIER study (2.4 mmol/L). The most recent LDL-C measurement prior to baseline (≥ 1.8 mmol/L as per inclusion criteria) was recorded after the inclusion event (MI, NS, or PAD) in 84% of study patients and before the inclusion event in 16% of study patients. Concurrent use of other cardiovascular drugs was common, with 74% using aspirin or P2Y12 inhibitors, 46% using beta blockers, and 51% using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aldosterone antagonists. Common concurrent diagnoses at baseline were polyvascular disease (present in 13% of patients), diabetes (17% of patients) and hypertension (50% of patients).

5. Cumulative risk and event rates

The overall event rate for the composite primary outcome including cardiovascular death was 62.7 (95% CI: 59.2–66.2) per 1000 person-years and 43.9 (95% CI: 42.1–45.8) per 1000 person-years excluding cardiovascular death (Table 2). The overall event rate for the composite secondary outcome including cardiovascular death was 49.6 (95% CI: 46.5–52.7) per 1000 person-years, and 33.8 (95% CI: 32.2–35.4) per 1000 person-years excluding cardiovascular death. Event rates for the primary outcome were highest for patients with MI as the inclusion event. Event rates for the secondary outcome were highest in patients with non-hemorrhagic stroke as the inclusion event. Across outcomes, the event rate was higher among men than among women and increased with advancing age and increasing baseline LDL-C levels. Event rates for both the primary and secondary outcomes were substantially higher in patients with diabetes or polyvascular disease at baseline.

The cumulative incidence of the composite primary outcome (excluding cardiovascular death) was 20% (95% CI: 19%–21%) after 6 years of follow-up. This was only slightly higher than the cumulative incidence of the composite secondary outcome (excluding cardiovascular death) [16% (95% CI: 15%–17%)] (Fig. S2). Similarly, for the primary and secondary outcomes including cardiovascular death, the cumulative incidence of the primary outcome was only slightly higher than the secondary outcome after 2 years of follow-up (11%, 95% CI: 11%–12% vs. 9%, 95% CI: 9%–10%) (Fig. S2). Cardiovascular death was driven by MI (24%), stroke (23%), and heart failure (21%).

Table 1
Characteristics of patients with prevalent atherosclerotic cardiovascular disease (myocardial infarction, non-hemorrhagic stroke, or peripheral artery disease), Denmark, 2006–2009.

Total	10,722 (100.0%)
Age, median (25th–75th percentile)	69.2 (61.4–77.4)
Age groups	
40–49 years	601 (5.6%)
50–59 years	1701 (15.9%)
60–69 years	3299 (30.8%)
70–79 years	3181 (29.7%)
80–110 years	1940 (18.1%)
Gender	
Female	4246 (40%)
Male	6476 (60%)
Follow-up time	
Median follow-up time in years for the primary outcome excluding cardiovascular death (25th–75th percentile)*	6.0 (3.1–6.0)
Region of residence at baseline	
Central Denmark Region	7104 (66%)
North Denmark Region	3618 (34%)
Inclusion event (2006–2009)	
Myocardial infarction	3879 (36%)
Non-hemorrhagic stroke	4226 (39%)
Peripheral artery disease	2617 (24%)
Median time in years from inclusion event until January 1, 2010 (25th–75th percentile)	
Myocardial infarction	2.0 (0.9–3.3)
Non-hemorrhagic stroke	1.8 (0.8–3.0)
Peripheral artery disease	1.5 (0.6–2.8)
Previous cardiometabolic disease	
Myocardial infarction	4689 (44%)
Non-hemorrhagic stroke	4670 (44%)
Peripheral arterial disease	2920 (27%)
Polyvascular disease†	1442 (13%)
Hypertension	5367 (50%)
Diabetes	1771 (17%)
Drug use [90 days prior to baseline (January 1, 2010)]	
Ezetimibe	234 (2%)
Statin	10,614 (99%)
Low intensity‡	544 (5%)
Moderate intensity‡	8342 (78%)
High intensity‡	1728 (16%)
Statin non-users	108 (1%)
Aspirin, P2Y12 inhibitors, or both	7882 (74%)
Beta blockers	4955 (46%)
ACE-inhibitors or ARBs, aldosterone antagonists, or both	5514 (51%)
LDL-C measurements (most recent measurement prior to baseline)	
Median (25th–75th quartile)	2.55 (2.00–2.80)
≥ 1.8 mmol/L	10,722 (100.0%)
≥ 2.5 mmol/L	4610 (43.0%)
≥ 3.0 mmol/L	2258 (21.1%)
≥ 3.5 mmol/L	1189 (11.1%)
≥ 4.0 mmol/L	638 (6.0%)

Abbreviations: ACE-inhibitors; angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers, LDL-C, low-density lipid cholesterol.
Data are numbers (%) unless otherwise specified.
* Median follow-up time is 6 years because approximately 60% of patients did not experience the primary outcome or any censoring during follow-up. Hence approximately 60% of patients had 6 years of follow-up.
† > 1 type of atherosclerotic disease (myocardial infarction, non-hemorrhagic stroke, or peripheral artery disease) with look-back to 1977.
‡ Cumulative simvastatin-equivalent dose.

6. LDL-C levels and lipid-lowering therapy during follow-up

Throughout follow-up, approximately 75% of patients had LDL-C

Table 2
Rates of cardiovascular events (per 1000 person-years) with 95% confidence intervals, overall and by sex, age group, baseline LDL-C level, lipid-lowering therapy, inclusion event, diabetes, and polyvascular disease.

	Primary outcome		Secondary outcome	
	CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization*	MI, stroke, hospitalization for unstable angina, coronary revascularization	CV death, MI, stroke*	MI, stroke
Overall	62.7 (59.2–66.2)	43.9 (42.1–45.8)	49.6 (46.5–52.7)	33.8 (32.2–35.4)
Sex				
Female	56.7 (51.4–62.1)	40.1 (37.3–42.9)	46.5 (41.7–51.3)	31.8 (29.3–34.2)
Male	66.6 (62.0–71.3)	46.4 (44.0–48.9)	51.6 (47.5–55.7)	35.1 (33.0–37.2)
Age groups				
40–49 years	53.6 (40.1–67.2)	40.6 (33.5–47.8)	34.0 (23.3–44.6)	28.0 (22.2–33.8)
50–59 years	48.0 (40.4–55.6)	38.8 (34.6–42.9)	33.3 (27.1–39.6)	27.2 (23.7–30.6)
60–69 years	51.2 (45.5–56.8)	39.1 (36.1–42.2)	37.0 (32.2–41.7)	28.5 (25.9–31.0)
70–79 years	66.1 (59.4–72.8)	44.8 (41.3–48.3)	54.8 (48.7–60.9)	36.0 (32.9–39.0)
80–110 years	95.9 (85.3–106.5)	61.1 (55.3–66.9)	85.8 (75.9–95.8)	52.9 (47.5–58.2)
LDL-C				
≥1.8 mmol/L	62.7 (59.2–66.2)	43.9 (42.1–45.8)	49.6 (46.5–52.7)	33.8 (32.2–35.4)
≥2.5 mmol/L	66.7 (61.2–72.3)	46.7 (43.8–49.6)	52.7 (47.8–57.6)	36.3 (33.8–38.9)
≥3.0 mmol/L	76.1 (67.6–84.7)	51.9 (47.4–56.4)	61.4 (53.8–69.0)	41.2 (37.3–45.2)
≥3.5 mmol/L	80.6 (68.4–92.7)	51.7 (45.5–57.9)	66.7 (55.7–77.6)	41.6 (36.1–47.0)
≥4.0 mmol/L	78.1 (61.7–94.5)	50.0 (41.7–58.4)	62.6 (48.1–77.2)	40.1 (32.7–47.4)
Ezetimibe use				
No	62.5 (59.0–66.1)	43.8 (41.9–45.7)	49.6 (46.5–52.8)	33.8 (32.2–35.4)
Yes	70.2 (45.1–95.3)	48.9 (35.8–61.9)	50.3 (29.3–71.3)	32.6 (22.2–43.0)
Statin use				
No	81.7 (41.7–121.8)	55.0 (34.6–75.4)	54.6 (22.3–86.8)	38.8 (22.2–55.4)
Yes	62.5 (59.0–66.1)	43.8 (41.9–45.7)	49.6 (46.4–52.7)	33.7 (32.1–35.3)
Low intensity	70.0 (53.2–86.7)	48.1 (39.1–57.1)	51.0 (36.9–65.1)	35.2 (27.7–42.7)
Moderate intensity	60.7 (56.7–64.6)	42.6 (40.5–44.6)	48.9 (45.4–52.4)	33.4 (31.6–35.2)
High intensity	69.1 (59.9–78.3)	48.5 (43.7–53.3)	52.2 (44.2–60.1)	35.0 (31.0–39.0)
Inclusion event				
Myocardial infarction	68.3 (62.2–74.5)	45.9 (42.8–49.1)	47.3 (42.2–52.3)	30.6 (28.1–33.1)
Non-hemorrhagic stroke	64.9 (59.1–70.6)	45.0 (42.0–48.1)	58.1 (52.7–63.5)	39.9 (37.1–42.8)
Peripheral artery disease	51.2 (44.8–57.6)	39.2 (35.7–42.7)	39.7 (34.1–45.3)	29.1 (26.1–32.1)
Diabetes				
No	58.5 (54.8–62.2)	41.5 (39.6–43.5)	45.5 (42.2–48.8)	31.7 (30.0–33.4)
Yes	85.0 (74.7–95.2)	57.7 (52.2–63.1)	71.2 (61.9–80.5)	45.7 (40.9–50.5)
Polyvascular disease				
No	56.0 (52.5–59.6)	39.7 (37.8–41.5)	43.5 (40.4–46.6)	29.9 (28.3–31.5)
Yes	108.7 (95.7–121.8)	77.1 (69.8–84.4)	91.9 (80.0–103.8)	63.6 (57.1–70.1)

Abbreviations: CV, cardiovascular; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction.
*Restricted to 2 years of follow-up (until end 2011) due to restrictions in data availability for cardiovascular death.

measurements each year. The proportion of patients achieving the guideline-recommended LDL-C level (below 1.8 mmol/L) increased from 19% at the end of first year of follow-up to 25% at the end of the fourth year of follow-up and remained at this level until the end of follow-up. Thus, by the end of follow-up, 75% of patients had not reached the guideline-recommended LDL-C level of < 1.8 mmol/L, with 44% having an LDL-C level between 1.8 and 2.5 mmol/L, 23% having an LDL-C level between 2.5 and 3.5 mmol/L, and 9% having an LDL-C level above 3.5 mmol/L (Fig. 1).

As per the inclusion criteria, all patients received statin or ezetimibe therapy at baseline, with > 99% receiving statin therapy. This proportion decreased over time. At the end of follow-up, only two-thirds (67%) of patients were receiving statin therapy. The reason for this decrease was not recorded in the data, but may relate to a combination of poor adherence and the strict definition of current use (redemption of a prescription within 90 days before end of each year of follow-up). Among statin users, individuals on high-intensity statin therapy increased from 16% at baseline to nearly all statin users (97%) at the end of follow-up (Fig. 2).

7. Discussion

In this population-based cohort study of patients with prevalent atherosclerotic cardiovascular disease, we reported event rates and cumulative incidences for composite cardiovascular outcomes in a setting similar to cardiovascular outcome trials of PCSK9 inhibitors, such as the FOURIER trial [7]. Event rates for both the primary and secondary outcomes increased with increasing baseline LDL-C levels and were substantially higher in subgroups of patients with previously diagnosed diabetes or polyvascular disease.

The latest guidelines on cholesterol management from the European Society of Cardiology [17] and ACC/AHA [18] recommend an LDL-C concentration < 1.8 mmol/L for very high-risk patients with prevalent atherosclerotic cardiovascular disease. In our study population of such patients, only 25% with LDL-C measurements (≈75% of all patients) reached this target LDL-C level by the end of follow-up. This is consistent with findings reported for the EUROASPIRE IV study, in which only 20% of patients with coronary heart disease achieved LDL-C levels < 1.8 mmol/L [5]. Interestingly, we observed the failure of a large proportion of our study population to reach guideline-recommended LDL-C levels, even after several years of follow-up, despite a significant increase in the proportion of statin users receiving high-intensity statin therapy—rising from 16% of statin users at baseline to 97% at the end of follow-up.

The 2013 ACC/AHA cholesterol guideline [19] recommended minimal use of non-statin therapies and eliminated specific LDL-C

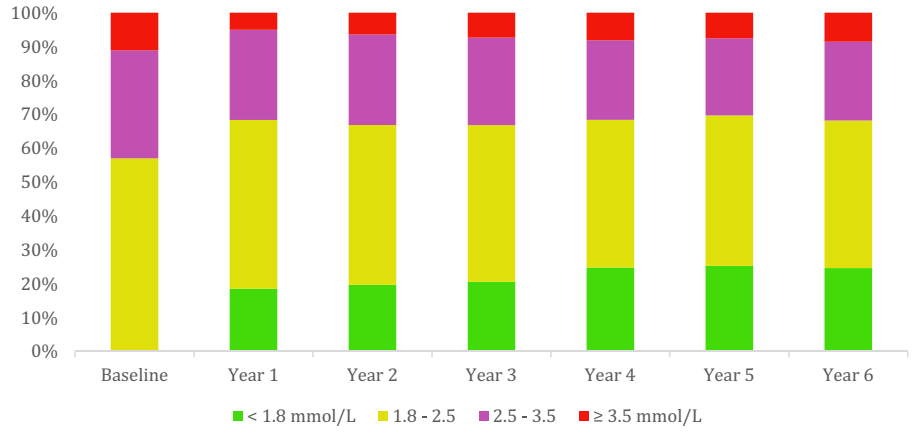
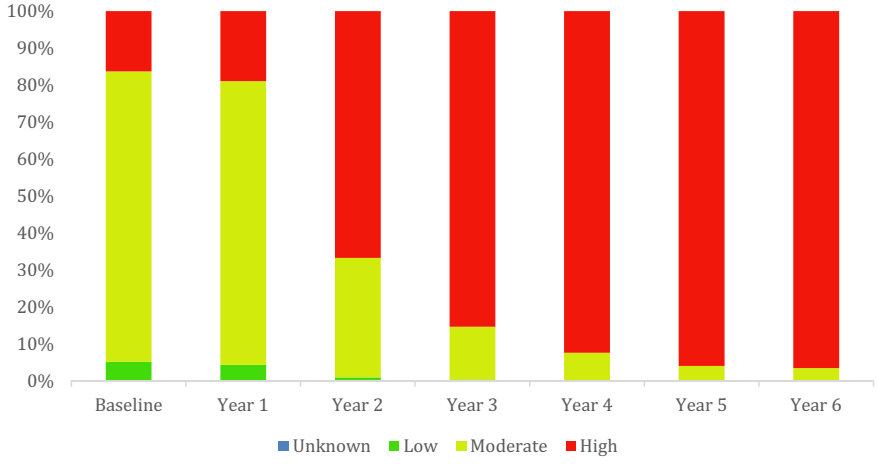


Fig. 1. Distribution of low-density lipoprotein cholesterol (LDL-C) levels (mmol/L) at baseline and during follow-up*.
*For each year of follow-up, approximately 25% of the study population did not have an LDL-C measurement and are therefore not included in the above distribution [2992 (29%) in 2010, 2640 (27%) in 2011, 2426 (27%) in 2012, 2196 (25%) in 2013, 2137 (26%) in 2014, and 1964 (26%) in 2015].

Study participants with LDL-C measurements during follow-up, n (%)							
Total	10722	7211	7051	6743	6437	5954	5621
< 1.8	0 (0)	1334 (19)	1385 (20)	1385 (21)	1593 (25)	1502 (25)	1382 (25)
1.8-2.5	6112 (5)	3594 (50)	3327 (47)	3120 (46)	2810 (44)	2647 (45)	2449 (44)
2.5-3.5	3421 (79)	1919 (27)	1888 (27)	1745 (26)	1510 (24)	1356 (23)	1310 (23)
≥ 3.5	1189 (16)	364 (5)	451 (6)	493 (7)	524 (8)	449 (8)	480 (9)
Total study participants during follow-up							
Total	10722	10203	9691	9169	8633	8091	7585

*For each year of follow-up, approximately 25% of the study population did not have an LDL-C measurement and are therefore not included in the above distribution [2992 (29%) in 2010, 2640 (27%) in 2011, 2426 (27%) in 2012, 2196 (25%) in 2013, 2137 (26%) in 2014, and 1964 (26%) in 2015].

treatment goals. This was based on lack of available clinical trial evidence supporting a strategy of targeting specific LDL-C levels or the addition of non-statin therapies to statins to further lower atherosclerotic cardiovascular disease events. Since then, strong trial evidence has emerged to support the addition of ezetimibe [8] and PCSK9 inhibitors [6,7,20] to statin therapy in patients with atherosclerotic cardiovascular disease. As a consequence, the new 2018 ACC/AHA guideline on the Management of Blood Cholesterol [18] recommends



Study participants in statin therapy, n (%)							
Total	10614	7813	7205	6640	6024	5585	5043
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (0,2)
Low	544 (5)	388 (4)	65 (1)	21 (0.3)	7 (0)	1 (0)	3 (0)
Moderate	8342 (79)	5995 (77)	2332 (32)	949 (14)	449 (8)	224 (4)	163 (3)
High	1728 (16)	1480 (19)	4808 (67)	5670 (85)	5568 (92)	5360 (96)	4869 (97)
Total study participants during follow-up							
Total	10,722	10,203	9691	9169	8633	8091	7585

Fig. 2. Distribution of intensity of statin therapy at baseline and during follow-up.

adding ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥1.8 mmol/L in very high-risk patients with atherosclerotic cardiovascular disease. If the LDL-C level still remains ≥1.8 mmol/L with maximally tolerated statin and ezetimibe therapy, the new guideline recommends adding a PCSK9 inhibitor. In light of the 2018 cholesterol guidelines, and considering our results demonstrating that few patients with atherosclerotic cardiovascular disease receiving high-intensity statin therapy reach LDL-C levels < 1.8 mmol/L, there is a substantial unmet medical need for further therapy in these patients.

Several issues should be considered when interpreting our results. The main strength of our study is its population-based design with complete follow-up, limiting the risk of selection bias arising from selective inclusion of specific hospitals, health insurance systems, or income levels [11]. Another strength is that definitions of cardiovascular diseases in general have high positive predictive values in the Danish National Patient Registry [21]. MI and NS both have positive predictive values above 90%, while PAD has a positive predictive value of approximately 70% [22].

Among potential concerns is inclusion of patients with chronic atherosclerotic disease who had survived from their qualifying event until January 1, 2010. The 4-year window (from 2006 to 2010) allowed the inclusion of a population with relatively recent disease activity. However, this window also conferred a period of up to 4 years of immortal time, which could lead to underestimation of cardiovascular risk in the short term following diagnosis of atherosclerotic disease. Another concern is that only a few patients (1% of the cohort) were non-statin users at baseline and subgroup analyses of these patients indicated higher event rates. However, precision was low and this finding should be interpreted with caution due to possible healthy user bias in those taking statins.

It is important to note that as an LDL-C level ≥ 1.8 mmol/L was a required inclusion criterion, laboratory measurement errors may have resulted in inclusion inaccuracy and misclassification of patients in analyses stratified by LDL-C levels. As well, we lacked measurements of LDL-C concentrations for about 25% of patients in any given year during follow-up. This likely reflects real-world clinical practice, in which an individual may not have LDL-C measured every year following an atherosclerotic event. The distribution of LDL-C concentration levels in patients with no measurements was unknown and could be different from those with measurements during follow-up. Thus, LDL-C levels may depend on the reason for lack of measurements, which may include non-adherence or levels of LDL-C that, as deemed by the treating physician, require less frequent follow-up tests. Importantly, although approximately 25% of patients did not have an LDL-C measurement in any given year during follow-up, only 8% of patients had no available LDL-C measurements in the entire follow-up period. The new guidelines call for frequent and regular measurements to evaluate treatment goals and possible indications for add-on therapies.

In the analysis stratified by baseline statin use, confounding by indication for intensity of statin use presumably biased the results towards higher event rates in patients with high-intensity statin use. As a consequence, patients on high- and low-intensity statin therapy had largely similar event rates.

Due to data availability, the study was restricted to patients admitted to hospitals in the Central and North Denmark Regions, which limits the generalizability of the study results. However, our results are most likely generalizable to other parts of Denmark, as the Danish healthcare system is homogeneous in structure and practice and there is generally high adherence to guidelines by clinicians across the country [10]. The Danish population is generally considered fairly representative of Western European countries, but generalization to other populations requires caution.

In this study, we investigated risk of cardiovascular outcomes, utilization of statin therapy, and LDL-C trajectories in a real-world population with established cardiovascular disease and at very high risk of recurrent cardiovascular events. Across outcomes, the event rate increased with increasing baseline LDL-C levels and was higher in patients with diabetes or polyvascular disease. Although all patients were at very high risk as per inclusion criteria and the majority was receiving high-intensity statin therapy, only 25% achieved the recommended target LDL-C level of ≤1.8 mmol/L by the end of follow-up. Most of these patients are candidates for additional lipid-lowering therapies, such as ezetimibe and PCSK9 inhibitors, according to newly published guidelines [18].

Contributors

J. Sundbøll, A.P. Larsen, and H.T. Sørensen contributed to the conception of the work. J. Sundbøll and A.P. Larsen contributed to the design of the work. J. Sundbøll and K. Veres contributed to the acquisition of data for the work. J. Sundbøll, K. Veres, and A.P. Larsen contributed to the analysis and interpretation of data. J. Sundbøll drafted the manuscript. All authors critically revised the manuscript and gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.09.034.

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