Efficacy of Lipid-Lowering Therapy During Cardiac Rehabilitation in Patients With Diabetes Mellitus and Coronary Heart Disease

Thomas Wittlinger (dr.wittlinger@gmx.de)
Asklepios Harzklinik Goslar
Bernhard Schwaab
Curschmann Hospital: Curschmann-Klinik
Heinz Voeller
University of Applied Sciences Brandenburg: Technische Hochschule Brandenburg
Christa Bongarth
Hospital Höhenried
Viktoria Heinze
Paracelsus Hospital Bad Suderode: Paracelsus-Harz-Klinik Bad Suderode
Kristina Eckrich
Hospital Tharandter Wald
Manja Guha
Hospital Sendessal Bremen
Michael Richter
University Hospital Halle: Universitatsklinikum Halle
Axel Schlitt
Paracelsus Harz-Hospital: Paracelsus-Harz-Klinik Bad Suderode

Research Article

Keywords: coronary heart disease, cardiac rehabilitation, diabetes mellitus, lipid-lowering therapy

Posted Date: May 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-529134/v1

Abstract

Background

Cardiac rehabilitation (CR) in patients with coronary heart disease (CHD) aims to increase adherence to a healthy lifestyle and to secondary preventive medication. CR is able to improve quality of life and prognosis in CHD patients. This is particularly relevant for CHD patients with diabetes mellitus.

Design

A prospective, multicenter registry study with patients from six rehabilitation centers in Germany.

Methods

During CR, 1100 patients with a minimum age of 18 years and CHD documented by coronary angiography were included in a LLT registry.

Results

In 369 patients (33.9 %), diabetes mellitus was diagnosed. Diabetic patients were older (65.5 ± 9.0 vs. 62.2 ± 10.9 years, $p < 0.001$) than nondiabetic patients and more likely to be obese (BMI: 30.2 ± 5.2 kg/m2 vs. 27.8 ± 4.2 kg/m2, $p < 0.001$). Analysis indicated that diabetic patients were more likely to show LDL cholesterol levels below 55 mg/dL than patients without diabetes at the start of CR (Odds Ratio (OR) 1.9; 95 % CI 1.3 to 2.9) until 3 months of follow-up (OR 1.9; 95 % CI 1.2 to 2.9). During 12 months of follow-up, overall and LDL cholesterol levels decreased within the first 3 months and remained at the lower level thereafter ($p < 0.001$), irrespective of prevalent diabetes. At the end of the follow-up, LDL cholesterol did not differ significantly between patients with or without diabetes mellitus ($p = 0.413$).

Conclusion

Within 3 months after CR, total and LDL cholesterol were significantly reduced, irrespective of prevalent diabetes mellitus. In addition, CHD patients with diabetes responded faster to LTT than nondiabetic patients, suggesting that diabetic patients benefit more from LLT treatment during CR.

Introduction

Diabetes mellitus constitutes a major risk factor for developing coronary heart disease (CHD) and potentiates the risk for fatal events in patients who already have CHD [1]. Standard treatment of CHD in patients with and without diabetes typically comprises a combination of lifestyle changes, e.g., physical activity on a regular basis, cessation of smoking, and adoption of a healthier diet, and secondary preventive medication. The pharmacotherapy includes angiotensin-receptor blockers, ACE inhibitors, beta-blocking agents, and platelet inhibitors. Here, lipid-lowering drugs represent one of the most important therapeutic interventions [2].

Currently, medical consensus recommends lipid-lowering therapy (LLT) for all patients who have developed CHD, irrespective of whether they have diabetes [3, 4]. This treatment is independent of the initial level of low-density lipoprotein (LDL) cholesterol. LLT aims to reduce the LDL cholesterol level to below 55 mg/dL (1.4 mmol/L) and/or to decrease the LDL cholesterol level by at least 50 % [5]. Since 2019, guidelines have recommended reducing LDL cholesterol to even less than 40 mg/dL in very high-risk patients, for example, after a second CHD-related event [3].

The cornerstone of LLT is administration of a maximum dose of statins. A number of studies have demonstrated that high-potency statins (e.g., atorvastatin, rosuvastatin) are superior to low-potency statins (e.g., pravastatin, simvastatin) [6–8]. However, some patients do not respond sufficiently to statin monotherapy. Moreover, statin therapy can cause severe adverse effects, such as myotoxicity, which occurs in the form of myopathy, myalgia, myositis, or rhabdomyolysis [9, 10]. A recent study associated high doses of statins with an increased risk for osteoporosis [11]. In addition, compliance often poses problems because high cholesterol levels go unnoticed, and patients may skip or even stop taking the drug [12, 13].

Alternatives to statins are limited. Treatment with fibrates showed only weak effects, whereas niacin and inhibitors of cholesterylester transfer protein are not available for clinical use [14, 15]. The only available option for patients who respond poorly to statins and for those who have a low tolerance for statins is combination therapy with either ezetimibe or inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) [16, 17]. For example, combination therapy with ezetimibe and simvastatin reduced LDL cholesterol levels over a 7-year follow-up period and yielded a 1.8 % reduction in a combined endpoint of nonfatal myocardial infarction or stroke as well as lowering rates of cardiovascular death [18]. Furthermore, the PCSK9 inhibitors alirocumab and evolocumab showed in recent trials a 50 % reduction in LDL cholesterol levels in patients who previously received high doses of statins (as monotherapy or in combination with ezetimibe) and also improved the outcome at clinical endpoints [19–22]. Treatment with either ezetimibe or PCSK9 inhibitors reduced fatal events in CHD patients with diabetes even more effectively than in CHD patients without diabetes [23, 24]. The new prodrug bempedoic acid (BA) is an upstream inhibitor of hepatic cholesterol biosynthesis [25] and significantly reduced LDL cholesterol in a clinical study [26]. BA was approved in early 2020 for LLT in combination with statins or other lipid-lowering compounds [27]. In addition, BA has also been approved as monotherapy or as combination therapy with ezetimibe in patients with low statin tolerance.

Obviously, the effect of LLT depends on adherence [28]. Participation in cardiac rehabilitation (CR) leads not only to better adherence but also to a significant reduction in mortality among CHD patients [29].

In this analysis of the German multicenter Lipid-Lowering-Therapy-Rehabilitation registry (LLT-R), we focused on the effect of LLT in patients with diabetes mellitus and CHD.

Methods

Patient data

The LLT-R registry included 1100 patients who were admitted to one of the six participating German rehabilitation clinics. Inclusion criteria for this study were a minimum age of 18 years, diagnosis of CHD, and enrollment in LLT. The only exclusion criterion was the absence of written informed consent. The ethics committee of the Medical Association of Saxony-Anhalt and the local ethics committees of the participating clinics approved this study (ClinicalTrials.gov Identifier: NCT02749279).

Diabetes was defined as previously diagnosed (under treatment) or newly diagnosed disease during CR according to current guidelines (i.e., HbA1c > 6.5 % or 48 mmol/mol, fasting glucose > 7 mmol/L, random plasma glucose > 11.0 mmol/L or 2 hours plasma glucose > 11.0 mmol/L in an oral glucose tolerance test) [1].

A central database (online-CRF) recorded all relevant baseline parameters, which included indication for rehabilitation, LLT and other drug treatments, all comorbidities, age, sex, BMI, and standard laboratory parameters (e.g., total, LDL, and HDL cholesterol and triglycerides). Moreover, the database contained information on LLT at the beginning of CR and at discharge as well as the advice given to general practitioners on how LLT should be managed after discharge.

During follow-up, patients were contacted by mail 3 and 12 months after discharge to inquire about drug therapy (in particular concerning LLT) and rehospitalization, especially in connection with atherosclerotic diseases, such as recurrent acute coronary syndromes (ACS). Additional information was collected on the rationale and the responsible party for changes in medication. In addition, data on total, LDL, and HDL cholesterol as well as triglyceride levels were collected during follow-up. Patients who failed to return the questionnaires were contacted via telephone to conduct an interview with the patient or his/her relatives. Occasionally, the patient's physician was contacted as well. Civil registration offices were contacted if this information could not be retrieved from these sources, and information was requested about current addresses or date of death. This study employed a monitoring protocol that was developed by the Coordination Center for Clinical Studies, Martin Luther-University Halle Wittenberg, Germany (KKS Halle).

Statistical analysis

Continuous variables were described as mean and standard deviation, skewed variables as median and 25 % and 75 % quartiles. Categorical variables were documented as a percentage. A t-test was used to compare metric, normally distributed variables. For skewed variables, the Mann-Whitney U-test was employed. The chi-squared test was used for normally distributed, categorical variables. Results were deemed significant for p-values lower than 0.05. Statistical analysis was performed with SPSS Statistics (IBM® SPSS® Statistics 25, Chicago, IL).

Results

Patient characteristics

Patient characteristics are presented in Table 1. The registry included 76.1 % male and 23.9 % female patients. Main diagnoses were NSTEMI (31.8 %), STEMI (29.6 %), and CABG surgery (26.4 %). In 369 patients (33.9 %), diabetes mellitus was diagnosed. On average, diabetic patients were 3 years older than nondiabetic patients (65.5 ± 9.0 years vs. 62.2 ± 10.9 years, $p < 0.001$). In addition, diabetic patients showed a higher BMI (30.2 ± 5.2 kg/m^2 vs. 27.8 ± 4.2 kg/m^2), larger waist circumference (107.8 ± 12.9 cm vs. 101.2 ± 11.6 cm), higher systolic blood pressure (135.6 ± 21.9 mmHg vs. 132 ± 19.9 mmHg, $p < 0.001$), and higher heart rate (75.8 ± 11.6 bpm vs. 71.9 ± 12.4 bpm, $p < 0.001$) than nondiabetic patients. Furthermore, renal function was reduced in diabetic patients (creatinine: 1.1 ± 0.5 mg/dL vs. 1.0 ± 0.3 mg/dL; eGFR: 74.0 ± 22.2 mL/min vs. 78.8 ± 18.0 mL/min, $p < 0.001$ for both), and hemoglobin levels were lower (12.9 ± 1.9 g/dL vs. 13.5 ± 3.7 g/dL, $p < 0.001$). Information on HbA1c, which was available for only 243 diabetics (65.9 %), was in an acceptable range of 6.7 ± 0.9 % (or 50 ± 10 mmol/mol). Diabetic patients showed three-vessel CHD significantly more often than patients without diabetes ($p < 0.001$; Table 1).

Table 1
Overview of patient characteristics at the end of CR

Characteristic		All patients				without diabetes				with diabetes			
		N	%	Mean	Stdev	N	%	Mean	Stdev	N	%	Mean	Stdev
Age [years]		1087	100	63.4	10.4	716	65.9	62.2	10.9	369	33.9	65.6	9.0
Body Weight [kg]		1083	100	84.9	16.5	714	65.9	83.1	15.5	367	33.9	88.4	17.9
BMI [kg/m²]		1082	100	28.6	4.7	711	65.7	27.8	4.2	369	34.1	30.2	5.2
Waist circumference [cm]		904	100	103.5	12.5	588	65.0	101.2	11.6	315	34.8	107.8	12.9
Systole [mmHg]		1086	100	133.2	20.6	715	65.8	132.0	19.9	369	34.0	135.6	21.9
Diastole [mmHg]		1086	100	78.0	11.4	715	65.8	78.2	11.3	369	34.0	77.7	11.6
Heart rate [bpm]		1085	100	73.2	12.3	714	65.8	71.9	12.4	369	34.0	75.8	11.6
Creatine [mg/dL]		1084	100	1.0	0.4	713	65.8	1.0	0.3	369	34.0	1.1	0.5
GFR [mL/min]		1083	100	77.1	19.7	712	65.7	78.7	18.0	369	34.1	74.0	22.2
Hemoglobin [g/dL]		1075	100	13.2	5.6	709	66.0	13.5	3.7	366	34.0	12.6	1.9
HBA1c [%]										243		6.7	0.9
Sex	Male	826	76.1			557	77.8			269	72.9		
	Female	259	23.9			159	22.2			100	27.1		
Indication for admission	NSTEMI	345	31.8			231	32.3			114	30.9		
	STEMI	321	29.6			239	33.4			82	22.2		
	CABG	286	26.4			165	23.0			121	32.8		
	PCI/Stent	61	5.6			35	4.9			26	7.0		
	Valve	37	3.4			25	3.5			12	3.3		
	Others	35	3.2			21	2.9			14	3.8		
Affected blood vessels	1-CAD	289	25.0			203	28.6			65	17.9		
	2-CAD	274	25.5			200	28.1			74	20.4		
	3-CAD	532	49.5			308	43.3			224	61.7		

[a] statistical difference between patients with diabetes and without. Stdev, standard deviation; BMI, body mass index; GFR, glomerular filtration rate; NSTEMI, elevation myocardial infarction; STEMI, ST elevation myocardial infarction; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention

Low LDL levels among diabetic and nondiabetic patients

The impact of diabetes mellitus on LLT was evaluated for patients with LDL cholesterol levels below 55 mg/dL, as recommended in recent guidelines [5]. The data from this registry showed that patients with diabetes mellitus were more likely to reach this goal by the time of admission to CR than nondiabetic patients (OR 1.9; 95 % CI 1.3 to 2.9; Fig. 1).

In addition, the group with LDL cholesterol < 55 mg/dL contained more diabetic than nondiabetic patients (chi-squared test, p = 0.001). The same trend was observed at the time of discharge, but the analysis failed to reach statistical significance (chi-squared test, p = 0.068). At 3 months after CR, diabetes patients were again more likely to have LDL cholesterol levels < 55 mg/dL than those without diabetes (OR 1.9; 95 % CI 1.2 to 2.9). Once again, there were more diabetic patients than nondiabetic patients in the group with LDL cholesterol < 55 mg/dL (chi-squared test, p = 0.006). After 12 months of follow-up, however, these results did not differ between the groups (chi-squared test, p = 0.413) (Fig. 1).

Figure 1. Patient population during study period according to LDL cholesterol levels that are classified as < 55 mg/dL and > 55 mg/dL (in black and gray). Patients are also subdivided in diabetic (red and orange) and nondiabetic (blue and turquois) patients. The statistically significant difference between diabetic and nondiabetic patients was evaluated with the Pearson's chi-squared test (** indicates p-value < 0.01).

Lipid levels of the patients during CR

A time course of lipid levels is presented in Fig. 2. Statistical analysis showed a significant reduction in total cholesterol: 156.0 ± 37.5 mg/dL at discharge to 149.6 ± 42.5 mg/dL at 3 months after CR (p = 0.002). This lower level was confirmed at the end of follow-up at 12 months (146.2 ± 37.3 mg/dL; p < 0.001). Similarly, LDL cholesterol dropped within 3 months from 91.4 ± 30.8 mg/dL at discharge to 81.2 ± 30.2 mg/dL at 3 months after CR (p < 0.001), remaining at this level until the end of the follow-up (79.3 ± 27.2 mg/dL; p < 0.001). These results did not differ significantly between patients with and without diabetes mellitus (Fig. 2a, b). In contrast, HDL cholesterol increased from 45.0 ± 13.8 mg/dL at discharge to 49.5 ± 14.8 mg/dL at 3 months (p < 0.001), remaining at

this level until 12 months of follow-up (49.5 ± 14.4 mg/dL; p < 0.001). Moreover, HDL cholesterol levels differed significantly between patients with and without diabetes mellitus (p < 0.01; Fig. 2c). For triglycerides the differences between the two patient groups were significant (p = 0.027) (Fig. 2d). However, the average triglyceride levels for all patients in this registry were 137.5 ± 77.0 mg/dL at the beginning of CR and remained virtually unchanged at 135.5 ± 78.9 mg/dL on average after 12 months of follow-up.

Figure 2. Changes in lipid levels in patients with and without diabetes mellitus during study period. Levels of overall cholesterol (A), LDL cholesterol (B), HDL cholesterol (C), and triglycerides (D) are presented at the beginning (M0) and the end of the cardiac rehabilitation (M1) as well as 3 months (M3) and 12 months (M12) after discharge. The graphs show the mean and the error bars represent the 95 % confidence interval. Patients with diabetes are indicated in red, patients without in blue.

LLT during study period

This registry also assessed the differences in LLT between diabetic and nondiabetic patients (Fig. 3). There was no significant difference for either statins (Fig. 3a) or ezetimib (Fig. 3b) in the two groups.

Figure 3. Distribution of LLT drugs in the patient population during the study period. The bar graph shows a comparison of the administration of statins (A) and ezetemib (B) among diabetic and nondiabetic patients at different time points. The number above the bar graph indicates the percentage of diabetics or nondiabetics, respectively, who received the drug. The number in the bar graph presents the total number of patients. The number at the x-axis shows the total amount of patients at this particular study period.

Drug therapy

Besides lipid-lowering drugs, concomitant medication was analyzed during CR (see Table 2). The analysis did not show any significant difference between diabetic and nondiabetic patients for oral anticoagulants or platelets inhibitors, with Prasugrel being the only exception: Prasugrel was used less frequently by diabetic than nondiabetic patients (14.8 % vs. 27.9 %, p < 0.001). Regarding antihypertensive drugs, diabetic patients used significantly more diuretics (56.4 % vs. 38.1 %, p < 0.001), angiotensin II receptor blockers (ARB; 37.5 % vs. 28.6 %, p = 0.005), and calcium channel blockers (CCB; 30.4 % vs. 18.2 %, p < 0.001) than patients without diabetes. In contrast, diabetic patients were medicated less frequently with angiotensin-converting enzyme (ACE) inhibitors (57.6 % vs. 66.1 %) (p = 0.007).

Table 2
Comparison of diabetics vs. non-diabetics patients at baseline during non-LLT drug therapy

Characteristic		All patients		Without diabetes		With diabetes		Δ [a]
		N	%	N	%	N	%	p-value
Platelet inhibitors	ASA	1031	97.6	680	97.8	351	97.2	0.535
	Clopidogrel	251	25.8	151	24.0	100	29.2	0.080
	Prasugrel	224	23.3	174	27.9	50	14.8	**0.000**
	Ticagrelor	342	34.4	232	35.9	110	31.6	0.178
Oral anticoagulants	Vitamin K antagonist	64	33.7	39	32.2	25	36.2	0.575
	Dabigatran	52	28.0	28	23.9	24	34.8	0.111
	Rivaroxaban	5	2.8	2	1.8	3	4.5	0.363
	Edoxaban	6	3.4	6	5.4	0	0.0	0.085
	Apixaban	25	13.7	21	18.3	4	6.0	0.020
Anti-hypertensives	Diuretics	446	44.5	249	38.1	197	56.4	**0.000**
	ACE inhibitors	654	63.2	449	66.1	205	57.6	**0.007**
	ARB	307	31.7	180	28.6	127	37.5	**0.005**
	Renin inhibitors	3	0.3	3	0.5	0	0.0	0.556
	CCB	221	22.5	117	18.2	104	30.4	**0.000**
	Beta blocker	959	90.4	632	90.5	327	90.1	0.809
	MRAs	121	12.5	84	13.4	37	10.9	0.281

[a] statistical difference between patients with diabetes and without.

ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist

Antidiabetic drugs

In Table 3, antidiabetic medication use is presented. Metformin was the most commonly used antidiabetic drug in 48.0 % of the patients at admission and remained the preferred drug through the 12-month follow-up period (51.7 % of the patients). DDP-4 inhibitors were also used frequently according to the registry data (26.8 % at admission and 26.5 % at the end of the study). The use of insulin declined from 33.3 % at admission to 26.9 % at the end of the documented follow-up. Other antidiabetic drugs, such as sulfonylureas, GLP1 agonists, and meglitinides, were used in less than 5 % of the patients at any time. Of note, SGLT2 inhibitor use increased from 3.3 % at admission to 7.3 % during the 12-months follow-up period.

Table 3
Antidiabetic drugs among patients with diabetes mellitus during study period

Antidiabetics	Admission		Demission		3-months follow-up		12-months follow-up	
	n = 369		n = 364		n = 235		n = 234	
	N	%	N	%	N	%	N	%
Any antidiabetics	272	73.7	265	72.8	165	70.2	164	70.1
Metformin	177	48.0	194	53.3	126	53.6	121	51.7
Sulfonylureas	18	4.9	6	1.6	6	2.6	8	3.4
DPP-4 inhibitors	99	26.8	103	28.3	57	24.3	62	26.5
GLP1 agonists	7	1.9	9	2.5	3	1.3	7	3.0
SGTL2 inhibitors	12	3.3	21	5.8	16	6.8	17	7.3
Meglitinides	2	0.5	2	0.5	3	1.3	2	0.9
Insulin	123	33.3	108	29.7	56	23.8	63	26.9

Discussion

Cardiac rehabilitation (CR) is a fundamental component for successful long-term CHD treatment [30–32]. Data from almost 100,000 CHD patients enrolled in about 150 randomized trials have demonstrated the benefit of CR on both cardiovascular and total mortality [33, 34]. Moreover, many studies established that CR improves quality of life as well [35, 36]. In Germany, standard of care for CHD patients after ACS or CABG surgery comprises a multimodal 3-week CR at specialized rehabilitation centers [29, 35, 37–39]).

The multicenter LLT-R registry provided a representative cross-section of CHD patients and the treatment situation during and after CR in Germany. The registry data are based on only one exclusion criterion (i.e., the lack of informed consent) and the overall characteristics of the patient cohort, such as an average age of 63 years and less than 25 % females [29, 37–39].

Multimodal rehabilitation in Germany attempts to optimize drug therapy and to educate patients on the impact and the possible adverse effects of drugs in order to increase compliance with drug treatment [29, 37–39]. Further, CR commonly implements intensive programs on five days a week, including psychosocial support, physical exercise, and nutrition counseling [29]. Examples of improvements during start and end of rehabilitation include decreases in systolic blood pressure, heart rate, and waist circumference, but not in BMI [29, 37]. These findings are in excellent agreement with our observation regarding the unchanged body weight during follow-up after discharge from CR. Furthermore, effective CR could also account for the observed decline in insulin therapy during the course of LLT in the registry.

In agreement with the literature, this registry showed that total and LDL cholesterol levels changed within the first 3 months after CR, and then remained at that level, irrespective of prevalent diabetes mellitus. By contrast, the HDL levels in nondiabetic patients remained constant 3 months after CR, whereas HDL levels in diabetic patients continued to increase in the same period. In addition, our analysis indicated a faster decline in LDL cholesterol levels below 55 mg/dL in diabetes mellitus patients than in patients without diabetes. It should be stated, however, that the few measurement time points in the follow-up period provide only a low resolution of the kinetics of these adjustments.

In the cohort of this CR registry, 33.9 % of patients had received a diagnosis of diabetes mellitus (Table 1), whereas the overall rate of diabetic patients among all cardiac events in the German population varies between only 10 % and 16 % [40]. The overrepresentation of patients with diabetes mellitus in the CR registry cohort can very likely be attributed to the higher number of high-risk patients, such as elderly people who have suffered myocardial infarction and who are admitted more frequently to CR than younger diabetic patients with less severe cardiac events. Nonetheless, this discrepancy between the general population and the registry is a coincidental observation that requires thorough statistical assessment. In any case, the findings presented here have implications for CR patients or patients with recurrent cardiac events. This is particularly important in light of the continuously increasing magnitude of this patient group due to the growing number of multimorbid and older patients.

There are several limitations of this registry. First of all, it is difficult to interpret the data set due to the observational and nonrandomized design of the patient cohort. Changing the design of this study by introducing a control group is almost impossible as every patient in Germany has the litigable right to participate in CR after ACS or CABG [29, 37–39]. Nonetheless, this study aimed for the highest possible data quality. The Coordination Center for Clinical Studies, Martin Luther-University Halle Wittenberg, Germany (KKS Halle), enrolled patients consecutively on a prospective basis in order to provide adequate monitoring and to record all relevant patient information.

In addition, there may be potential incoherencies in LLT medication in this registry. In general, the study showed no differences in treatment of diabetic and nondiabetic patients during LTT. Nonetheless, patients received different drugs during the course of CR in order to address clinical needs, such as duration and severity of disease as well as comorbidities. Consequently, these changes in medication confound the association between treatment and outcome, thus introducing channeling or allocation biases. However, rehabilitation centers and patients enrolled in prospective studies are more likely to adhere to guideline-oriented therapy than patients outside of such centers or studies.

Moreover, different types of diabetes mellitus could not be addressed separately in this registry as data on the specific types were limited and inconclusive.

Lastly, a follow-up period of 12 months is rather short for monitoring lifelong chronic diseases. Hence, a longer follow-up period might have shown further differences between patients with and without diabetes mellitus.

Conclusion

This study demonstrated that LLT is able to reduce LDL cholesterol within a short time period of 3 months in patients with CHD. The data showed that CR is highly effective in implementing LLT and in reducing LDL cholesterol in patients with CHD. According to these data, concomitant diabetes mellitus in addition to antidiabetic medication did not negatively affect the efficacy of LLT during CR. On the contrary, patients with diabetes seemed to benefit most from CR, as they reached LDL treatment goals significantly better than patients without diabetes mellitus during CR.

Declarations

Ethics approval and consent to participate:

The ethics committee of the Medical Association of Saxony-Anhalt and the local ethics committees of the participating clinics approved this study (ClinicalTrials.gov Identifier: NCT02749279).

All patients signed an informed consent before study entry

Consent for publication:

All author agree to publication

Availability of data and materials

all source data are available upon request

Competing interest

Not applicable

Funding

Not applicable

Authors contribution

Thomas Wittlinger: validation, conzeptualization, methodology, Writing original draft

Bernhard Schwaab: study conception, data curation, investigation, writing-review and editing

Heinz Völler: data curation, investigation, wrting-review and editing

Christa Bongarth: data curation, investigation

Viktoria Heinze: data curation, investigation

Kristina Eckrich: data curation, investigation

Manju Guha: data curation, investigation

Michael Richter: Conzeptualization, methodology, data curation

Axel Schlitt: Conzeptualization, methodology, data curation, investigation, writing-review and editing

Acknowledgements

Not applicable

References

1. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255-323. Epub 2019/09/10. doi: 10.1093/eurheartj/ehz486. PubMed PMID: 31497854.
2. Reiner Z, De Backer G, Fras Z, Kotseva K, Tokgozoglu L, Wood D, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries–Findings from the EUROASPIRE IV survey. Atherosclerosis. 2016;246:243-50. Epub 2016/01/27. doi: 10.1016/j.atherosclerosis.2016.01.018. PubMed PMID: 26812002.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88. Epub 2019/09/11. doi: 10.1093/eurheartj/ehz455. PubMed PMID: 31504418.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81. Epub 2016/05/26. doi: 10.1093/eurheartj/ehw106. PubMed PMID: 27222591; PubMed Central PMCID: PMCPMC4986030.
5. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016;37(39):2999-3058. Epub 2016/08/28. doi: 10.1093/eurheartj/ehw272. PubMed PMID: 27567407.
6. Laks T, Keba E, Leiner M, Merilind E, Petersen M, Reinmets S, et al. Achieving lipid goals with rosuvastatin compared with simvastatin in high risk patients in real clinical practice: a randomized, open-label, parallel-group, multi-center study: the DISCOVERY-Beta study. Vasc Health Risk Manag. 2008;4(6):1407-16. Epub 2008/01/01. doi: 10.2147/vhrm.s4151. PubMed PMID: 19337553; PubMed Central PMCID: PMCPMC2663459.
7. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285(13):1711-8. Epub 2001/04/13. doi: 10.1001/jama.285.13.1711. PubMed PMID: 11277825.
8. Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). Diabetes Care. 2005;28(5):1151-7. Epub 2005/04/28. doi: 10.2337/diacare.28.5.1151. PubMed PMID: 15855581.
9. Ramkumar S, Raghunath A, Raghunath S. Statin Therapy: Review of Safety and Potential Side Effects. Acta Cardiol Sin. 2016;32(6):631-9. Epub 2016/12/03. doi: 10.6515/acs20160611a. PubMed PMID: 27899849; PubMed Central PMCID: PMCPMC5126440.
10. Tomaszewski M, Stepien KM, Tomaszewska J, Czuczwar SJ. Statin-induced myopathies. Pharmacol Rep. 2011;63(4):859-66. Epub 2011/10/18. doi: 10.1016/s1734-1140(11)70601-6. PubMed PMID: 22001973.
11. Leutner M, Matzhold C, Bellach L, Deischinger C, Harreiter J, Thurner S, et al. Diagnosis of osteoporosis in statin-treated patients is dose-dependent. Ann Rheum Dis. 2019;78(12):1706-11. Epub 2019/09/29. doi: 10.1136/annrheumdis-2019-215714. PubMed PMID: 31558481; PubMed Central PMCID: PMCPMC6900255.
12. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H, et al. Persistence of use of lipid-lowering medications - A cross-national study. Jama-J Am Med Assoc. 1998;279(18):1458-62. doi: DOI 10.1001/jama.279.18.1458. PubMed PMID: WOS:000073463500035.
13. Colantonio LD, Rosenson RS, Deng L, Monda KL, Dai Y, Farkouh ME, et al. Adherence to Statin Therapy Among US Adults Between 2007 and 2014. J Am Heart Assoc. 2019;8(1):e010376. Epub 2019/01/09. doi: 10.1161/JAHA.118.010376. PubMed PMID: 30616455; PubMed Central PMCID: PMCPMC6405715.
14. Catapano AL, Farnier M, Foody JM, Toth PP, Tomassini JE, Brudi P, et al. Combination therapy in dyslipidemia: where are we now? Atherosclerosis. 2014;237(1):319-35. Epub 2014/10/10. doi: 10.1016/j.atherosclerosis.2014.09.026. PubMed PMID: 25299967.
15. Scognamiglio M, Costa D, Sorriento A, Napoli C. Current Drugs and Nutraceuticals for the Treatment of Patients with Dyslipidemias. Curr Pharm Des. 2019;25(1):85-95. Epub 2019/02/02. doi: 10.2174/1381612825666190130101108. PubMed PMID: 30706799.
16. Fischer S, Julius U. Management of patients with statin intolerance. Atheroscler Suppl. 2017;30:33-7. Epub 2017/11/04. doi: 10.1016/j.atherosclerosissup.2017.05.013. PubMed PMID: 29096858.
17. Saxon DR, Eckel RH. Statin Intolerance: A Literature Review and Management Strategies. Prog Cardiovasc Dis. 2016;59(2):153-64. Epub 2016/08/09. doi: 10.1016/j.pcad.2016.07.009. PubMed PMID: 27497504.
18. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(25):2387-97. Epub 2015/06/04. doi: 10.1056/NEJMoa1410489. PubMed PMID: 26039521.
19. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet. 2012;380(9858):2007-17. Epub 2012/11/13. doi: 10.1016/S0140-6736(12)61770-X. PubMed PMID: 23141813; PubMed Central PMCID: PMCPMC4347805.
20. Raal FJ, Tuomilehto J, Sposito AC, Fonseca FA, Averna M, Farnier M, et al. Treatment effect of alirocumab according to age group, smoking status, and hypertension: Pooled analysis from 10 randomized ODYSSEY studies. J Clin Lipidol. 2019;13(5):735-43. Epub 2019/08/05. doi: 10.1016/j.jacl.2019.06.006. PubMed PMID: 31377052.
21. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-22. Epub 2017/03/18. doi: 10.1056/NEJMoa1615664. PubMed PMID: 28304224.
22. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018;379(22):2097-107. Epub 2018/11/08. doi: 10.1056/NEJMoa1801174. PubMed PMID: 30403574.

23. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalan R, Spinar J, et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation. 2018;137(15):1571-82. Epub 2017/12/22. doi: 10.1161/CIRCULATIONAHA.117.030950. PubMed PMID: 29263150.
24. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5(12):941-50. Epub 2017/09/21. doi: 10.1016/S2213-8587(17)30313-3. PubMed PMID: 28927706.
25. Pinkosky SL, Newton RS, Day EA, Ford RJ, Lhotak S, Austin RC, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. Nat Commun. 2016;7:13457. Epub 2016/11/29. doi: 10.1038/ncomms13457. PubMed PMID: 27892461; PubMed Central PMCID: PMCPMC5133702 from Esperion Therapeutics, Inc. The remaining authors declare no competing financial interests.
26. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. N Engl J Med. 2019;380(11):1022-32. Epub 2019/03/14. doi: 10.1056/NEJMoa1803917. PubMed PMID: 30865796.
27. Markham A. Bempedoic Acid: First Approval. Drugs. 2020;80(7):747-53. Epub 2020/04/22. doi: 10.1007/s40265-020-01308-w. PubMed PMID: 32314225.
28. Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J. 2008;155(4):772-9. Epub 2008/03/29. doi: 10.1016/j.ahj.2007.12.011. PubMed PMID: 18371492.
29. Rauch B, Riemer T, Schwaab B, Schneider S, Diller F, Gohlke H, et al. Short-term comprehensive cardiac rehabilitation after AMI is associated with reduced 1-year mortality: results from the OMEGA study. Eur J Prev Cardiol. 2014;21(9):1060-9. Epub 2013/04/06. doi: 10.1177/2047487313486040. PubMed PMID: 23559535.
30. Anderson LJ, Taylor RS. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. Int J Cardiol. 2014;177(2):348-61. Epub 2014/12/03. doi: 10.1016/j.ijcard.2014.10.011. PubMed PMID: 25456575.
31. Kim C, Youn JE, Choi HE. The effect of a self exercise program in cardiac rehabilitation for patients with coronary artery disease. Ann Rehabil Med. 2011;35(3):381-7. Epub 2012/04/17. doi: 10.5535/arm.2011.35.3.381. PubMed PMID: 22506148; PubMed Central PMCID: PMCPMC3309221.
32. Kwan G, Balady GJ. Cardiac rehabilitation 2012: advancing the field through emerging science. Circulation. 2012;125(7):e369-73. Epub 2012/02/23. doi: 10.1161/CIRCULATIONAHA.112.093310. PubMed PMID: 22354982.
33. Anderson L, Taylor RS. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2014;(12):CD011273. Epub 2014/12/17. doi: 10.1002/14651858.CD011273.pub2. PubMed PMID: 25503364; PubMed Central PMCID: PMCPMC7087435.
34. Gielen S, Laughlin MH, O'Conner C, Duncker DJ. Exercise training in patients with heart disease: review of beneficial effects and clinical recommendations. Prog Cardiovasc Dis. 2015;57(4):347-55. Epub 2014/12/03. doi: 10.1016/j.pcad.2014.10.001. PubMed PMID: 25459973.
35. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2016;(1):CD001800. Epub 2016/01/06. doi: 10.1002/14651858.CD001800.pub3. PubMed PMID: 26730878; PubMed Central PMCID: PMCPMC6491180.
36. Rauch B, Davos CH, Doherty P, Saure D, Metzendorf MI, Salzwedel A, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). Eur J Prev Cardiol. 2016;23(18):1914-39. Epub 2016/11/01. doi: 10.1177/2047487316671181. PubMed PMID: 27777324; PubMed Central PMCID: PMCPMC5119625.
37. Junger C, Rauch B, Schneider S, Liebhart N, Rauch G, Senges J, et al. Effect of early short-term cardiac rehabilitation after acute ST-elevation and non-ST-elevation myocardial infarction on 1-year mortality. Curr Med Res Opin. 2010;26(4):803-11. Epub 2010/02/04. doi: 10.1185/03007991003604216. PubMed PMID: 20121656.
38. Schlitt A, Wischmann P, Wienke A, Hoepfner F, Noack F, Silber RE, et al. Rehabilitation in Patients With Coronary Heart Disease: Participation and Its Effect on Prognosis. Dtsch Arztebl Int. 2015;112(31-32):527-34. Epub 2015/09/04. doi: 10.3238/arztebl.2015.0527. PubMed PMID: 26334980; PubMed Central PMCID: PMCPMC4980305.
39. Schwaab B, Waldmann A, Katalinic A, Sheikhzadeh A, Raspe H. In-patient cardiac rehabilitation versus medical care - a prospective multicentre controlled 12 months follow-up in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2011;18(4):581-6. Epub 2011/04/01. doi: 10.1177/1741826710389392. PubMed PMID: 21450643.
40. Dornquast C, Kroll LE, Neuhauser HK, Willich SN, Reinhold T, Busch MA. Regional Differences in the Prevalence of Cardiovascular Disease. Dtsch Arztebl Int. 2016;113(42):704-11. Epub 2016/11/22. doi: 10.3238/arztebl.2016.0704. PubMed PMID: 27866565; PubMed Central PMCID: PMCPMC5143789.

Figures

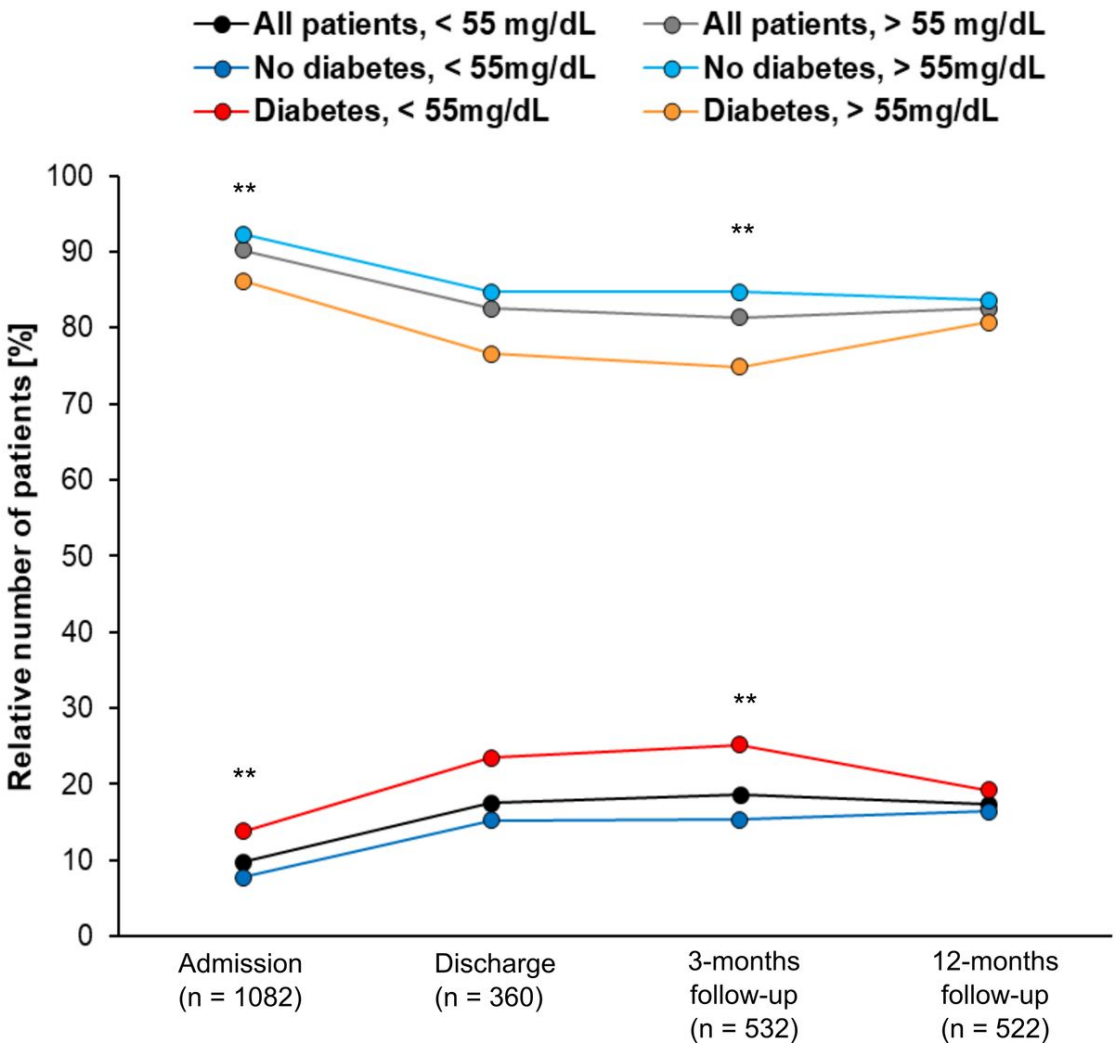

Figure 1

Patient population during study period according to LDL cholesterol levels that are classified as < 55 mg/dL and > 55 mg/dL (in black and gray). Patients are also subdivided in diabetic (red and orange) and nondiabetic (blue and turquois) patients. The statistically significant difference between diabetic and nondiabetic patients was evaluated with the Pearson's chi-squared test (** indicates p-value < 0.01).

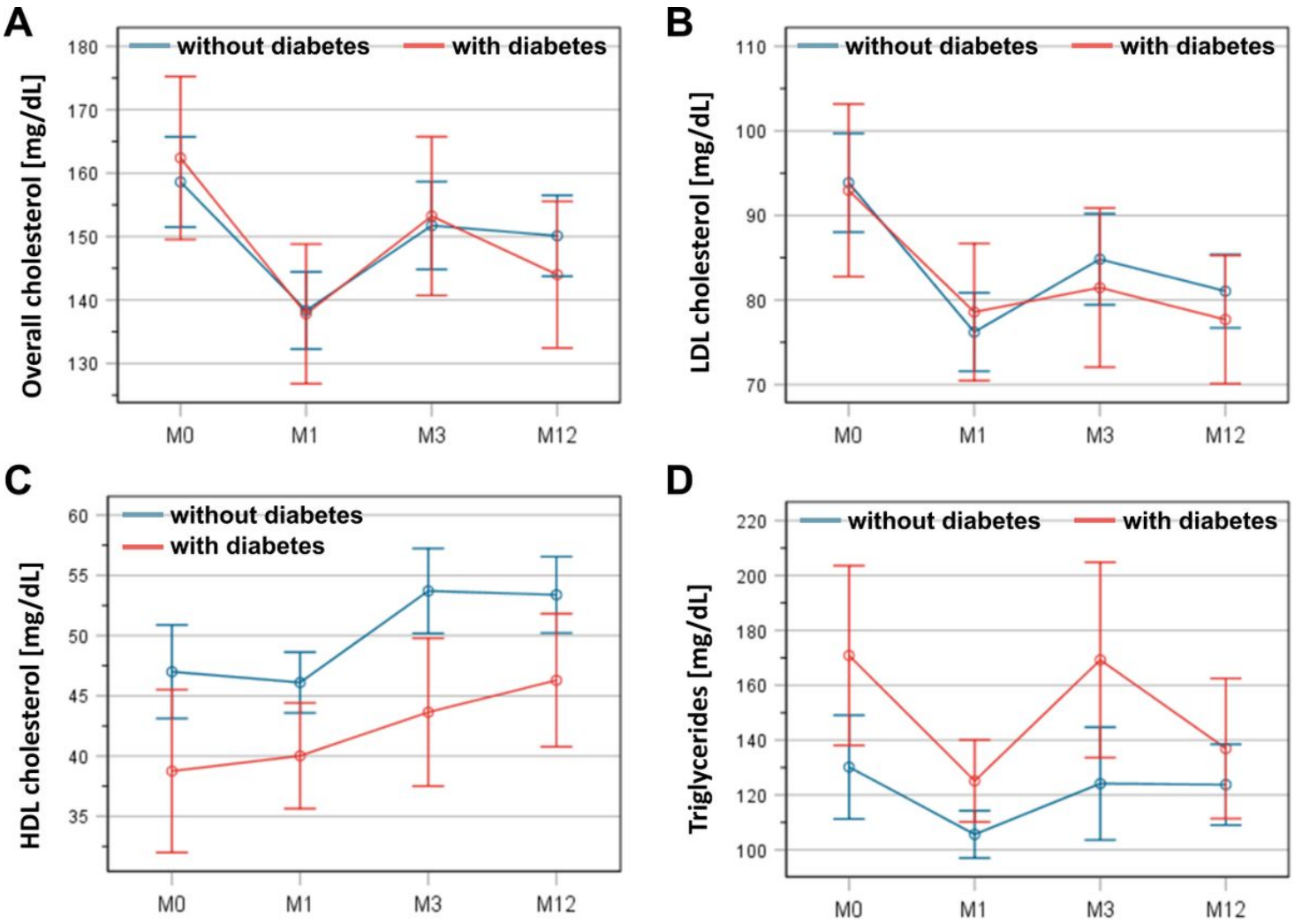

Figure 2

Changes in lipid levels in patients with and without diabetes mellitus during study period. Levels of overall cholesterol (A), LDL cholesterol (B), HDL cholesterol (C), and triglycerides (D) are presented at the beginning (M0) and the end of the cardiac rehabilitation (M1) as well as 3 months (M3) and 12 months (M12) after discharge. The graphs show the mean and the error bars represent the 95 % confidence interval. Patients with diabetes are indicated in red, patients without in blue.

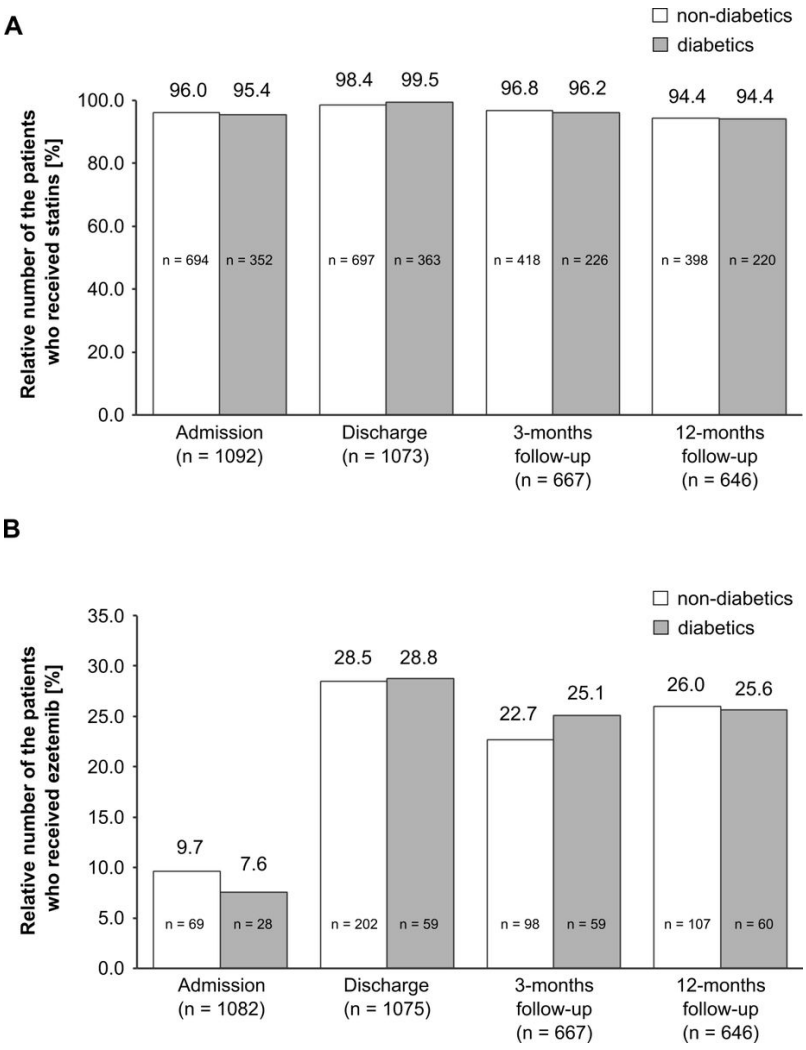

Figure 3

Distribution of LLT drugs in the patient population during the study period. The bar graph shows a comparison of the administration of statins (A) and ezetemib (B) among diabetic and nondiabetic patients at different time points. The number above the bar graph indicates the percentage of diabetics or nondiabetics, respectively, who received the drug. The number in the bar graph presents the total number of patients. The number at the x-axis shows the total amount of patients at this particular study period.