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Impact of LDL-C lowering on recurrent cardiovascular events and hospitalization in secondary prevention in German clinical practice

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Summary
Background: Large, randomized, controlled trials have shown that lowering low-density lipoprotein cholesterol (LDL-C) reduces risk of cardiovascular (CV) morbidity and mortality. It is unclear whether similar risk reduction is attained in clinical practice. The effect of early LDL-C goal achievement on future CV events also remains to be investigated. The objectives were to (i) investigate risk of recurrent CV events and influence of factors such as lipid levels on the risk of such events and (ii) explore effect of *early* LDL-C goal attainment on future CV events and hospitalization.
Methods and results: Randomly drawn patients (n = 603) from randomly drawn practices (n = 62) were retrospectively evaluated for a median of 3.6 years (1998—2002) on lipid-lowering therapy. Results of time to event analysis show that the hazard rate of recurrent CV events was highest in the first six months following an index event. Revascularization at baseline, high baseline co-morbidity and high LDL-C level increased the hazard rate of recurrent CV events. Probit analysis of panel data indicates that goal attainment during the first six months and treatment by a cardiologist reduced the risk of future recurrent CV events and all-cause hospitalization.

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Conclusion: High LDL-C level significantly contributes to risk of CV morbidity. The potential for preventing CV morbidity is highest in the first six months because *goal attainment within the first six months* after the index event significantly reduces the risk of a future recurrent CV event. Our results support early goal attainment and aggressive LDL-C reduction to achieve a lower incidence of CV events and hospitalization.

Introduction

There is considerable evidence from several large, randomized clinical trials that lowering low-density lipoprotein cholesterol (LDL-C) with statins reduces risk of cardiovascular morbidity and mortality [1—9]. These findings have led to National Cholesterol Education Program (NCEP) Adult Treatment Panel III [10] (ATP) and the European Joint Task Force [11] guidelines for aggressive cardiovascular risk management that includes effective LDL-C reduction. Failure to achieve treatment goals has been shown to cause increased cardiovascular morbidity and mortality [8,9].

Patients with established coronary heart disease (CHD) have a substantial absolute risk-reduction potential and are therefore given high priority for cardiovascular risk factor modification. For best outcomes their LDL-C levels should be consistently maintained below 100 mg/dL (2.59 mmol/L) [9—11]. In a controlled study of a large number of patients who recently had an acute coronary syndrome (ACS), the PROVE-IT study demonstrated that sustained aggressive therapy with a high potency statin provided greater protection against death or major cardiovascular events compared to a standard regimen among these patients [12]. However, it is not clear whether similar reduction in risk is attained in actual clinical practice. Additionally, many of these studies have shown a reduction in LDL-C and CVD morbidity and mortality concurrent with statin therapy. But the effect of early achievement of guideline recommendations in LDL-C reduction on future CV events still remains to be investigated.

This retrospective cohort study was conducted to address these issues in the management of hypercholesterolemia in general practice and cardiology outpatient settings in Germany. A key goal was to analyze CV events and CV hospitalizations after initiation of lipid-lowering therapy in CHD patients in Germany. The objectives were to:

1. investigate the risk of CV events and the influence of factors such as lipid levels on the risk of such events and
2. explore the effect of early goal attainment on future CV events and hospitalization.

Methods

Study design

In this multicenter, retrospective, observational study, 6000 primary-care practices (GPs/internists) and 1200 cardiology practices were contacted after they were randomly chosen from the universe of all practices in Germany. Consent to participate was obtained from 237 practices, of which 53 primary-care and 9 cardiology practices were again randomly selected and enrolled. The objective was to obtain information on 500 CHD patients in primary care and 100 CHD patients in cardiology care, a ratio that reflects the actual practice patterns in CHD aftercare in Germany. Data were originally collected for a study on the effect of pre-treatment LDL-C level and pre-treatment risk factors on the effectiveness of lipid-lowering therapy in males and females [13]. The current study used the same data to conduct additional analyses to address the above goals. No additional data were collected for this study.

Data were collected by trained research personnel (Kendle Int., Inc., Munich), who interviewed the physicians with the help of standardized data collection forms regarding the patient's year of birth, sex, height, body weight, current or former cigarette smoking, familial history (parents or siblings with myocardial infarction (MI) before the age of 60), counseling of the patient with regard to diet and exercise, cardiovascular history, concurrent diseases and therapies before and after initiation of lipid-lowering therapy, blood pressure, all lipid lowering therapies (drug name, date of prescription, dosage strength, package size, daily dose) and all serum lipid levels including the sample dates. Data on fasting status or the laboratory methods used to determine lipid levels were limited.

Assessment of goal attainment in this observational study was based on LDL-C measurements taken as part of the clinical management of hypercholesterolemia. Evaluation of LDL-C goal attainment was conducted just before the event, within the first six months of the index date and within each six month period following the index date.

Statin potency was assessed in two ways: statin potency at lipid-lowering therapy initiation, and changes in statin potency that occurred with changes in the prescribed regimen throughout the course of therapy. The data were collected during the period 15-Sep-02 to 15-Nov-02. Patient anonymity was maintained at all times.

Patient selection

Patients were selected for entry in this study based on *a priori* inclusion and exclusion criteria as follows:

(1) initial antilipidemic prescription between 1 July, 1998 and 30 June, 1999 with no prior antilipidemic prescription;
(2) physician-verified CHD based on prior angiographic results or electrocardiogram changes indicative of CHD, prior MI, prior angina (stable or unstable), prior peripheral vascular disease (PVD), prior diabetes mellitus, prior stroke, and/or prior revascularization attempt—coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) with or without stent placement;
(3) 18 years of age and older;
(4) absence of liver disease (interferes with hepatic LDL-C production);
(5) at least two years of clinical follow-up and secondary preventive care after initiation of lipid-lowering therapy;
(6) at least one LDL-C measurement within one year prior to the start of lipid-lowering therapy;
(7) available prescribing information for lipid-lowering therapy; and
(8) at least 2 LDL-C measurements after initiation of lipid-lowering therapy.

A total of 605 patients met the study inclusion criteria. Two patients whose treatment was started with fibrates were removed from the sample because of the focus on initial therapy with statins. From the remaining 603 patients, 16 were deleted because they had only one prescription or lab visit resulting in a sample of 587 patients.

Definitions and measurements

Physician characteristics

Physicians who initiated lipid-lowering therapy in this study were classified by age (<50 years, $\geqslant$50 years), gender, type of practice (cardiologist/general practitioner), individual versus group practice, community size of the practice location (small [$\leqslant$19,999]; large [$\geqslant$20,000]), and practice size based on the number of patients seen per quarter (small [$\leqslant$1799]; large [$\geqslant$1800]). Since the community size and the practice size variables were correlated, a single variable combining the two was used in the analysis.

Statin potency

A six-point scale was developed, based on an evaluation of the equipotency of available statins made by Maron and colleagues [14]. High initial potency was defined as potency greater than 3 on this scale.

CV event

CV event was defined as occurrence of revascularization, acute MI, stable or unstable angina, atherectomy, ischemic stroke, endarterectomy or death due to any of the above causes.

Fatalities were included if they were reported as caused by CVD and were treated like any other CV event. In the time-to-first-event model, in which we were interested in the first event, if death was preceded by another CV event, that death was not considered a CV event. There were 17 deaths during the study period of which seven were classified as due to CVD. Of these seven deaths, four were preceded by another CV event and so in the analysis, we considered only the precedent CV event. In three cases, death was the only event; however, in two cases the deaths occurred after the end of the study period and were considered censored at study period end. This left only one death to be included in the analysis as an event.

In the panel data analysis, again the first CV event during every six-month period was analyzed. If death was the only event (and if reported as caused by CVD) during that period, it was included in the analysis.

Charlson age co-morbidity index

A baseline co-morbidity index as suggested by Charlson and her colleagues [15] was used.

Hospitalization

Hospitalization was identified in the data by a binary variable with a value of 1 if hospitalized and 0 otherwise. If hospitalization occurred due to a CV event then it was coded as CVD hospitalization.

Treatment regimen changes

Therapeutic regimen changes made after the initially prescribed statin and dose were considered in the analysis based on a hierarchy:

- *Switch to combination therapy*—when patients were switched to a combination of a statin (same or different statin) and fibrates/resins at any time during follow-up period.
- *Switch in monotherapy*—when patients were changed to another statin from initially prescribed monotherapy at any time during the follow-up period.
- *Dosage titration*—when patients were maintained on the statin initially prescribed; however, the dose of this agent was titrated upward or downward.
- *No action*—when patients were maintained on the initial statin without any of the above changes.

Switch to a combination therapy, change to a different statin with an upward revision in potency, and up titration were defined as aggressive or intensive lipid management. Where switch to an intensive statin therapy was used, a switch just before the event of interest was identified.

Sustained intensive statin therapy

When the switch to an intensive regimen was not reversed during the period of interest, it was coded as sustained intensive statin therapy.

Patient characteristics

Patient's age (<63 years, $\geqslant$63 years based on the mean value of the sample), gender, LDL-C levels just before the first event, prior angina, prior diabetes mellitus, prior stent placement, other baseline cardiac prescriptions, prior CHF/LVH, and prior obesity were included in the analysis.

Goal attainment

LDL-C goal attainment was based on ATP III and German guidelines which recommend LDL-C levels <100 mg/dL.

Statistical methods

CV events were analyzed in two different ways to describe the change in risk over time and to assess the impact of different factors (patient, physician, treatment, and cholesterol levels) on the risk of recurrent CV events.

CV event risk was examined by modeling the time to first recurrent CV event using survival analysis. As it was suspected that there would be a change in the hazard rate of recurrent CV events with time, a piecewise exponential model was fitted. This was done by splitting the total time to event (or the total follow-up time if the patient did not have an event) into yearly ''spells'' and fitting an exponential model of survival time to each year segment. Although other parametric models could be fitted, the exponential model has a simple relationship with hazard rate and so is more easily interpretable. This approach is particularly amenable to evaluate the pattern of CV events over time and to incorporate time-dependent covariates into the models [16].

The effect of early LDL-C goal attainment on risk of future recurrent CV events was investigated using a probit model applied to a panel data. In particular, effect of LDL-C reduction within the first six months of initiation of lipid-lowering therapy on subsequent occurrence of a CV event was analyzed in these models. This type of analysis has been used to study the probability of certain events in several studies [17—19]. The total follow-up period starting after nine months from the index date was divided into six-month periods. The probability of an event within each six month period was estimated using a probit model. A period of nine months was chosen as the basis for future events so that sufficient time would be available for stabilization after the index date.

The index date used here is the date of initiation of lipid-lowering therapy. Because all the patients were known to be new to lipid-lowering therapy and because they were all CHD patients, we believe that the date of initiation of lipid-lowering therapy and the date of initial CHD event were most likely to coincide. Therefore, we treated the date of initiation of lipid-lowering therapy as the date of initial (index) CHD event.

Tolerance and variance inflation factor were checked to insure that there was no collinearity among the co-variates.

Results

Baseline characteristics

Patient characteristics

In this sample of physician-verified CHD patients, the mean age was 63 years and female patients constituted 32.4%. At baseline, mean LDL-C was 169.84 mg/dL, mean total cholesterol was 258.18 mg/dL, mean HDL-C was 46.20 mg/dL and mean triglycerides level was 212.70 mg/dL (Table 1). Prior to lipid lowering therapy (LLT) initiation, one-third had an acute MI and approximately 36% had a revascularization procedure (CABG or PTCA with or without stents). One-third of the patients were diabetic, 77% of patients were hypertensive and 75% were obese or overweight.

Table 1 Patient characteristics

Variable	All patients (N = 587)	Patients treated by cardiology practices (N = 110)	Patients treated by general practices (N = 477)
Treated by cardiologist	110 (18.74%)	—	—
Diabetes at baseline	187 (31.86%)	35 (31.82%)	152 (31.87%)
High initial potency at baseline	103 (17.55%)	19 (17.27%)	84 (17.61%)
Intensive treatment within six months of index event	94 (16.01%)	22 (20.00%)	72 (15.09%)
Patient age at baseline	62.83 (SD = 9.97)	62.60 (SD = 9.06)	62.89 (SD = 10.16)
# of cardiac prescriptions at baseline	2.57 (SD = 1.53)	2.73 (SD = 1.65)	2.53 (SD = 1.50)
CABG at baseline	96 (16.35%)	17 (15.45%)	79 (16.56%)
PTCA at baseline	128 (21.88%)	19 (17.27%)	109 (22.95%)
Stent at baseline	76 (12.97%)	15 (13.64%)	61 (12.82%)
Revascularization at baseline	212 (36.12%)	34 (30.91%)	178 (37.32%)
LVH at baseline	204 (34.75%)	49 (44.55%)	155 (32.49%)*
MI at baseline	190 (32.37%)	48 (43.64%)	142 (29.77%)*
CHF/LVH at baseline	253 (43.25%)	59 (53.64%)	194 (40.84%)*
Mean total cholesterol at baseline	258.18 (SD = 50.23)	252.73 (SD = 35.68)	259.48 (SD = 53.07)
Mean LDL-C at baseline	169.84 (SD = 41.76)	169.00 (SD = 35.07)	170.03 (SD = 43.19)
Mean HDL-C at baseline	46.20 (SD = 13.91)	46.45 (SD = 14.78)	46.14 (SD = 13.71)
Mean triglycerides at baseline	212.70 (SD = 148.52)	220.86 (SD = 174.31)	210.72 (SD = 141.69)
Charlson age co-morbidity index	4.42 (SD = 1.87)	4.39 (SD = 1.87)	4.42 (SD = 1.87)
% Reaching target LDL-C level within six months of index event	73 (12.44%)	19 (17.27%)	54 (11.32%)
Final cholesterol level	213.89 (SD = 50.64)	212.54 (SD = 47.64)	214.21 (SD = 51.37)
Final LDL-C Level	127.86 (SD = 41.43)	127.61 (SD = 39.45)	127.92 (SD = 41.92)
Change in final LDL-C level from baseline	−21.03% (SD = 31.39)	−22.04% (SD = 27.18)	−20.79% (SD = 32.30)
% Reaching target LDL-C level at final lab	145 (24.70%)	27 (24.55%)	118 (24.74%)
Prescription persistence	0.73 (SD = 0.26)	0.66 (SD = 0.32)	0.74 (SD = 0.25)*
Initial statin potency	2.54 (SD = 0.95)	2.45 (SD = 1.09)	2.56 (SD = 0.91)
# of co-morbidities at baseline	0.23 (SD = 0.56)	0.15 (SD = 0.40)	0.25 (SD = 0.59)*

Statin potency scale based on dose equipotency adapted from Maron et al. [14].
* Difference between cardiology and general practices significant at $p \leqslant 0.05$.

Since this analysis is concerned about the effect of early goal achievement on future events, differences between those who achieved target LDL-C within six months of the index event and those who did not are listed in Table 2. The former group had significantly lower baseline and final cholesterol and LDL-C levels.

Physician characteristics

Patients included in this study were initiated on LLT by one of 62 general practitioners or cardiologists in Germany. Most patients (75.0%) were initiated on LLT by a male physician. More patients were treated by physicians in individual practices (56.6%) than those in group practices (43.4%). A majority (51.5%) of the patients were treated by physicians practicing in communities with a population less than 20,000. Approximately 80.6% of patients were initiated on LLT in practices where the average number of patients seen per quarter was <1800. Patients treated in cardiology and general practices were similar in their demographics but cardiology practices treated more patients with LVH and/or MI at baseline. On the other hand, patients in cardiology practices had fewer baseline co-morbidities than those in general practices (Table 1).

Factors affecting time to first CV event

The piecewise exponential model indicates that the hazard rate varied with time in this sample of German patients with CHD (Table 3). The risk of a recurrent CV event was the highest in the first six months and fell subsequently. The overall period index is very significant while among the individual period variables, the index for the first six months has a p value of 0.029. The indicator for cardiologist is not significant at $p = 0.05$ having a p value of 0.082. CABG at baseline ($p = 0.0334$), number of cardiac prescriptions at baseline ($p = 0.0323$)

Table 2 Differences between patients achieving goal and not achieving goal within six months of index event

Variable	Patients achieving goal within six months ($N = 73$)	Patients not achieving goal within six months ($N = 514$)
Treated by cardiologist	19 (26.03%)	91 (17.70%)
Diabetes at baseline	26 (35.62%)	161 (31.32%)
High initial potency at baseline	11 (15.07%)	92 (17.90%)
Intensive treatment within six months of index event	15 (20.55%)	79 (15.37%)
At goal at baseline	21 (28.77%)	5 (0.97%)
Patient age at baseline	61.78 (SD = 10.38)	62.98 (SD = 9.91)
# of cardiac prescriptions at baseline	2.82 (SD = 1.73)	2.53 (SD = 1.49)
CABG at baseline	13 (17.81%)	83 (16.15%)
PTCA at baseline	18 (24.66%)	110 (21.48%)
Stent at baseline	13 (17.81%)	63 (12.28%)
MI at baseline	30 (41.10%)	160 (31.13%)
CHF/LVH at baseline	33 (45.21%)	220 (42.97%)
Mean total cholesterol at baseline	221.84 (SD = 37.43)	263.44 (SD = 49.69)*
Mean LDL-C at baseline	129.92 (SD = 40.57)	175.51 (SD = 38.76)*
Mean HDL-C at baseline	44.34 (SD = 14.32)	46.46 (SD = 13.85)
Charlson age co-morbidity index	4.51 (SD = 1.71)	4.40 (SD = 1.89)
Final cholesterol level	183.15 (SD = 44.67)	218.30 (SD = 49.95)*
Final LDL-C level	99.70 (SD = 34.38)	131.86 (SD = 40.82)*
Prescription persistence	0.77 (SD = 0.25)	0.72 (SD = 0.27)
Initial statin potency	2.45 (SD = 1.09)	2.56 (SD = 0.91)
# of co-morbidities at baseline	0.23 (SD = 0.54)	0.23 (SD = 0.57)

Statin potency scale based on dose equipotency adapted from Maron et al. [14].
* Difference between the two groups significant at $p \leqslant 0.05$.

Table 3 Determinants of time to first recurrent CV event (piecewise exponential model) number of patients = 585, number of spells = 2352

Variable	Estimated coefficient	95% CI	p Value	# First recurrent CV events in each period
Cardiologist	0.3351	−0.0430 to 0.7133	0.0824	
CABG at baseline	−0.3709	−0.7127 to −0.0291	0.0334	
# of cardiac prescriptions at baseline	−0.0999	−0.1913 to −0.0084	0.0323	
LDL-C level prior to the CV event	−0.0036	−0.0067 to −0.0006	0.0201	
Sustained treatment with a high potency statin prior to the CV event	−0.3155	−0.6353 to 0.0043	0.0532	
Period index			<0.0001	
First six months	−2.2030	−4.1796 to −0.2263	0.0289	71
Next six months	−1.4942	−3.4881 to 0.4996	0.1419	30
Year 2	−1.3385	−3.3218 to 0.6448	0.1859	43
Year 3	−1.4719	−3.4557 to 0.5118	0.1459	41
Year 4	−1.1726	−3.1787 to 0.8335	0.2520	21

Statin potency scale based on dose equipotency adapted from Maron et al. [14].

and a high LDL-C level prior to the event ($p = 0.0201$) all decrease the time to a first recurrent CV event significantly. An intensive statin regimen before the event is not significant ($p = 0.0532$). The effects of these variables are more easily understood if we flip the signs and consider their effects on the hazard rate. A baseline CABG procedure increases the hazard of a recurrent CV event. Similarly, the larger the number of baseline prescriptions, the higher the risk of a recurrent CV event. Higher LDL-C level is clearly an indicator of a higher risk of a CV event. Taking the exponential of the negative of the estimated coefficient for LDL-C level, the effect of LDL-C level on the hazard rate can be obtained. This process yields a value of 1.004. In other words, the

hazard rate increases by 4% for every 10 mg/dL increase in the LDL-C.

Effect of early goal attainment on future events

The probit models address the probability of future events (Table 4). The results are similar to the piecewise exponential model. The risk of a recurrent CV event after nine months from the index date is positively related to the number of baseline co-morbidities, as indicated by the Charlson age co-morbidity index ($p = 0.0251$), and to the occurrence of a CV event in the previous six month period ($p < 0.0001$). The risk is decreased with treatment by a cardiologist ($p < 0.0001$), and goal attainment within the first six months of the index date ($p = 0.0122$). The results are similar for all-cause hospitalization events, except that the number of baseline cardiac prescriptions and intensive treatment during the first six month period significantly increase the risk of all-cause hospitalization ($p = 0.0052$ and $p = 0.0294$ respectively). Goal attainment within the first six months of the index date is consistently significant and has similar coefficient values for all three dependent variables. We also investigated the effect of goal attainment in the *previous* six month period on the probability of a recurrent CV event and hospitalization (CVD and non-CVD) in the current six month period and surprisingly found that to be insignificant (results not reported). We also performed the same panel data analysis by dividing the entire follow-up period (instead of starting after nine months from the index date) and obtained similar results (Table 5) although the effect of goal attainment within the first six months on all-cause hospitalization was not significant. Goal attainment within the first six months of the index event decreased the risk of a recurrent CV event in the future. But the goal attainment in the six month period *prior* to an event had no effect.

Table 4 Effect of goal attainment within first six months on occurrence of subsequent event after nine months (probit models of panel data. Number of spells = 3885)

Variable	Any hospitalization			CVD hospitalization			Any recurrent CV event		
	Estimated coefficient	95% CI	*p* Value	Estimated coefficient	95% CI	*p* Value	Estimated coefficient	95% CI	*p* Value
Cardiologist	−0.3345	−0.5196 to −0.1493	0.0004	−0.3776	−0.5977 to − 0.1574	0.0008	−0.4718	−0.6651 to −0.2784	<0.0001
Charlson age co-morbidity index	0.0757	0.0408–0.1107	<0.0001	0.0520	0.0127–0.0912	0.0095	0.0390	0.0049–0.0732	0.0251
# of cardiac prescriptions at baseline	0.0640	0.0191–0.1088	0.0052	0.0395	−0.0107 to 0.0896	0.1228	0.0414	−0.0019 to 0.0847	0.0607
Any CV event during previous six months	0.5016	0.3285–0.6747	<0.0001	0.5220	0.3343–0.7096	<0.0001	0.5669	0.4005–0.7333	<0.0001
Treatment with high potency statin during first six months	0.1758	0.0176–0.3341	0.0294	0.1646	−0.0128 to 0.3420	0.0691	0.0608	−0.0991 to 0.2206	0.4562
Goal attainment within first six months	−0.2612	−0.4754 to −0.0470	0.0168	−0.2941	−0.5457 to −0.0425	0.0220	−0.2679	−0.4774 to −0.0584	0.0122

Statin potency scale based on dose equipotency adapted from Maron et al. [14].

Discussion

This study explores the benefits of lipid-lowering therapy and early goal attainment in terms of risk of a recurrent CV event and future hospitalization. Large scale controlled trials [1–9,12] have shown clear reductions in CVD mortality and morbidity from aggressive lipid-lowering therapy with statins. The objectives of this study are, therefore, in accordance with these earlier studies. This

Table 5 Effect of goal attainment within first six months on occurrence of subsequent event in any six month period (probit models of panel data. CV events and number of spells = 4161)

Variable	Any hospitalization			CVD Hospitalization			Any recurrent CV event		
	Estimated coefficient	95% CI	*p* Value	Estimated coefficient	95% CI	*p* Value	Estimated coefficient	95% CI	*p* Value
Cardiologist	−0.2610	−0.4323 to −0.0897	0.0028	−0.2752	−0.4730 to −0.0774	0.0064	−0.4020	−0.5823 to −0.2216	<0.0001
Charlson age co-morbidity index	0.0799	0.0461–0.1137	<0.0001	0.0582	0.0205–0.0959	0.0025	0.0365	0.0034–0.0695	0.0307
# of cardiac prescriptions at baseline	0.0645	0.0217–0.1074	0.0032	0.0352	−0.0124 to 0.0828	0.1476	0.0428	0.0012–0.0843	0.0436
Any CV event during previous six months	0.4946	0.3244–0.6649	<0.0001	0.5389	0.3565–0.7214	<0.0001	0.6349	0.4737–0.7960	<0.0001
Treatment with high potency statin during first six months	0.2114	0.0607–0.3620	0.0060	0.1999	0.0322–0.3676	0.0195	0.0833	−0.0703 to 0.2369	0.2880
Goal attainment within first six months	−0.1921	−0.3897 to 0.0054	0.0566	−0.1992	−0.4247 to 0.0264	0.0835	−0.2282	−0.4258 to −0.0305	0.0237

Statin potency scale based on dose equipotency adapted from Maron et al. [14].

study primarily differs from others in the assessment of changes in lipid-lowering therapy and reduction in LDL-C on CVD morbidity and in the evaluation of the effect of early goal attainment on risk of any future recurrent CV events and hospitalization.

The longitudinal nature of the study permits an in-depth examination of the effect of goal attainment on future risk of hospitalization. The multiple types of analyses of risk of CVD morbidity confer high internal validity to the findings. The absence of protocol-driven criteria for patient inclusion has limited issues of selection bias. It is free from the problems associated with study designs that potentially influence the results. Therefore the study has a high degree of external validity.

The retrospective nature of the data does have some limitations particularly with respect to availability of data. One limitation is that event information is based on chart review and, therefore, what was reported by physicians. The reported events could not be adjudicated by an independent review committee. There may also be a potential for unobserved heterogeneity that is not accounted for by the included variables. Clearly, patients who attain goal and those who do not are likely to differ in their baseline characteristics. Not being able to control for all confounding variables could affect the results. However, a large number of variables such as baseline morbidities, gender, family history and health care provider characteristics were included in the analyses and are not reported if they were found not significant. The baseline morbidity conditions and age were summarized into the Charlson co-morbidity index. Therefore, there is reason for a certain level of confidence in the results.

There are several important findings from this study. The first is that in the sample of CHD patients studied, the hazard rate of recurrent CV events was the highest in the first six months after the index date and started declining thereafter. This can be seen in the number of first CV events in each period in Table 3. Several earlier studies have also shown such a pattern. The likelihood for revascularization intervention was the highest in the first year following treatment assignment [20]. Similarly, the risk of cardiac death or (MI) was more than five times higher in the first year after revascularization than in subsequent years of follow-up [21]. Our results are consistent with these studies.

The second important finding is that a high LDL-C level prior to the event significantly reduces the time to the first recurrent CV event (or increases

the hazard rate). To compare with studies that have demonstrated a lower incidence of CV events with a lowering of LDL-C, our study finds that the hazard rate of a recurrent CV event decreases by about 11% for a 30 mg/dL reduction in LDL-C. The PROVE-IT study reported a reduction of 33 mg/dL in LDL-C and a 16% reduction in the number of clinical events in the group treated with a high potency statin and attributed much of that benefit to LDL-C reduction [12]. Similarly, in the HPS study a reduction of 40 mg/dL in LDL-C was accompanied by a 25% reduction in CV events [3]. This result combined with the finding that the risk is the highest in the first six months suggests that the potential for preventing CVD morbidity through aggressive lipid management in clinical practice is also the highest in the first six months.

The panel data analysis provides the third important finding that early goal attainment (within the first six months) reduces the risk of future (after nine months) recurrent CV events, hospitalization due to CVD or all-cause hospitalization. The finding regarding LDL-C reduction is reinforced in this analysis. The panel data analysis offers additional and stronger evidence that goal attainment within the first six months of the index event is important in reducing the risk of a future event. An important feature of the panel data design is that the time dependent nature of the explanatory variables can be accounted for by this method. For example, we could investigate whether goal attainment in the immediate preceding six months had any effect on the occurrence of a CV event in the current period. An interesting and potentially a major finding is that goal attainment within the first six months (i.e. within six months of the index event) and not within the previous six month period (i.e. six months prior to subsequent events) significantly reduces the risk of a future CV event as well as hospitalization. Additional analysis on this aspect using other data sets is needed before a conclusive opinion can be formed. It therefore appears that patients with established CHD have a high risk of future CVD events as well as hospitalization and attain protection against recurrent cardiovascular events from early LDL-C reduction and goal attainment. The PROVE-IT [12] and the MIRACL [22] studies also suggest that patients with CHD can derive particular benefit from early and intensive lipid lowering.

Finally, this analysis shows that treatment by a cardiologist at the time of occurrence of the index event clearly reduces the risk of future recurrent CV events or hospitalization. Potentially this could mean that cardiologists tend to manage lipid levels more aggressively although Table 1 does not suggest this.

To answer the question if there was any additional benefit to the aggressive statin regimen, we also included the variable of sustained intensive statin regimen during the first six months in the analysis. This variable i.e. sustained treatment with a high potency statin during the first six months, after controlling for early goal attainment, increases the risk of hospitalization due to any cause but not the risk of recurrent CV events or hospitalization due to CV events. In order to interpret this result for risk of all-cause hospitalization, one must control for (i) other baseline co-morbidity conditions and (ii) severity of baseline co-morbidity conditions. Other baseline co-morbidity conditions were controlled for by Charlson age co-morbidity index which also increases the risk of hospitalization (Table 4). However, the Charlson age co-morbidity index includes all the CHD risk factors and other conditions but not the severity of these conditions. The residual CHD and other severity is accounted for by the variable of sustained intensive statin regimen during the first six months. Hence we think this somewhat counter-intuitive result, particularly for all-cause hospitalization, is probably because the patient population receiving sustained treatment with high potency statin had an inherently higher risk of hospitalization due to any event to begin with and hence were more aggressively treated (residual confounding by indication).

It also appears that the allowance of a stabilization period after an index event avoids any confounding due to concurrent therapy. The results are stronger when the panel data are created nine months, rather than six months, after the index event.

Taken together, our results strongly support efforts to aggressively reduce LDL-C and early goal attainment in order to achieve a lower incidence of recurrent CV events and future hospitalization. While the finding regarding the use of aggressive statin regimen for all-cause hospitalization seems anomalous, it should be noted that this was obtained with only one dependent variable and after controlling for early goal attainment and is potentially due to the nature of patients who are receiving aggressive lipid-lowering therapy i.e. inherently higher risk of hospitalization due to any cause. The study clearly demonstrates that emphasis should be on achieving NCEP lipid goals especially within the first six months of the index event and patients not achieving LDL-C goal fail to derive full benefits from lipid-lowering therapy.

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