CKJX839A1CZ01 Abstract

Title

A prospective multicentric study to evaluate the impact of long-term digital education vs standard of care on LDL-C levels in post myocardial infarction patients in the Czech Republic

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NIS Type

No Novartis Drug non-PASS NIS with primary data collection

Rationale and background

Coronary artery disease is the leading cause of mortality in the Czech Republic. Approximately 50,000 deaths are attributed to diseases of the circulatory system each year in the Czech Republic. Advances in treatment have improved survival after the initial event, but patients after a myocardial infarction (MI) are at elevated risk of recurrent coronary events and mortality.

Patient involvement in therapeutic strategies leading to lifestyle changes and increasing adherence to beneficial treatment is important for high-risk coronary artery disease patients. Adherence to both healthy lifestyle choices and to prescribed lipid lowering medication in post myocardial infarction patients was assessed in the past and was found to be exceptionally low.

A structured adult education program is a well-explored measure to increase adherence to the prescribed medication and to lifestyle modifications. Several studies showed positive long-lasting effects of educational programs on low density lipoprotein cholesterol (LDL-C) levels and other established modifiable markers of cardiovascular risk. Although the same improvement of secondary prevention was confirmed by two local studies, a systematic patient's education after myocardial infarction has not been implemented in the secondary prevention program in the Czech Republic. The reason for not adopting these proposals in routine practice may be the burden on Health Care Resources (HCR), both financial and organizational.

The purpose of this study was to demonstrate the impact of digital education on the cardiovascular risk factors in post-MI patients and to generate evidence for broad implementation of the proposed education program. The implementation of proposed education is expected to increase patients' adherence to post-MI treatment, to increase percentage of patients in secondary prevention treated to LDL-C target levels by increasing patients' involvement in treatment decisions and to increase the adherence to lifestyle modifications. The combination of increased adherence to lipid lowering treatment, more active role of the patient in treatment decisions, and lifestyle modifications is expected to result in measurable differences in specific indices of cardiovascular risk such as LDL-C and therefore improve the overall status of secondary prevention in the Czech Republic, if implemented. Furthermore, the education plan proposed in this study was designed to pose minimal burden on Health Care Resources, which would have helped to overcome the barriers in the broad implementation of structured education.

Research question and objectives

The primary objective of the study was to describe the effect of the proposed educational program for post-MI patients on LDL-C at month 12 after the event compared to routine clinical practice.

The secondary objectives included characterization of the impact of education compared to routine clinical practice on achieving target LDL-C level, levels of other lipid parameters, body metrics, life-style modifications and adherence to lipid-lowering treatment. The study also collected data to describe target

population characteristics, pharmacological treatment in post-MI patients, and the adherence and satisfaction with the proposed educational system.

Study design

The local (Czech Republic), multi-center, prospective, descriptive study was a non-treatment interventional, two-armed stratified randomized (1:1), not blinded, controlled (parallel group) study in hospitalized adult patients after first myocardial infarction with two arms to evaluate the effect of systematic education program on the 12-months change of LDL-C. Patients were randomized into two arms: interventional and control. The interventional arm received the systematic educational intervention. The control arm was treated in the clinical routine mode, i.e., the education of the patient followed routine practice, and no added education was provided by the HCPs (Healthcare Professionals). The post-MI treatment in both arms followed the standard of care (SOC). The End of Study (EOS) visit was performed at month 12 at the place of the initial hospitalization.

Setting and study population

It was planned to enroll 120 adult patients after a first myocardial infarction in 5 sites.

This was a non-interventional study and did not impose a therapy protocol, or a diagnostic/therapeutic procedure. Patients were treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only this data was to be collected as part of the study.

Enrolled patients were followed for 12 months. The treating physician was asked to complete the appropriate electronic case report forms (eCRF) at two timepoints 12 months apart.

Variables and data sources

Variables included lipid parameters, body metrics, behavioral outcomes, demographics, living conditions, clinical characteristics, family history pharmacological treatment, the adherence and satisfaction with the proposed educational plan and composite cardiovascular endpoint.

Data sources included and were not limited to medical notes, electronic medical records, hospital discharge files documented during routine care, and analytics about adherence to proposed educational plan from the online educational platform.

Statistical methods

All planned analysis for the primary and secondary objectives were descriptive with no inferential statistics, i.e. no statistical testing for comparison of patient groups. To quantify effect size in primary and secondary endpoint variables between the study groups, two types of measures were implemented as post-hoc analysis. Cohen’s d was used for continuous variables, while Cramér’s V was used for categorical variables.

Randomization was stratified by site, age, and baseline LDL-C level. Furthermore, the analysis of the primary endpoints was repeated in the following subgroups of patients to evaluate possible impact of demographic and baseline characteristics: age (18-64, 65+ years), gender, center, diabetes (yes/no), baseline LDL-C (≤3 mmol/L, >3 mmol/L) and education (2 levels: university degree, no university degrees).

Results

The DEDUCA study was conducted from 8th March 2023 to 24th October 2024 at 5 centers in the Czech Republic, which enrolled 121 patients in total.

All enrolled patients met eligibility criteria and were randomized. Out of 121 randomized patients, 59 patients were assigned to interventional arm and 62 patients to control arm. 105 (86.8%) patients completed the study (50 patients in interventional arm and 55 patients in control arm). 94 (77.7%) patients met criteria to be included in the efficacy set (39 patients in interventional arm and 55 patients in control arm).

Distribution of participants was well balanced across 5 centers with the following number of patients enrolled by each center: 32 (26.4%) patients in 2 centers, 24 (19.8%) patients, 17 (14.0%) patients and 16 (13.2%) patients.

Out of 16 (13.2%) patients who prematurely discontinued the study, 10 patients were lost to follow up (7 in interventional arm and 3 in control arm), 2 patients died (both from control arm) and 4 patients reported other reason (2 in interventional arm and 2 in control arm).

Population characteristics

In the efficacy set, the majority of subjects were males (69.2% in interventional arm and 83.6% in control arm) of mean (standard deviation - SD) age 56.6 (11.97) years in interventional arm and 56.9 (10.95) years. The proportion of patients at the age of 65 years and over was similar in both arms (25.6% in interventional arm and 25.5% in control arm). With respect to the level of education, except lower proportion of patients with secondary education with diploma in interventional arm vs control arm (25.6% vs 40.0%), no important differences based on employment status, region or education level were observed.

The proportions of patients by marital status and household (living alone vs not alone) were similar in both arms in the efficacy set. With respect to other living and family conditions, no substantial differences were observed between interventional arm vs control arm except the following characteristics: income of 21 000–30 999 CZK (23.1% vs 32.7%) and of 31 000–40 999 CZK (25.6% vs 16.4%), having 3 children (20.5% vs 12.7%) and residency in town with 50 001–100 000 inhabitants (7.7% vs 3.6%) or > 100 000 inhabitants (15.4% vs 25.5%).

At Baseline in the efficacy set, there were less patients with diabetes in interventional arm vs control arm (12.8% vs 21.8%). No important differences between interventional arm vs control arm were recorded in other medical history aspects as follows: atherosclerotic cardiovascular disease (ASCVD) in family history (28.2% vs 29.1%), any other relevant protocol-solicited medical history (56.4% vs 49.1%) and any other relevant general medical history (20.5% vs 14.5%). No patient enrolled in the study suffered from chronic kidney disease at Baseline. Of note, no patient experienced 3-point major adverse cardiovascular event (MACE) within one year after the first event, i.e. Month 12 of the DEDUCA study.

Overall, both treatment groups were balanced and homogenous, since no important differences in baseline and demographic characteristics were observed.

Primary endpoints analysis

During DEDUCA study, the LDL-C level decreased substantially from Baseline to Month 12 in both arms. However, the effect as based on standardized difference in mean (SD) between interventional vs control arm was small (Cohen's d = 0.212) for absolute LDL-C change [-1.305 (1.0830) mmol/L vs -1.577 (1.4089) mmol/ L, respectively] and very small (Cohen's d = 0.022) for relative LDL-C change [-39.530 (27.7739) % vs -40.191 (31.7552) %, respectively].

Of note, baseline LDL-C was slightly lower in interventional arm in comparison to control arm [3.189 (0.8919) mmol/ L vs 3.452 (1.1846) mmol/ L], but both arms had similar LDL-C level at Month 12 [1.885 (0.9785) mmol/ L vs 1.875 (0.8458) mmol/ L, respectively].

Except center and education level - university degree, small or very small effects were observed in all subgroups as based on comparisons between interventional vs control arms by absolute and relative LDL-C changes from Baseline to Month 12 as well as LDL-C levels at Baseline and at Month 12.

Medium effect was detected between interventional vs control arms in the mean (SD) of absolute LDL-C change [-1.179 (0.8604) mmol/L vs -2.013 (1.3049) mmol/L, respectively] in center 3 (Cohen's d = 0.750) and in the mean (SD) of relative LDL-C change [-56.158 (9.7203) % vs -41.782 (30.8942) %, respectively] in center 2 (Cohen's d = 0.529). In center 4, the difference between mean (SD) LDL-C level in interventional vs control arm indicated large effect (Cohen's d = 0.863) at Baseline [2.967 (1.4080) mmol/L vs 4.263 (1.5317) mmol/L] and medium effect (Cohen's d = 0.708) at Month 12 [1.457 (0.1716) mmol/L vs 2.140 (1.1102) mmol/L]. However, there were only 3 patients in interventional arm and 7 patients in control arm enrolled at center 4. All the other differences within centers showed small or very small effects.

Medium effect (Cohen's d = 0.538) was also observed in the subgroup with university degree, when comparing the mean (SD) of relative LDL-C change in interventional arm vs control arm [-49.935 (12.7970) % vs -39.203 (24.4749) %]. All the other differences within education levels showed small or very small effects.

While the primary objective focused on differences between treatment arms, the subgroup analysis

provided detailed description of LDL-C levels in the target population in the real-life settings. Interestingly, mean (SD) baseline LDL-C levels in both arms are higher in younger patients and patients without diabetes in comparison to older patients and patients with diabetes. Generally, more substantial decrease in LDL-C level over 12 months was observed in subgroups with higher value at Baseline.

Subgroups by baseline LDL-C ≤3 mmol/L vs >3 mmol/L also confirmed that LDL-C change from Baseline to Month 12 was more substantial in the subgroup with higher LDL-C level at Baseline.

On the other hand, patients enrolled at center 1 had LDL-C levels at Baseline similar to values reported from the other centers, but both mean and median relative LDL-C changes were lower in comparison to the other centers.

Secondary endpoints analysis

Overall, the effect based on differences in interventional arm vs control arm was small or very small for all variables assessed as secondary endpoints, except the proportion of patients who ceased smoking at Month 12 (94.4% vs 57.6%), the proportion of patients who increased low intensity physical activity by Month 12 (53.8%) vs 21.8%) and the proportion of patients by estimated number of steps walked daily at Baseline.

Altogether, 10 (25.6%) patients in interventional arm and 14 (25.5%) patients in control arm achieved LDL-C target level at Month 12 according to the 2019 ESC/EAS Guidelines.

Absolute and relative changes in lipid parameters [total cholesterol, high-density lipoprotein cholesterol (HDL-C), very low- density lipoprotein cholesterol (VLDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides and lipoprotein(a) [Lp(a)] from Baseline to Month 12 show improvement in all parameters except Lp(a).

From Baseline to Month 12, the mean (SD) systolic and diastolic blood pressure slightly increased, heart rate slightly decreased, and body mass index (BMI) and waist circumference remained stable in both interventional and control arms.

Out of 18 patients who were active smokers at Baseline in interventional arm, 17 (94.4%) quit smoking by Month 12, while out of 33 active smokers at Baseline in control arm, 19 (57.6%) quit smoking by Month 12. In both arms, the median number of cigarettes smoked per week substantially decreased over 12 months (from 112 to 35 cigarettes in interventional arm and from 105 to 35 cigarettes in control arm).

Nearly one half of patients changed their diet according to the recommendations by Month 12 after the event (with the exception of about only one quarter of patients who increased consumption of poultry). The greatest differences in rates of patients who improved their diet between interventional vs control arm were observed in decreased consumption of red meat (46.2% vs 23.6%), sugar-added beverages (56.4% vs 38.2%), white flour pastries (33.3% vs (45.5%) and sweets (51.3% vs 41.8%). The differences in rates of patients who improved their diet were similar in both arms in the other collected diet modifications.

Daily consumption of any alcohol was quite low in both arms and both at Baseline and Month 12 [all medians 0, except median number of beers (0.5L) consumed daily in control arm of 0.4 at Baseline and of 0.1 at Month 12]. The proportions of patients who decreased consumption of alcohol were slightly higher in control arm in comparison to interventional arm.

Average estimated time spent by physical activities per week at Baseline and Month 12 was similar in both treatment arms. Number of steps walked daily (<5000, 5000–7500, 7500–10000, 10000–12500 and >12500) was overall higher in control arm (medium effect), but the change in distribution among categories was similar at Month 12 (small effect). Increase of low, medium and high intensity physical activity was reported by higher proportions of patients in the interventional arm in comparison to control arm.

While 10 (25.6%) patients in interventional arm and 6 (10.9%) patients in control arm were already registered at cardiologist at Baseline, 29 (74.4%) patients in interventional arm and 46 (83.6%) patients in control arm were registered by Month 12. Only 1 (1.8%) patient from control arm hadn´t been registered up to Month 12.

The number of patients who used statins in the last month increased from 6 (15.4%) patients at Baseline to 35 (89.7%) at Month 12 in interventional arm and from 10 (18.2%) patients at Baseline to 50 (90.9%) patients at Month 12 in control arm. If adherence was defined as taking medications as prescribed >75%

of the time in the past month, the number of adherent patients increased from 7 (17.9%) patients at Baseline to 34 (87.2%) at Month 12 in interventional arm and from 9 (16.4%) patients at Baseline to 47 (85.5%) patients at Month 12 in control arm.

With respect to pharmacological therapy related to MI at Baseline and at Month 12, no important differences were observed between interventional and control arms. Only 1 patient in each arm didn´t receive any MI related therapy at Baseline and 100% of patients in both arms reported such therapy at Month 12. In the interventional arm vs control arm, high-intensity statin and statin ezetimibe combination was administered to 94.9% and 43.6% of patients vs 96.4% and 34.5% of patients, respectively. PCSK9 inhibitor was recorded in 1 patient from control arm. Of note, inclisiran was recorded in 1 patient in interventional arm and in 2 patients in control arm within category Other lipid-lowering therapy. All patients received antiplatelet therapy and the majority received antihypertensives (97.4% in interventional arm and 89.1% in control arm).

While no patient met reimbursement criteria for PCSK9 antibodies treatment at Baseline, 3 (7.7%) patients in interventional arm and 5 (9.1%) patients in control arm were eligible to receive this therapy at Month 12. However, only 1 (1.8%) patient from control arm was actually receiving PCSK9 inhibitor therapy.

Despite small differences mostly in season 1 and 4 with low number of patients (10 and 2 patients in both arms, respectively), no noticeable seasonal effect was observed in the analysis of behavioral secondary outcomes. Similar analysis was applied to centers. However, there were quite small numbers of patients again, especially in interventional arm (3, 4 and 7 patients in center 4, 2 and 5 respectively).

Conclusion

The DEDUCA study provided robust evidence of substantial improvements in post-MI patients over 1 year after the event in terms of lipid parameters, life-style modifications and adherence to lipid-lowering treatment. Reduction of LDL-C was similar in both treatment arms, but smoking cessation and increase of low intensity physical activity was reported more frequently in patients who underwent the educational program. The DEDUCA study confirmed that the LDL-C goal attainment in patients with very high CV risk is difficult to achieve and that lipid-lowering combination therapy and use of PCSK9 antibodies are rather suboptimal.

List of abbreviations

ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
eCRF	Electronic Case Report/Record Form
HCR	Health Care Resources
HDL-C	High Density Lipoprotein Cholesterol
LDL-C	Low Density Lipoprotein Cholesterol
Lp(a)	Lipoprotein(a)
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
NIS	Non-Interventional Study
Non-HDL-C	Non-High Density Lipoprotein Cholesterol
PASS	Post-Authorization Safety Study
PCSK9	Proprotein Convertase Subtilisin/Kexin 9
SD	Standard Deviation
SOC	Standard of Care
VLDL-C	Very Low Density Lipoprotein Cholesterol