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Disconcordance between ESC prevention guidelines and observed lipid profiles in patients with known coronary artery disease☆

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ABSTRACT

Background: We aimed to describe whether updated low-density lipoprotein (LDL)-targets in patients with manifest coronary artery disease (CAD) led to a change in lipid profile over time.
Methods: We retrospectively included patients with manifest CAD from 2009–2010, 2012–2013, and 2015–2016 (n = 500 each). Lipid levels and medication at the different time-points as well as rate of accordance to guidelines (<100 for 2009–2010, <70 mg/dl for 2012–2013 and 2015–2016) were evaluated.
Results: Overall, 1500 subjects (mean age: 68.4 ± 11.2 years, 75.8% male) from 813 attending primary care physicians were included. Mean LDL-level was 98.0 ± 35.7 mg/dl, whereas 34.1% reached LDL-targets according to guidelines as applied at each time-point. Reduction of LDL-goals in 2011 lead to an initial decrease in LDL from 98.3 ± 33.4 mg/dl in 2009–2010 to 93.9 ± 36.3 mg/dl in 2012–2013 ($p = 0.045$). This effect was no longer present in 2015–2016 (101.6 ± 36.6 mg/dl, $p = 0.17$). The rate of patients meeting recommended LDL-targets decreased over time (2009–2010: 56.6%, 2012–2013: 25.4%, 2015–2016: 20.2%, $p < 0.0001$ for trend). Likewise, the frequency of statin-intake decreased over time (93.6% in 2009–2010 to 83.7% in 2015-2016, $p < 0.0001$). While use of medium intensity statins was most frequent (69.4%), only 20.9% of patients with medium intensity statins reached LDL-targets according to guidelines.
Conclusion: In a large clinical cohort of patients with known coronary artery disease, reduction of LDL-targets in ESC-guidelines in 2011 led to an initial decline in LDL-levels, while this effect was attenuated over time with the majority of patients missing treatment goals. Higher acceptance and compliance of statin therapy is warranted to utilize its effect in secondary prevention in CAD-patients.

1. Introduction

Overwhelming evidence documents the strong association of plasma low-density lipoprotein (LDL)-cholesterol with risk of coronary artery disease (CAD) events and the effectiveness of lipid lowering therapy on the reduction of cardiovascular events in secondary prevention [1–7]. Following the growing evidence, the European Society of Cardiology (ESC) first incorporated low-density lipoprotein targets, using a target of <100 mg/dl for patients with known CAD in 1994 [8]. In 2011, the LDL-target was reduced to <70 mg/dl, which is also recommended according current guidelines [9,10]. While statins are the first-line lipid-modifying treatment for patients with CAD as reducing both LDL-cholesterol levels and cardiovascular events [11–15], several studies in clinical practice have shown a gap between the recommendations in clinical guidelines and the actual lipid profile of high risk populations, especially in Europe [16–20]. However, whether the change in LDL-targets in ESC-guidelines resulted in a reduction of LDL in patients with CAD over time has not been evaluated. Therefore, we set out to evaluate the change in patterns of lipid lowering therapy and its success in achieving LDL-targets over time in a real-world registry cohort of patients with manifest CAD.

2. Methods

2.1. Study cohort

We retrospectively enrolled patients ≥ 18 years old with known CAD (diagnosis at least 30 days prior to presentation) that received assessment of cholesterol-levels and medication for clinical indications in the years 2009–2010 (n = 500), 2012–2013 (n = 500) and 2015–2016 (n = 500). Patients had to be on stable medical therapy for at

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least 30 days including stable lipid lowering therapy. Patients were randomly selected from hospital admissions and included both elective and emergency admissions at the West German Heart and Vascular Center Essen. Of these patients 24,4% were hospitalized due to an ACS, 37,9%, due stable CAD and 37,7% due a non-cardiac reason. Patients at each timeframes were not identical. The timeframes were set as 1–2 years before as well as 1–2 and 4–5 years after modification of LDL-targets according to ESC guidelines for patients with known CAD in 2011 [9]. Patients with LDL-apheresis, end-stage renal disease, familial hypercholesterolemia, and prior medical documentation of statin-intolerance were excluded from the analysis. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (17-7458-BO).

2.2. Risk factors and clinical diagnosis

Presence of known CAD manifestation was assessed from all available hospital records and defined as previous revascularization therapy, at least 30 days prior to the present admission. Cholesterol levels, demographic characteristics, cardiovascular risk factors, and medical therapy were assessed from available patient records. Statin therapy was categorized as low-, moderate-, high- intensity according to the 2013 ACC/AHA definitions [21]. Lipid levels were categorized as meeting or missing ESC-guidelines according to recommendations at time of assessment (<100 mg/dl for 2009–2010, <70 mg/dl for 2012–2013 and 2015–2016).

2.3. Statistical analysis

The baseline characteristics are presented as mean ± standard deviation for continuous variables and as frequency and percentages for categorical variables and stratified by time-point of assessment. Two-sided *t*-test was used for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, and Fishers-Exact test or Chi-square test for categorical variables for comparisons of baseline characteristics at first vs. last time-points. Frequency of patients according to LDL-groups and statin intensity are stratified by time-point. Difference in frequency of accordance to ESC-recommendations and time-points were compared using Fishers-Exact test, comparing the first to the last period. All analyses were performed using SAS software (Version 9.2, SAS Institute Inc.). A p-value of <0.05 indicated statistical significance.

3. Results

A total of 1,500 patients (mean age: 68.4 ± 11.2 years, 75.8% male) from 813 referring primary care physicians in 98 cities of Germany were included in our analysis. Table 1 summarizes the baseline demographic and clinical characteristics of the patients, stratified by time-point of assessment. Overall, 522 subjects (34.8%) had prior coronary artery bypass grafting and 399 patients (26.6%) had prior ST-elevation myocardial infarction. There was a trend towards an increase in age, BMI, and triglycerides over time (age: 67.1 ± 10.8 to 69.6 ± 11.7 years, p = 0.005; BMI: 27.5 ± 4.4 to 28.1 ± 5.4 kg/m^2, p=0.09; triglycerides: 152.9 ± 94.1 to 167.3 ± 148.4 mg/dl, p = 0.07, in 2009–2010 and 2015–2016, respectively), while the rate of hypertension (≥90%) was high at all periods. Combining data of all patients from 2009 to 2016, mean LDL-level was 98.0 ± 35.7 mg/dl, whereas 34.1% reached LDL-targets according to guidelines as applied at each time-point.

3.1. Trend in LDL-levels over time

Reduction of LDL-goals in 2011 lead to an initial decrease in LDL-cholesterol from 98.3 ± 33.4 mg/dl in 2009–2010 to 93.9 ± 36.3mg/dl in 2012–2013 (p = 0.045). However, mean LDL-cholesterol increased to 101.6 ± 36.6 mg/dl in 2015–2016, representing a non-statistically significant difference compared to 2009–2010 (p = 0.17, Fig. 1). Likewise, rate of patients meeting recommended LDL-targets decreased over time (2009–2010: 56.6%, 2012–2013: 25.4%, 2015–2016: 20.2%, p < 0.0001 for trend). In accordance, the use of any statin medication decreased over time (93.6% in 2009–2010 to 83.7% in 2015–2016, p < 0.0001).

Table 1
Study sample characteristics. Data is presented as mean and standard deviation for continuous variables and as frequency and percentages for categorical variables.

	2009/2010 (n = 500)	2012/2013 (n = 500)	2015/2016 (n = 500)	p-Value
Age	67.1 ± 10.8	68.6 ± 10.8	69.6 ± 11.7	0.0005
BMI (kg/m^2)	27.5 ± 4.4	28.1 ± 4.8	28.1 ± 5.4	0.09
Sex (male)	376 (75.2)	379 (75.8)	382 (76.4)	0.67
Total cholesterol (mg/dl)	175.2 ± 41.4	165.8 ± 44.8	169.2 ± 44.8	0.04
HDL-cholesterol (mg/dl)	49.1 ± 16.3	47.0 ± 14.4	47.5 ± 14.5	0.11
LDL-cholesterol (mg/dl)	98.3 ± 33.4	93.9 ± 36.3	101.6 ± 36.5	0.14
Triglyceride (mg/dl)	152.9 ± 94.1	157.2 ± 94.4	167.3 ± 148.4	0.07
Statins (%)	468 (93.6)	445 (89.0)	418 (83.6)	<0.0001
Non-statin (%)	24 (4.8)	9 (1.8)	27 (5.4)	0.66
Hypertension	487 (97.4)	493 (98.6)	449 (89.8)	0.20
Diabetes (%)	152 (30.4)	198 (39.6)	167 (33.4)	0.08
Family history	157 (31.3)	171 (34.2)	132 (26.4)	0.35
Smoking				0.09
– Current	69 (13.8)	84 (16.8)	70 (14.0)	
– Former	160 (32.0)	162 (32.4)	118 (23.6)	

SD: standard deviation, BMI: body mass index, LDL: low density lipoprotein, HDL: high density lipoprotein.

3.2. Trends in statin therapy over time

The use of medium-intensity statins was most frequent (69.4%) at all time-points, while frequency of high intensity statin increased to 35% in 2015–2016, applying definitions for intensity of statin therapy as by current American Heart Association/American College of Cardiology guidelines (Fig. 2) [21]. This was predominantly explained by an increase of the prescription of atorvastatin over time, while usage of simvastatin and rosuvastatin decreased (Fig. 3a). Only very few patients were treated with lovastatin, fluvastatin, or pravastatin at each time-point without a significant change over time. In contrast to changes in type of statin, dosages of statin therapy were not relevantly different over time (Fig. 3b).

Combining data from all time-points, 37.1% of patients in the medium-intensity statin group achieved LDL-levels below recommended ESC-targets, while frequency of meeting ESC recommendations was slightly lower for low- and high-intensity statin therapy (32.5% and 30.03%, respectively), while only 25.6% of patients without any statin therapy reached ESC-targets. Stratifying by time-point, we observed that in 2009–2010 the recommended LDL-targets of <100 mg was achieved in the majority of patients with medium-intensity statin therapy, while only 40% reached LDL-goals despite high-intensity statins (Supplementary figure). In contrast, in 2015–2016, the highest rate of patients meeting ESC-recommendations regarding LDL-levels were observed in patients receiving high-intensity statin therapy.

3.3. Non-statin lipid lowering therapy

Overall, 60 patients (4%) were treated with non-statin lipid lowering therapy (Ezetimibe in 51 patients, fibrates, niacin or acid sequesters in 9 patients). In 2012 and 2013, frequency of non-statin therapy was lowest (9 patients), whereas its use was not significantly different comparing 2009 and 2010 (24 patients) to 2015 and 2016 (27 patients, p = 0.67). 18 patients received a non-statin alone, whereas the combination of a statin and a non-statin was administered in 42 patients. Among patients receiving both statins and non-statins, frequency of

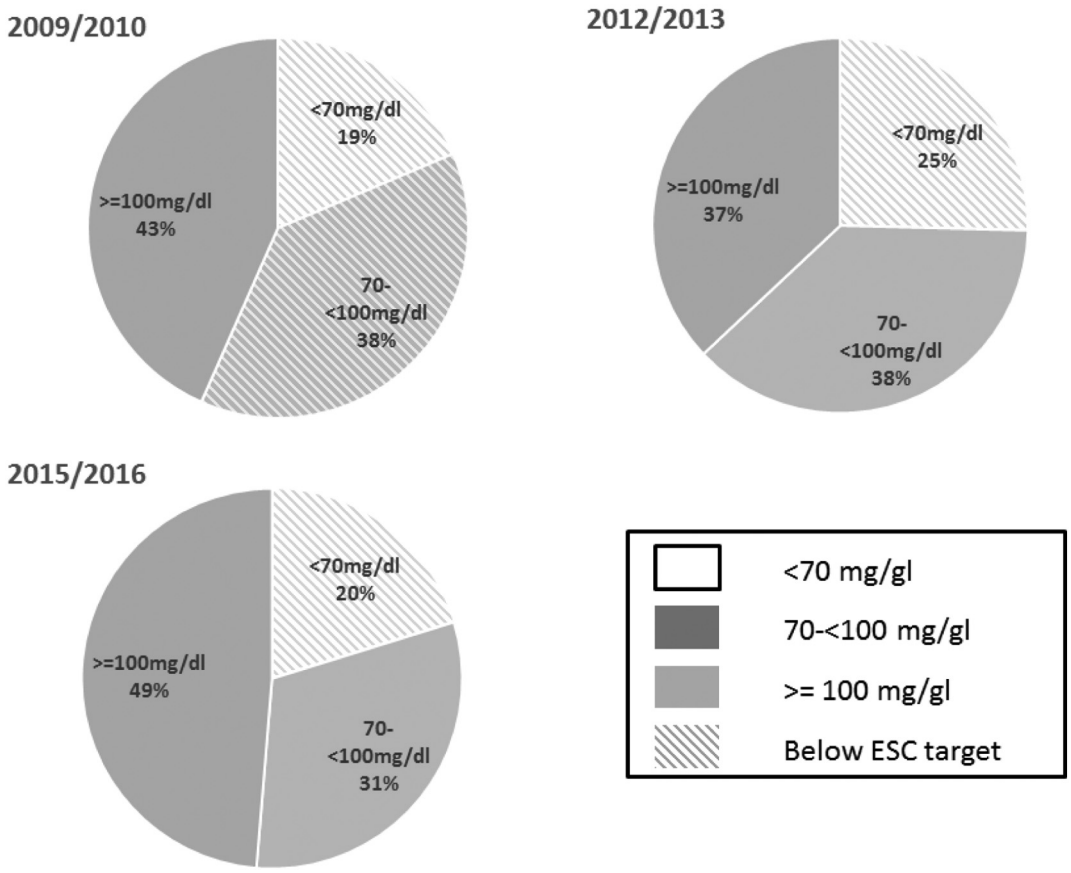

Fig. 1. Levels of LDL-cholesterol in patients with manifest CAD, stratified by year of presentation and according to ESC Guidelines.

achieving treatment targets was slightly higher than in patients without dual lipid-lowering therapy, however, not reaching statistical significance due to the low absolute numbers (38.1% vs. 34.0%, p = 0.62).

4. Discussion

In a large real-world registry with 1500 patients from 813 primary care physicians in 98 German cities we observed that the reduction of LDL-targets in ESC guidelines from 2011 led to an initial decrease in LDL-cholesterol in patients with manifest CAD, whereas this effect was attenuated over time with LDL-cholesterols in 2015 and 2016 being even higher compared to 2009 and 2010. Going in hand, we observed an increase of CAD-patients without statin therapy over time. While the availability of generic atorvastatin led to an increase in its usage and hence high-intensity statin therapy in 2015 and 2016 compared to 2009–2013, dosages of statin therapy did not change over time. As a more intensive statin therapy would be available in many patients as reflected by a high frequency of low and medium intensified therapy and low utilization of a combination of statins with non-statin lipid-lowering drugs at each time-point, our results underline the disconcordance between ESC guidelines and actual treatment in daily clinical routine.

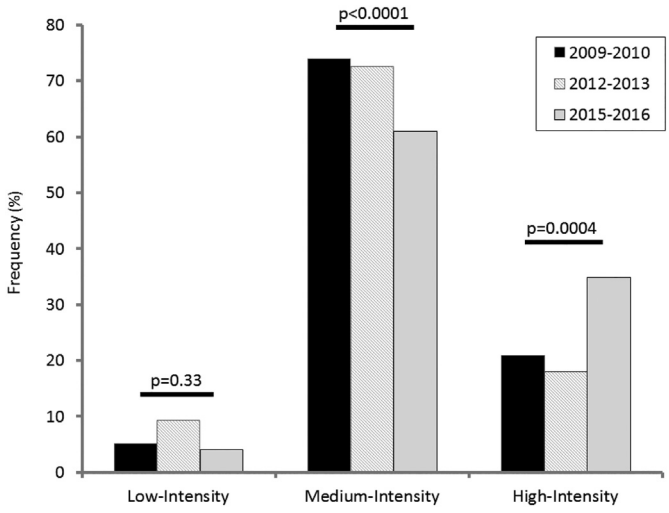

Fig. 2. Frequency of low-, medium-, and high-intensity statin therapy in 2009–2010, 2012–2013 and 2015–2016. Current American Heart Association/American College of Cardiology guidelines definition for intensity of statin therapy was used [21].

In a recent survey among 2625 high risk patients on atorvastatin, 10.5% of patients achieved an LDL-target of <70 mg/dl, whereas more than 60% of patients were assessed by their physicians to have clinically met the target [20]. Similarly, the data from DYSIS II showed that use of lipid lowering therapy was widespread and improved after hospitalization for an ACS. However, the intensity of such a therapy was only moderate in both the CHD and ACS cohorts with only 37% reaching the target value of <70 mg/dl LDL-C within 120 days since hospital discharge [22].

These results, underlined by a high rate of patients receiving no or low-intensity statin therapy in our study, demonstrate that in patients with known manifest CAD, LDL-cholesterol levels above ESC-targets are accepted in the majority of patients and treating physicians despite availability of more aggressive treatment options. However, we also observed an increasing proportion of patients missing LDL-targets despite high intensity statin therapy, which might be reflected by a shift towards an increased need for aggressive treatment in this population over time.

Given the linear relationship between LDL and atherosclerosis progression with even further LDL-reduction below the target of 70mg/dl

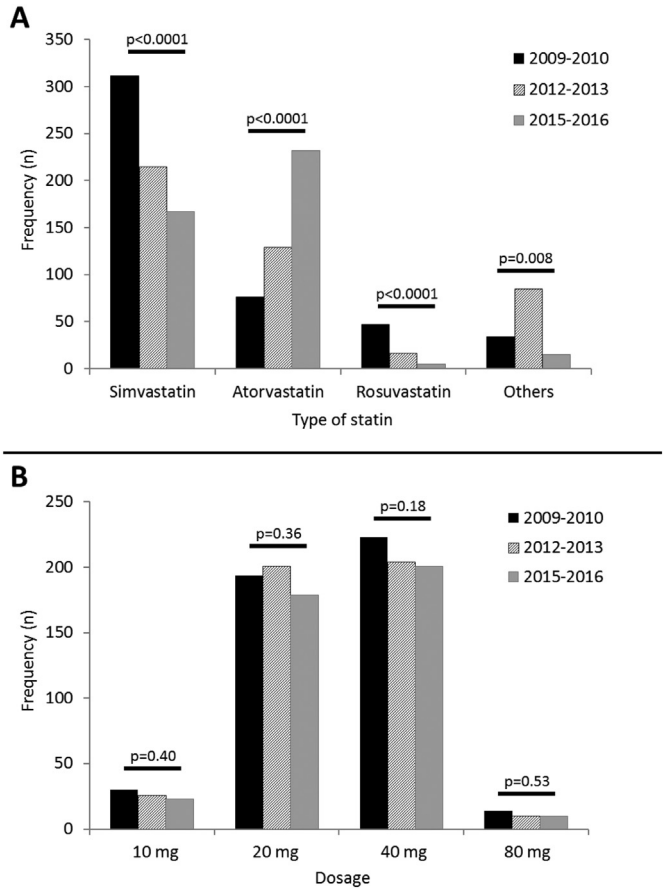

Fig. 3. Frequency of type of statin and statin dosage in 2009–2010, 2012–2013, and 2015–2016.

leading to reduction in cardiovascular outcomes [23–27], our data suggests that clinical practice keeps the majority of our patients at harm. Antibodies to the proprotein convertase subtilisin-kexin type 9 (PCSK9) have proven to reduce LDL-levels in addition to statin therapy by 50% and more, reducing both coronary plaque burden and cardiovascular event probability [23,28]. However, given the limited acceptance of more aggressive statins by patients and treating physicians as documented in our study, the willingness to follow more cost-intensive treatments regimens may be questioned. Multi-disciplinary approaches on patient and population level for improvement of acceptance and adherence to effective lipid lowering therapy are warranted to maximize the benefits of standard treatment options [29]. Compared to ESC-guidelines, current American lipid-lowering guidelines suggest an earlier and more aggressive use of statins especially in primary prevention cohorts, leading towards recommendations for statin therapy in broader parts of the population [27,30,31]. Whether this approach leads to a sustained reduction of LDL-cholesterol levels in appropriate populations needs to be determined in future studies. While the reduction of LDL-targets by the ESC led to an initial reduction of LDL-levels in patients with manifest CAD in our study, potentially triggered by an increase in awareness regarding the medical need, this effect was diluted over time.

4.1. Limitations

Limitations of our study include the retrospective study design with no information regarding previous changes in lipid-lowering therapy of the patients. Given the retrospective design, assessing cross-sectional patient data, no information on follow-up is available. Moreover, given the retrospective nature, we were not able to assess any potential side effects of statin therapy, which may have limited its use in individual patients. However, the rate of patients with insufficient LDL-levels despite ability for a more aggressive statin therapy was relevantly higher than the described frequency of side effects of statin therapy in the literature. Therefore, this may have only marginally effected our results. In addition, not the same patients were evaluated over all three time-points. However, long-term follow-up of identical patients would have led to a more pronounced change in patient's age over time, ultimately leading to a decrease in generalizability of the follow-up cohorts. Lastly, our study is based on a predominantly Caucasian cohort; hence, its validity in other cohorts and ethnic groups remains uncertain.

5. Conclusions

In a large clinical cohort of patients with known coronary artery disease, reduction of LDL-targets in ESC-guidelines in 2011 led to an initial decline in LDL-cholesterol, while this effect was attenuated over time with the majority of patients missing treatment goals. Mechanisms increasing the acceptance and compliance of statin therapy are warranted to utilize its effect in secondary prevention of patients with manifest CAD.

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