Lipid-Lowering Prescription Patterns in Patients With Diabetes Mellitus or Cardiovascular Disease

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The purpose of this study is to describe lipid-lowering therapy (LLT) prescriptions and low-density lipoprotein cholesterol (LDL-C) monitoring in patients with diabetes mellitus (DM) with or without concomitant cardiovascular disease (CVD). Olmsted County, Minnesota residents with a first-ever diagnosis of DM or CVD (ischemic stroke/transient ischemic attack, myocardial infarction, unstable angina pectoris, or revascularization procedure) between 2005 and 2012 were classified as having DM only, CVD only, or CVD + DM. All LLT prescriptions and LDL-C measurements were obtained for 2 years after diagnosis. A total of 4,186, 2,368, and 724 patients had DM, CVD, and CVD + DM, respectively. Rates of LDL-C measurement were 1.31, 1.66, and 1.88 per person-year and 14%, 32%, and 42% of LDL-C measurements were <70 mg/dl in those with DM, CVD, and CVD + DM. Within 3 months after diagnosis, 47%, 71%, and 78% of patients with DM, CVD, and CVD + DM were prescribed LLT. Most prescriptions were for moderate-intensity statins. Under one-fifth of patients with CVD and CVD + DM were prescribed high-intensity statins. Predictors of high-intensity statin prescriptions included male sex, having CVD or CVD + DM, increasing LDL-C, and LDL-C measured more recently (2012 to 2014 vs before 2012). In conclusion, a large proportion of patients at high CVD risk are not adequately treated with LLT. Despite often being considered a risk equivalent, patients with DM have substantially lower rates of LLT prescriptions and lesser controlled LDL-C than those with CVD or CVD + DM. **(Am J Cardiol 2019;124:995−1001)**

Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for the development of cardiovascular disease (CVD) and is highly prevalent.[1] Although LDL-C reduction has improved in recent years with use of high-intensity statins, it has been estimated that up to 75% of high-risk statin-treated patients failed to achieve the guideline-recommended LDL-C thresholds.[2−4] Furthermore, a substantial proportion of high-risk patients (including those with CVD or diabetes mellitus [DM]) do not receive any lipid-lowering therapy (LLT).[5−13] Despite this evidence, there are limited available data capturing longitudinal LLT prescribing patterns and LDL-C levels from all sources of healthcare, without restriction on insurance coverage or type of provider. Specifically, documentation of prescription patterns is lacking but is critical as it may more accurately reflect physician awareness of CVD risk. Thus, we aimed to describe LLT prescribing patterns, frequency of LDL-C monitoring, and predictors of high-intensity statin prescriptions over a 2-year period after a first diagnosis of CVD or DM in patients from a comprehensive linked medical records system in a community in southeastern Minnesota.

Methods

This study was conducted utilizing the Rochester Epidemiology Project (REP), a records-linkage system encompassing >6 million person-years of follow-up for >500,000 unique patients residing in Olmsted County, Minnesota since 1966.[14] Nearly all healthcare is captured because only a few providers (including Mayo Clinic and Olmsted Medical Center) deliver most healthcare to local residents and all medical record data from these providers are captured by the REP. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

This population-based cohort consisted of patients with incident (first-ever) diagnoses of CVD or DM from January 1, 2005 through December 31, 2012. The list of diagnostic codes and rules used to define the index events are included in Appendix Table 1. Patients with CVD had a diagnosis of ischemic stroke/transient ischemic attack, myocardial infarction (MI), unstable angina pectoris, or a revascularization procedure. Patients with incident CVD were further classified into those with CVD only and those with CVD who had preexisting DM (CVD + DM). Patients without CVD but who had an incident diagnosis of DM were classified as DM only.

Outpatient prescription data were obtained from Mayo Clinic and Olmsted Medical Center from 3 months prior through 2 years after the initiating event. All outpatient prescriptions for LLT, including statin and nonstatin therapy were obtained. For each statin prescription, the strength,

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dose, and frequency were used to calculate average daily potency in order to classify statin prescriptions into low, moderate, and high intensity, as defined by the 2013 American College of Cardiology/American Heart Association Practice Guideline (Appendix Table 2).[15] Records were reviewed when data were missing or inconsistent to determine the correct daily potency.

Tobacco use, classified as ever/never, was based on patient-provided surveys. Body mass index was estimated as the median value of the 10 heights and 10 weights closest to and within 3 years of index. Select co-morbidities were ascertained using the Centers for Medicare and Medicaid Chronic Conditions Data Warehouse algorithms.[16] For all conditions we used the 5 years before the index date to determine the presence or absence of a co-morbidity. Finally, all LDL-C measurements for the 1 year before to 2 years after index were obtained.

Analyses were performed using SAS/STAT software, version 9.4. Patient characteristics across disease categories were compared using chi-squared tests for categorical variables and ANOVA for continuous variables. Characteristics of patients with 0 versus ≥1 LDL-C measurements from index to 2 years after index were compared using chi-square and ANOVA tests. Rates of LDL-C measurements over follow-up were compared among the 3 groups using Poisson regression. Predictors of high-intensity statin prescriptions were assessed using Cox proportional hazards regression, using age as the time scale. This analysis was restricted to patients not on a high-intensity statin at index and who had a baseline LDL-C measurement (a measurement within 1 year before or 30 days after index [n = 5,670]). The proportional hazards assumption of the Cox model was tested by plotting scaled Schoenfeld residuals.

Results

Between 2005 and 2012, a total of 4,186, 2,368, and 724 patients were diagnosed with DM, CVD, and CVD + DM, respectively. Patients with CVD were older and had a higher prevalence of co-morbidities compared to patients with DM; those with CVD + DM had the highest co-morbidity burden (Table 1).

A total of 493 (11.8%), 305 (12.9%), and 70 (9.7%) patients with DM, CVD, and CVD + DM, respectively, had no LDL-C measurements within the 2 years after index (Table 1). Patients with no LDL-C measurements were older (65.6 vs 61.5 years), more likely to be female (53.8% vs 46.0%), and more likely to have heart failure (21.1% vs 8.0%), chronic obstructive pulmonary disease (19.5% vs 9.9%), and chronic kidney disease (19.8% vs 9.9%) compared with patients who had at least 1 LDL-C measurement (all p values <0.001).

Patients with DM had the most infrequent rates of measurement of LDL-C, at 1.31 per person-year, with the

Table 1
Characteristics of the cohort at baseline and summary information on all follow-up low-density lipoprotein cholesterol measurements, by index event

Variable	DM (n = 4,186)	CVD (n = 2,368)	CVD + DM (n = 724)	p Value
Age (years)	56.6 ± 14.9	68.9 ± 15.2	70.2 ± 13.2	<0.001
Men	2,149 (51.3%)	1,324 (55.9%)	392 (54.1%)	0.002
Ever tobacco use	2,404 (60.0%)	1,526 (65.4%)	475 (66.8%)	<0.001
Missing	180	36	13	
Body mass index (kg/m^2)				
<25	402 (11.7%)	655 (29.0%)	116 (16.6%)	<0.001
25 to <30	806 (23.4%)	898 (39.7%)	213 (30.4%)	
≥30	2,241 (65.0%)	708 (31.3%)	372 (53.1%)	
Missing	737	107	23	
Hypertension	2,122 (50.7%)	1,435 (60.6%)	638 (88.1%)	<0.001
Heart failure	177 (4.2%)	320 (13.5%)	197 (27.2%)	<0.001
Chronic obstructive pulmonary disease	354 (8.5%)	325 (13.7%)	123 (17.0%)	<0.001
Chronic kidney disease	270 (6.5%)	297 (12.5%)	239 (33.0%)	<0.001
LLT prescriptions at index*				
None	2,900 (69.3%)	1,684 (71.1%)	314 (43.4%)	<0.001
High-intensity statin	156 (3.7%)	80 (3.4%)	64 (8.8%)	
Moderate-intensity statin	761 (18.2%)	435 (18.4%)	256 (35.4%)	
Low-intensity statin	211 (5.0%)	124 (5.2%)	61 (8.4%)	
Nonstatin therapy only	158 (3.8%)	45 (1.9%)	29 (4.0%)	
LDL-C summary information				
Patients who have full 2 years of follow-up	3,854 (92.1%)	1,919 (81.0%)	566 (78.2%)	<0.001
Patients with 0 LDL-C measurements	493 (11.8%)	305 (12.9%)	70 (9.7%)	0.059
Rate (95% CI) of LDL-C measurement per person-year	1.31 (1.28-1.33)	1.66 (1.62-1.70)	1.88 (1.81-1.96)	<0.001
Median (25th, 75th percentile) LDL-C, mg/dL	2.53 (2.04, 3.10)	2.09 (1.66, 2.69)	1.91 (1.53, 2.43)	<0.001
LDL-C ≥100 mg/dl	5,038 (48.3%)	1,943 (28.6%)	454 (19.6%)	<0.001
LDL-C 70-99 mg/dl	3,898 (37.4%)	2,642 (38.9%)	887 (38.3%)	
LDL-C <70 mg/dl	1,493 (14.3%)	2,203 (32.5%)	975 (42.1%)	

CVD = cardiovascular disease; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; SD = standard deviation.

* Defined using prescription information from 1 day before index date.

highest rates found in those with CVD + DM (1.88 per person-year; Table 1). In patients with DM, 14.3% of all LDL-C measurements over follow-up were <70 mg/dl; nearly half (48.3%) were ≥100 mg/dl. In patients with CVD and CVD + DM, respectively, 32.5% and 42.1% were <70 mg/dl whereas 28.6% and 19.6% were ≥100 mg/dl. The proportion of patients with available LDL-C measurements across time periods over follow-up ranged from 22.3% to 75.4% (Figure 1). For all groups, the rate of LDL-C measurement decreased substantially after the 0 to 3 months post-index. Rates were generally lower for patients with DM compared to patients with CVD + DM. Furthermore, the mean and median values of LDL-C were highest across all periods of follow-up for patients with DM (Figure 1).

Patients with DM were prescribed LLT at the lowest rates (Figure 2). Within the first 3 months after index, 47% of patients with DM were prescribed LLT, which increased modestly over time but remained under 60% over the 2 years of follow-up. Patients with CVD + DM had higher rates of LLT during the 3 months before index compared with patients with CVD only; however, the patterns for these 2 groups of patients were generally similar after index. Within the first 3 months after index, 71% and 78% of patients with CVD and CVD + DM, respectively, were prescribed LLT and the proportions remained relatively stable thereafter.

Daily rates of LLT by type and intensity of therapy are displayed in Figure 3. An increase in prescriptions for LLT was observed immediately after index and the majority of prescriptions were for moderate-intensity statins. Approximately 6% of patients with DM were prescribed high-intensity statins, and <20% of patients with CVD and CVD + DM were prescribed high-intensity statins. At 1 year after index, a drop in prescription rates was observed, which may indicate a lack of renewal of prescriptions for some patients.

In the subset of patients with available baseline LDL-C who were not on high-intensity statins at index (n = 5,670), predictors of receiving a high-intensity statin prescription post-index are presented in Figure 4. We observed a graded association with increasing LDL-C level, with a 7.1-fold higher probability of high-intensity statin prescription in those with LDL-C ≥130 mg/dl compared with LDL-C <70 mg/dl. Men and patients with LDL-C measured in more recent years (2012 to 2014 vs before 2012) were also more likely to be prescribed high-intensity statins. Patients with CVD alone or CVD + DM were 7 times more likely to be prescribed high-intensity statins than those with DM. The proportional hazards assumption was not met for patients in the CVD and CVD + DM groups aged <55 years. The estimates were higher for patients <55 years than for patients ≥55 years (hazard ratio [95% confidence interval] 11.33 [8.50-15.12] vs 6.02 [4.86-7.47] for CVD and 10.32 [6.29-16.30] vs 5.72 [4.24-7.71] for CVD + DM). Finally, we tested whether the association of LDL-C with high-intensity statin prescriptions differed by disease category. We found no difference in the effect of LDL-C with high-intensity statin prescriptions between patients with DM alone, CVD, and CVD + DM (p interaction = 0.11).

Discussion

In this community-based study focused on clinician prescribing patterns, patients with DM were the least likely to receive a prescription for LLT, although many clinicians consider DM to be a risk equivalent. The majority of prescriptions were for moderate-intensity statins. Fewer than 20% of patients with CVD or CVD + DM were prescribed high-intensity statins, and the proportion was much lower (6%) in those with DM alone. High-intensity statins were more likely to be prescribed in males, those with CVD or CVD + DM, those with increasing levels of LDL-C, and those having more recent LDL-C measurements. We found that patients with DM alone, as compared to those with CVD and CVD + DM, had the lowest rates of LDL-C measurement and lowest proportion of LDL-C values <70 mg/dl.

In our population, <50% of patients with DM received a prescription for LLT in the 3 months after diagnosis, and although the proportion treated increased with follow-up, <60% were prescribed LLT 2 years after diagnosis.

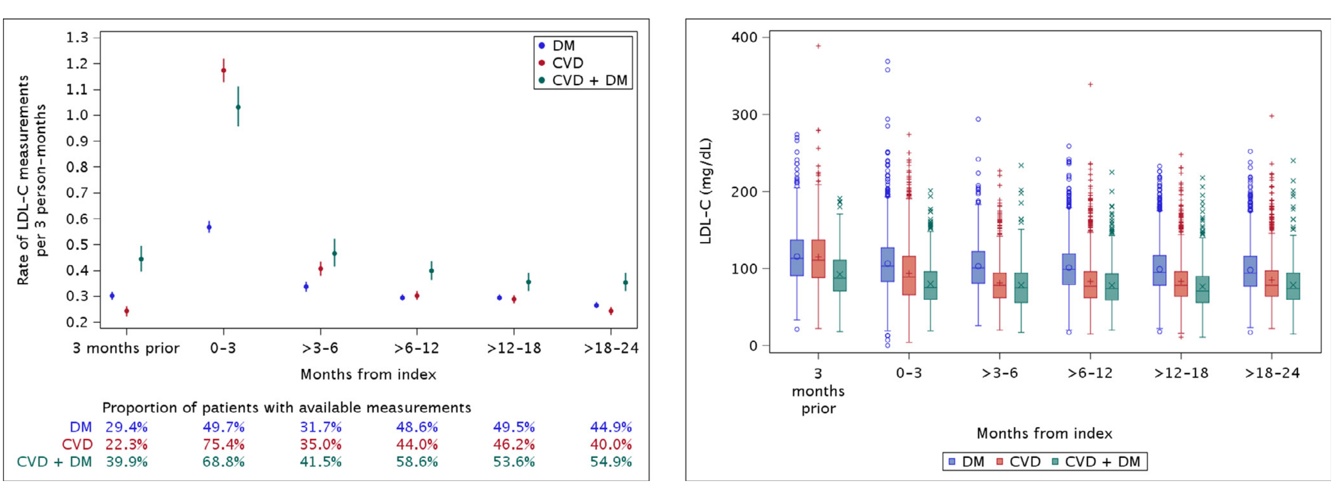

Figure 1. Overall rates (95% confidence interval) of low-density lipoprotein cholesterol measurements before and after index event in patients with diabetes mellitus, cardiovascular disease, and cardiovascular disease with concomitant diabetes mellitus (panel A). Distribution of low-density lipoprotein cholesterol measurements before and after index event in patients with diabetes mellitus, cardiovascular disease, and cardiovascular disease with concomitant diabetes mellitus (panel B). CVD = cardiovascular disease; DM = diabetes mellitus.

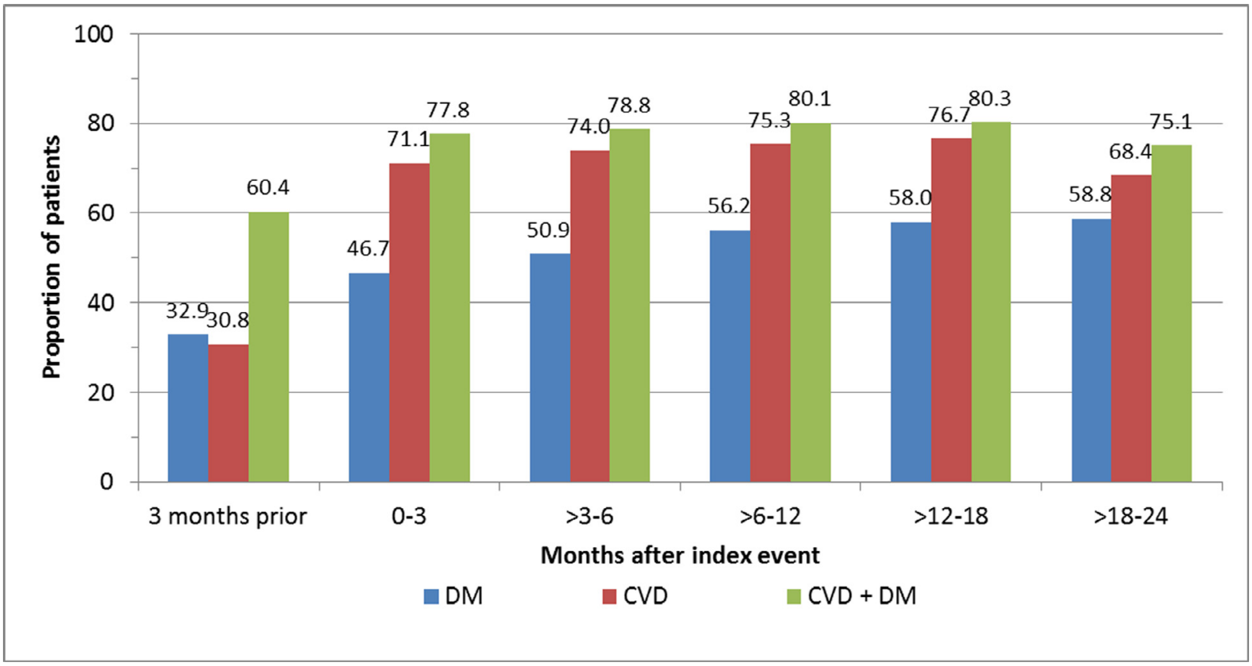

Figure 2. Proportion of patients on any lipid-lowering therapy before and after index event in patients with diabetes mellitus, cardiovascular disease, and cardiovascular disease with concomitant diabetes mellitus. CVD = cardiovascular disease; DM = diabetes mellitus.

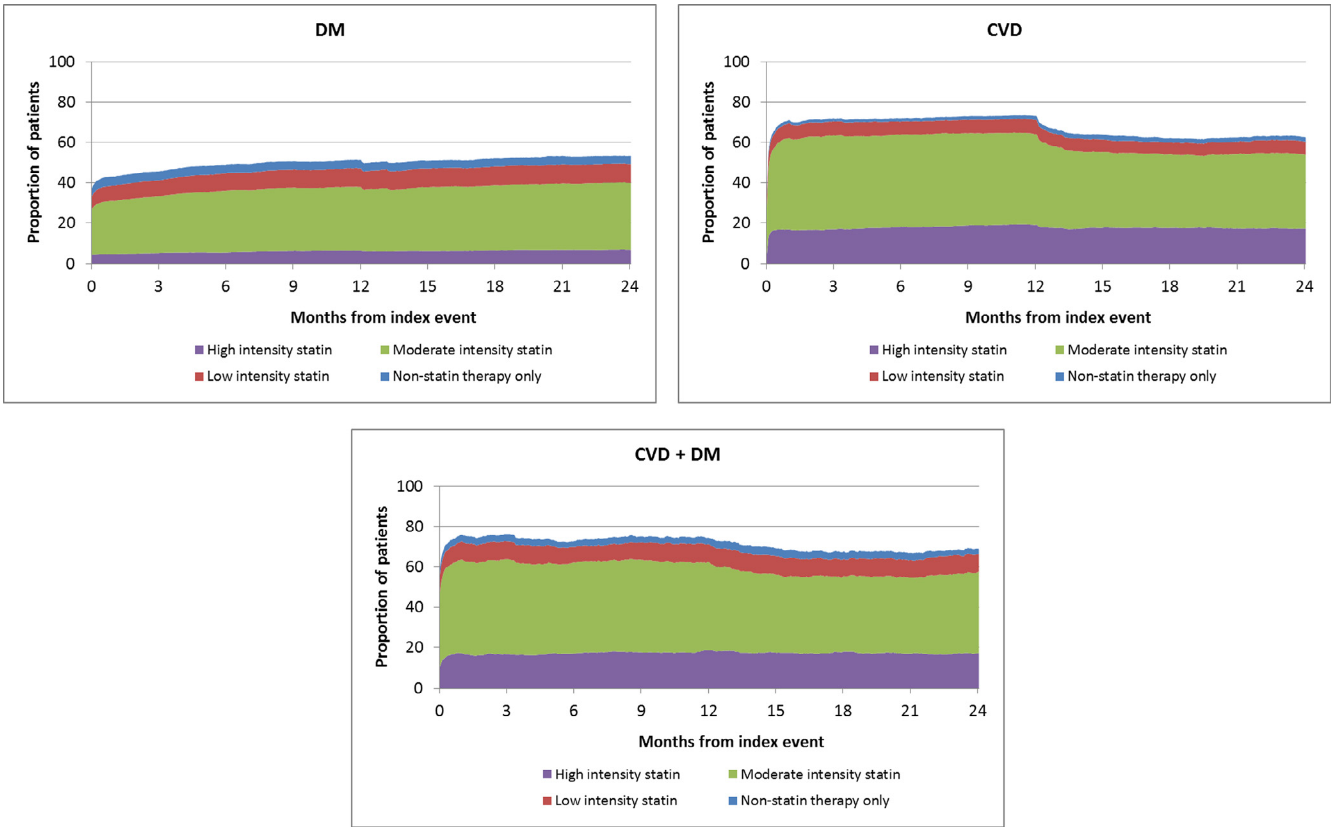

Figure 3. Daily rates of statin use in patients with diabetes mellitus (panel A), cardiovascular disease (panel B), and cardiovascular disease with concomitant diabetes mellitus (panel C). CVD = cardiovascular disease; DM = diabetes mellitus. The daily denominators were adjusted accordingly to account for deaths (n = 167, 408, and 152 patients in the diabetes mellitus, cardiovascular disease, and cardiovascular disease + diabetes mellitus groups, respectively) and losses to follow-up (n = 165, 41, and 6 patients in the diabetes mellitus, cardiovascular disease, and cardiovascular disease + diabetes mellitus groups, respectively).

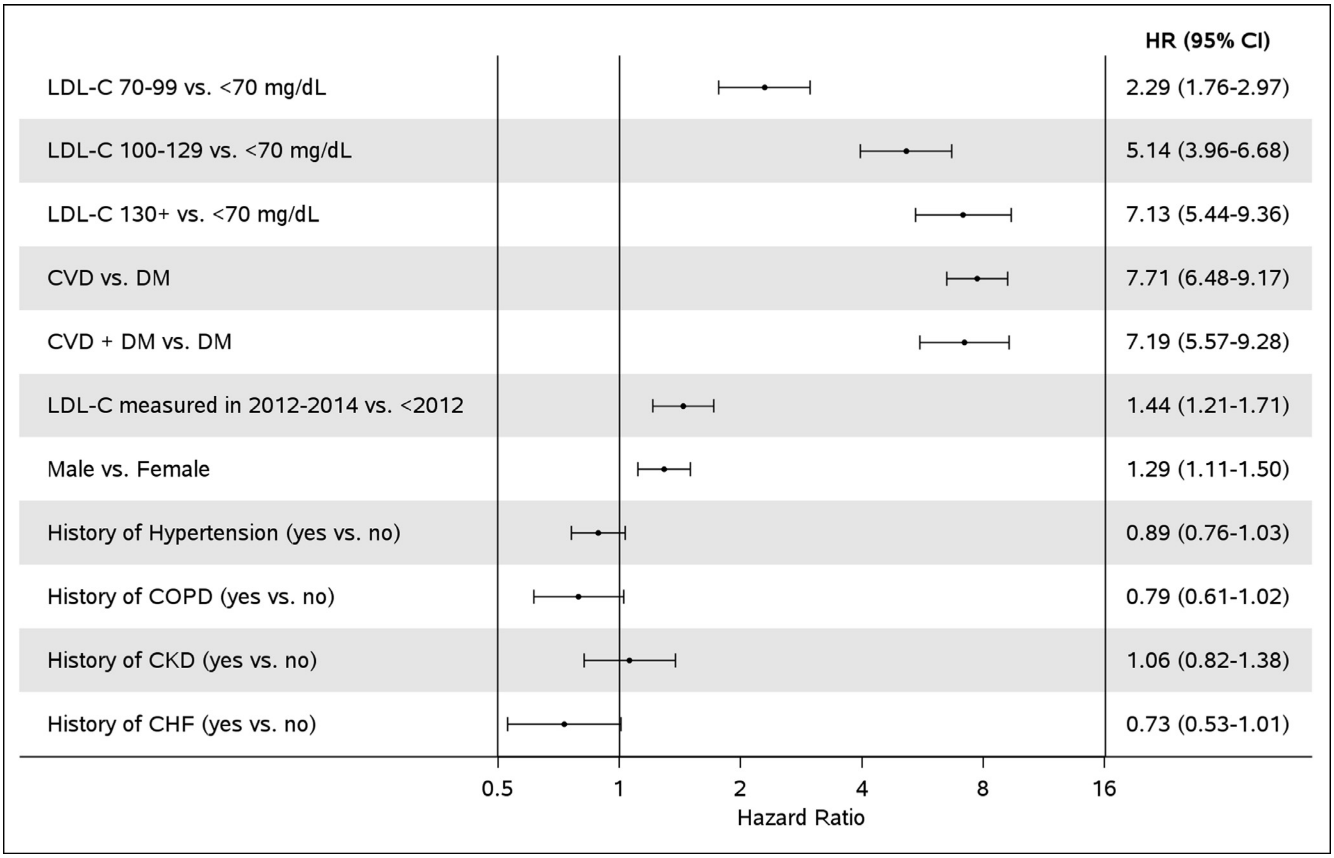

Figure 4. Predictors of high-intensity statin prescriptions in patients with an available baseline low-density lipoprotein cholesterol measurement (defined as a measurement within 1 year before to 30 days after index) and who were not on a high-intensity statin before the baseline low-density lipoprotein cholesterol measurement (n = 5,670). Hazard ratios are adjusted for all other variables in the figure. Low-density lipoprotein cholesterol and year of low-density lipoprotein cholesterol measurement were modeled as time-dependent variables. CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol.

Previous studies similarly report that patients with DM are undertreated. In the National Health and Nutritional Examination Survey, although use of statins in patients aged 40 to 75 years with DM increased from 26.2% in 1999 to 2002 to 49.5% in 2011 to 2014, the rates of high-intensity statins remained constant.[17] Data from the 2010 Medical Expenditure Panel Survey (MEPS) indicated that 52.0% of patients ≥40 years of age with DM self-reported use of statins.[6] Based on the MEPS data, a staggering 9 million patients in the United States with DM aged ≥40 years are not using statins.[6] In addition, approximately half of US adults with DM have a LDL-C of ≥100 mg/dl,[7] which was confirmed by our findings. Reasons for LLT underutilization may include provider opinions on the benefits of statins given the small risk of increasing hemoglobin A1c and fasting glucose.[18] Yet, the underutilization of LLT is particularly concerning given the evidence that statins in patients with DM reduce the risk of cardiovascular events by 22% to 37%.[19−21] The newest cholesterol guidelines call out the importance of regular monitoring of LDL-C levels, but also the importance of shared decision-making.[22] This could potentially improve the utilization of statins in this high-risk patient group.

Although LLT prescription rates were higher compared with DM, we nonetheless observed a substantial treatment gap with nearly one-quarter of patients with CVD not receiving a LLT prescription. In this population, prescriptions for LLT were higher than estimates from the 2010 MEPS (58.2%)[6] and the Optum Insight database from 2012 (67.9%),[3] but lower than the proportion of acute MI patients discharged on statins from hospitals in the Worcester, Massachusetts area,[8] from Translational Research Investigating Underlying Disparities in Acute MI Patients' Health Status study,[23] and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry−Get With The Guidelines and CathPCI databases,[24] which ranged between 85% and 91%. Among a 5% random sample of Medicare beneficiaries, only 58.8% of patients with coronary heart disease filled a statin prescription in the fourth quarter of 2011, of which 14.2% were for high-intensity statins.[5] The observed underprescribing of LLT in this study is concerning given that patients had their LDL-C monitored between 1 and 2 times per year and nearly 30% of LDL-C measurements in patients with CVD and 20% of LDL-C measurements in patients with CVD + DM were ≥100 mg/dl.

Moreover, the extent of the problem of undertreatment with LLT is compounded by poor adherence and persistence.[25] In a meta-analysis of >3 million statin users aged ≥65 years, 82.6% of patients using statins for secondary prevention were persistent at 1 year, but only 62.3% were adherent.[26] Data from MarketScan and Medicare found that both persistence and adherence to statin therapy in the year after treatment initiation were markedly lower in patients with DM compared with MI.[27] Thus, the proportion of patients with clear indications for LLT who are actually taking it is sorely inadequate, and those with DM are less likely to be adherent than patients with CVD. This is particularly concerning given the high medication burden of newly diagnosed DM patients (mean of 6.6 therapeutic classes of drugs),[28] which could heighten issues with nonadherence. Furthermore, it is unknown whether physician prescribing of LLT or patient adherence will be affected by use of newer antidiabetic agents, including sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 analogues, some of which have shown a CVD benefit, including reduced cardiovascular mortality and reduced heart failure admissions.[29] Thus, additional research is warranted to describe whether trends in LLT prescribing and adherence differ by antidiabetic treatment strategy.

A major strength of this study is the REP records-linkage system which provides for nearly complete coverage of patients' medical history. Second, the longitudinal nature of the data allowed the examination of prescription patterns before, immediately after, and in the 2-year period after a CVD or DM event which is not commonly described in the existing literature and provides valuable insights into real-world treatment patterns. Finally, we documented the extent of under-prescribing of LLT which more accurately reflects awareness of CVD risk and benefits versus harms of LLT treatment compared with studies using pharmacy claims data. A limitation of the REP is that because the demographic and ethnic characteristics of Olmsted County are representative of the Midwest region of the United States,[30] minority racial and ethnic groups are underrepresented. In addition, pharmacy claims data are not available in the REP, and thus, we could not calculate adherence to the prescribed therapy.

In this community-based study using high quality and largely complete-linked medical records, we found substantial under-prescribing of LLT in patients who had higher risk conditions of CVD and/or DM. Of concern, despite the substantial cardiovascular risk of those with DM, these patients were found to have fewer measurements of LDL-C, lower LLT prescription rates, and less well-controlled LDL-C compared to patients with CVD or CVD + DM. Additional research and educational efforts are needed to better understand why a treatment with proven benefits remains underutilized in patients known to be at high risk for future CVD events, and how to best combine medications to treat the multiple risk factors which often exist.

Disclosures

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Supplementary materials

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