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ORIGINAL ARTICLE

Dyslipidaemia management in the cardiac rehabilitation clinic of a tertiary referral centre: analysis of the impact of new ESC guidance on LDL-C target achievement

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Abstract

Background Optimisation of low-density lipoprotein cholesterol (LDL-C) targets is one component of cardiac rehabilitation (CR). The 2019 European Society of Cardiology (ESC) guidelines recommend lower LDL-C targets than those released in 2016.

Aims To determine the proportion of patients who met 2019 LDL-C targets and compare these to international standards; examine the effect of the introduction of the recent ESC guidelines on target achievement. Examine the choice of lipid lowering therapy (LLT) used in our cohort.

Methods Retrospective chart review of 163 patients who attended CR in 2019. Baseline LDL-C levels were calculated where applicable. Targets achieved were compared with the contemporary ESC guidance. Required LLT was estimated for those who were unable to meet their LDL-C target.

Results Overall, 96/163 (59%) patients met their absolute LDL-C targets, which was favourable when compared to international standards. Fewer patients treated using the 2019 ESC guidelines met their absolute, (63% (70/112) vs. 51% (26/51)), or relative LDL-C 43% (22/51) targets. A high intensity statin was prescribed in 63% (89/163) of patients and only 9% (5/163) patients were prescribed ezetimibe therapy; increased use of these agents may have led to a further 20% (33/162) of patients meeting their LDL-C targets. 13% (22/163) of patients likely require PCSK9i therapy.

Conclusions Patients may be more likely to meet LDL-C targets while enrolled in CR compared to standard care. Following the introduction of lower absolute LDL-C targets and additional > 50% LDL-C reduction from baseline requirement, fewer patients are meeting the LDL-C targets set out in the 2019 ESC dyslipidaemia guidelines. Additionally, many patients are not on maximum statin therapy, ezetimibe is under-prescribed, and a guideline-reimbursement gap exists for those who require PCSK9i therapy.

Keywords Dyslipidaemia · Ezetimibe · Lipids · Rehabilitation · Secondary prevention · Statin

Background

Release of new ESC Guidelines

In August 2019 the European Society of Cardiology (ESC) released its most recent dyslipidaemia management [1] (subsequently hereafter referred to as 'ESC 2019 guidelines').

The outcomes of several major clinical trials form the basis for these revisions. In particular, the FOURIER [2] and ODYSSEY OUTCOMES [3] trials. These trials demonstrated that the low-density lipoprotein cholesterol (LDL-C) reductions previously seen with the addition of a proprotein convertase subtilisin/kexin type 9 serine protease inhibitor (PCSK9i) to those high-risk patients on maximally tolerated statin therapy translate to a lower incidence of major cardiovascular events. Additionally, there appears to be no threshold for clinical benefit in lowering LDL-C levels in these high-risk patients. As such, these new guidelines have introduced lower LDL-C targets for those in the high and very high-risk categories and have recommended the use of a PCSK9 inhibitor in those at 'very high risk' who fail to meet their LDL-C target while prescribed a high intensity statin and ezetimibe.

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The 2019 ESC guidelines now specify that high and very high-risk patients should also aim to reduce their LDL-C levels below an absolute target, as well as a reduction in their LDL-C levels > 50% from baseline. Additionally, it is now recommended that those at 'very high risk' who fail to achieve their LDL-C target using both a high intensity statin and ezetimibe, a combination with a PCSK9i is recommended [1].

Cardiac rehabilitation

Cardiac rehabilitation is a supervised programme designed to improve cardiovascular health. It includes education on risk factor management, heart healthy living, exercise counselling and training. It is most often offered as part of a secondary prevention strategy for acute coronary syndrome (ACS) patients, but increasingly is being offered for non-ACS indications such as heart failure or valvopathies. It takes place over a four-phase process, with phase one and two occurring peri-admission. During this index admission to an acute hospital, a metabolic risk panel, including a lipid profile is measured. Phase three consists of a 6–12 week structured exercise and education programme, and it is during this time that lipid management is optimised.

Dyslipidaemia management and LLT titration

Conventionally, a lipid profile is obtained during an index admission, with lipid lowering therapy (LLT) prescribed or altered upon discharge from hospital. Patient lipid profiles are again measured at the initiation of phase 3 to ensure adequate clinical response, and LLT may be titrated by an advanced nurse prescriber (ANP).

Baseline LDL-C levels

The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications [1] (Fig. 1).

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate Intensity Statin	≈30%
High intensity Statin	≈50%
High Intensity Statin plus ezetimibe	≈65%
PCSK9 inhibitor	≈60%
PCSK9 inhibitor plus high intensity statin	≈75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈85%

Fig. 1 Adapted from 'ESC guidelines for the management of dyslipidaemia', 2019

Aims and objectives

To determine the proportion of our patients who completed cardiac rehabilitation in 2019 that reached their LDL-C targets, before and after the introduction of 2019 ESC guidelines.

To examine the choice of lipid lowering therapy (LLT) prescribed in our cohort, including changes to prescribing practice following the introduction of the 2019 ESC guidelines.

Methods

Retrospective chart review

A list of patients who completed phase 3 of cardiac rehab in 2019 was created using our centre's Patient Administration System (PAS). Those patients who did not complete phase 3 before Dec 31, 2019 were excluded. Four patients with missing LDL-C data were excluded. This returned 163 patients.

A retrospective chart review for these patients was undertaken. A database was created containing baseline patient characteristics including gender, age, BMI, cardiac risk factors, reason for cardiac rehabilitation (CR) referral and laboratory results. These results included prior lipid profile results and their contemporary lipid lowering therapy (LLT), final lipid profile at the end of phase 3 (taken as their 'post rehab' lipids) and corresponding LLT. For those patients prescribed a statin, the 'intensity' of the statin was classified as 'mild', 'moderate' or 'high', based on the expected LDL-C lowering effect the agent at a specific dose (Table S1).

For those patients who did not have a previous diagnosis of atherosclerotic cardiovascular disease (ASCVD) (as defined in the 2016 and 2019 ESC guidelines) and were managed as part of a primary prevention strategy, further fields were generated in order to risk stratify and determine their LDL target.

These fields included blood pressure and prior diagnosis of diabetes (with time since diagnosis and presence of end-organ damage, if applicable). Baseline serum creatinine was determined, and the Modification of Diet in Renal Disease Study (MDRD) equation was used to determine the estimated glomerular filtration rate. Those with chronic kidney disease were stratified as severe (< 30 mL), or moderate (30–60 mL/min). The presence of a markedly elevated single risk factor (e.g. BP > 180 systolic or

LDL > 8 mmol/L) was recorded. A SCORE risk was then calculated. These patients were then risk stratified using their highest scoring criteria.

For our secondary prevention cohort, the presence of a second vascular event within 2 years was considered; however, none of our patients fulfilled this criterion.

LDL-C targets

Either 2016 or 2019 ESC guideline LDL-C targets were applied to patients depending on if they started phase 3 of cardiac rehab prior to or post September 9, 2019, respectively (Fig. 2). This date represents a 10-day period to account for delays in implementation. Confirmation was obtained that the implementation of these guidelines was immediate.

For those patients treated using the 2016 guidance, achievement of either an LDL level below that recommended for their risk category *or* a reduction in LDL level over 50% was recorded as successful adherence to guidelines.

For those treated using the 2019 guidance, only those patients who achieved *both* their risk-specific LDL-C level and an over 50% reduction in their LDL-C level were recorded as adhering to the guidelines. For those patients in whom only a post-CR LDL-C level was available, achieving an LDL-C level below their recommended target was recorded as successfully adhering to guidance.

Baseline lipids

Baseline LDL-C values were determined where possible. Where available, this was taken as a lipid profile obtained while the patient was not prescribed LLT.

As most patients were already receiving LLT upon presentation, baseline LDL-C was calculated by recording the results of a lipid profile taken within the year prior to starting CR, as well as the LLT they were prescribed at this time. The projected LDL-C lowering effects of the LLT (Fig. 1) were used to calculate a baseline LDL-C.

It was not possible to calculate the baseline LDL-C values for 45 patients, due to missing data regarding their LLT or having only one lipid profile on file.

Risk Category	LDL-C Target (2016)	LDL-C Target (2019)
Recurrent vascular event <2years	N/A	<1.0
Very high	<1.8	<1.4
High	<2.6	<1.8
Moderate	<3.0	<2.6
Low	<3.0	<3.0

Fig. 2 LDL-C Level Targets for either cardiovascular risk category, stratified by guidelines used

LLT prescribing practices

The agent(s) and dose(es) that formed each patient's LLT were recorded at both the start and completion of phase 3 of CR. Increase in agent dosage or the introduction of a new agent was classified as an increase in LLT. A dose decrease or withdrawal of an agent was recorded as a decrease in LLT. Patients prescribed the same LLT at both the start and end of phase 3 were recorded as no change in LLT. Those switched to an equivalent agent(s) of similar expected LDL-C lowering efficacy (Fig. 1) were recorded as being changed to an equivalent LLT. Those who were recorded as not being prescribed LLT at the start of CR and then prescribed LLT were recorded as having been initiated on LLT. Alterations in LLT which could not be inferred for patients who did not have their initial or completion LLT recorded were recorded as an unknown change.

Predicted required LLT

For those who did not achieve their absolute LDL-C target at the end of CR and for whom contemporary LLT data was available ($n = 55$), the percentage reduction in their latest measured LDL-C required to reach their absolute LDL-C target was calculated. Using the estimated LDL-C lowering effects of different LLT regimes (Fig. 1), the approximate LDL-C lowering effect of their current LLT was noted, and the LLT regime that would be likely to achieve the additional percentage reduction in LDL-C was determined.

As an example, a 'very high' risk patient treated under the 2019 guidelines would have an LDL-C target of 1.4 mmol/L. If their LDL-C is measured as 2.0 mmol/L at the end of phase 3, then a 30% reduction in their current LDL-C is required to meet this target. Their prescribed LLT is atorvastatin 20 mg monotherapy (a moderate intensity statin at this dose), which can be expected to reduce LDL-C 30% from baseline. As can be seen from Fig. 1, up-titration of their LLT to a high intensity statin therapy in combination with ezetimibe would likely be required to achieve an *additional* 30% reduction in their LDL-C. Therefore, their predicted required LLT is recorded as a high intensity statin in combination with ezetimibe.

Statistical analysis

All statistical computations were performed in SPSS statistics (version 25; IBM, New York, USA). The alpha value was set at 0.05. Categorical data was described using counts and percentages where appropriate. When comparing the pre-2019 to post-2019 guideline cohorts, respective baseline categorical variables were compared using a Pearson's X^2 test for independent samples to control confounding factors and ensure both groups were well matched. When comparing column proportions, the chi-squared test was used.

Numerical data was described using mean and standard deviation where appropriate. Normality was confirmed both graphically and using the Shapiro-Wilks normality test. Due to the significant difference in population sizes, homogeneity of variances was confirmed using Levene's test before comparing continuous variables. Scale variables were described using the mean, 95% confidence intervals for the mean and an unpaired *t* test was performed when comparing groups.

Results

Baseline characteristics

Table 1 displays the baseline characteristics of all the patients who finished phase 3 of CR in 2019, stratified by the guidelines under which they were treated. The mean (SD) age of those who completed CR in 2019 was 62 (9) years, 76% (123/163) were male, with the majority (87%; 142/163) being treated as part of a secondary prevention strategy. Of those who did not have a diagnosis of ASCVD, 5 (3%) were in the 'high-risk' category, 16 (10%) were of 'moderate' risk, and there was 1 patient deemed to be of 'low' risk.

There were no significant differences with regard to age ($p=0.234$), gender ($p=0.560$), proportion of patients being treated for primary or secondary prevention ($p=0.520$) or risk category ($p=0.491$). The proportion of patients with established ASCVD was comparable across both 2016 guideline and 2019 guideline cohorts ($p=0.520$).

Significantly, more patients in the 2019 guideline cohort were on no LLT at the beginning of phase 3 ($p<0.005$) and a higher proportion of our 2016 guideline cohort began CR with a high intensity statin monotherapy ($p<0.005$).

Choice of lipid lowering therapy

Table 2 displays the LLT prescribed for each patient upon completion of CR in 2019, stratified by guidelines used. Overall, the most common LLT on completion of CR was a high intensity statin monotherapy (91/163, 56%), followed by a moderate intensity statin monotherapy (41/163, 25%). Two patients (1%) were treated with a high intensity statin and ezetimibe. Fourteen patients were on no lipid lowering therapy, 4 of whom had a documented refusal of LLT (2%). There was no significant difference, on the completion of CR, in the proportion of patients prescribed a high intensity statin therapy, either alone or in combination with ezetimibe, between the 2016 (64/112; 57%) and 2019 (29/51; 57%) cohort ($p=0.553$).

In total 5/163 (3%) of our cohort were prescribed ezetimibe therapy, either as a monotherapy or in combination with other LLT.

Titration of lipid lowering therapy

Overall, there was a significant difference in the prescribing practices between the 2016 and 2019 cohorts, which are summarised in Table 3. Patients treated under the 2019 guidelines were more likely to be initiated on LLT (31% vs. 13%; $p<0.005$) or have their LLT up-titrated (16% vs. 4%; $p=0.014$) and were less likely to be maintained on their current LLT (27% vs. 73%; $p<0.005$). There was no difference in the proportion of patients who had their LLT down-titrated (8% vs. 4%; $p=0.430$) or changed to another LLT with an equivalent expected LDL-C reducing effect (8% vs. 4%; $p=0.098$). There was a significantly higher proportion of patients treated under the 2019 guidelines for whom the titration of LLT could not be determined due to missing or incomplete data (16% vs. 3%; $p=0.023$).

Estimation of predicted required LLT

The estimated required LLT for those who completed CR in 2019 are summarised in Table 4.

Eighty-two percent (55/67) of patients who failed to meet their contemporary LDL-C level in 2019 had sufficient LDL-C and LLT data to estimate a predicted LLT. Seven percent (4/55) and 27% (15/55) are likely to require either a moderate or high intensity statin monotherapy, respectively, in order to meet their contemporary, absolute LDL-C target. Twenty-five (14/55) would likely require a high intensity statin and ezetimibe combination to meet their absolute LDL-C target. It is estimated 40% (22/55) of these patients would require a PCSK9i to reach their absolute LDL-C target, either in combination with a high intensity statin only (16%; 9/55) or in combination with a high intensity statin and ezetimibe (24%; 13/55).

Cholesterol

Table 5 displays the mean LDL-C results for those patients attending CR, both prior to starting (where available) and upon completion of CR. It also displays the number of patients who achieved their absolute LDL-C targets for their relevant risk category and applicable guidelines. The mean percentage reduction in LDL-C, where both a pre- and post-CR LDL-C was available, as well as the number of patients achieving an over 50% reduction in their baseline LDL-C is also displayed.

For those patients who completed Cr in 2019, 96/163 (59%) patients met their absolute LDL-C targets. The mean (95% CI) LDL-C reduction was 57% (52–62), with 61 patients of the 118 for whom pre-CR LDL-C was available (52%) achieving an over 50% reduction in their LDL-C levels. One hundred four (64%) patients were

Table 1 Baseline characteristics of those patients who completed CR in 2019

Guidelines	2016	2019	Total	*p*
Age				
Mean (SD)	63 (9)a	61 (11)a	62 (10)a	*0.234b*
Sex				
Female	26 (23)	14 (28)	40 (25)	*0.56*
Male	86 (77)	37 (73)	123 (76)	
Prevention strategy				
Primary prevention	13 (12)	8 (16)	21 (13)	
Secondary prevention	99 (88)	43 (84)	142 (87)	*0.52*
Risk category				
Very high	99 (88)	43 (84)	142 (87)	*0.491*
High	3 (3)	2 (4)	5 (3)	
Moderate	11 (10)	5 (10)	16 (10)	
Low	0 (0)	1 (2)	1 (1)	
Initial lipid lowering therapy				
No lipid lowering therapy	21 (19)	22 (43)	43 (26)	*0.009**
Low intensity statin	3 (3)	2 (4)	5 (3)	
Moderate intensity statin	34 (30)	10 (20)	44 (27)	
High intensity statin	50 (45)	29 (56)	91 (56)	
Moderate intensity statin + ezetimibe	2 (2)	0 (0)	2 (1)	
High intensity statin + ezetimibe	2 (2)	0 (0)	2 (1)	
Ezetimibe monotherapy	0 (0)	1 (2)	1 (1)	
Unknown/missing	0 (0)	9 (18)	9 (6)	
Family history				
None	42 (38)	12 (24)	54 (33)	
Yes	78 (70)	15 (29)	93 (57)	
Missing	4 (4)	27 (53)	31 (19)	
Smoking status				
Current	3 (3)	0 (0)	3 (2)	
Ex < 6 months	22 (20)	2 (4)	24 (15)	
Ex > 6 months	16 (14)	1 (2)	17 (10)	
Ex > 5 yrs	24 (21)	8 (16)	32 (20)	
Missing data	5 (5)	28 (55)	33 (20)	
Never	23 (21)	5 (10)	28 (17)	
Dyslipidaemia				
Yes	81 (46)	16 (44)	97 (46)	
No	95 (54)	20 (56)	115 (54)	

Table 1 displays the summary statistics for our 2019 patient cohort, stratified by guidelines under which they were treated, '2016' (2016 ESC Guidelines on Dyslipidaemia management) or '2019' (2019 ESC guidelines on Dyslipidaemia management). Initial lipid lowering therapy delineates the therapy the patient was prescribed on D1 of CR

Except where otherwise states, values are displayed as counts with column percentages displayed in brackets. Statistically significant p-values are displayed in italics

found to be treated in compliance with their contemporary guidelines. The distribution of either measured or calculated baseline LDL-C was not significantly different between both groups ($p = 0.006$).

With regard to those patients treated using the 2016 guidelines, 70/112 (63%) patients met their absolute LDL target. The mean (95% CI) reduction in LDL-C was 61% (56–66), and 50 out of the 81 patients for whom LDL data was available, 62% achieved LDL-C reductions > 50% of baseline. Eighty-two (73%) of those patients treated under the 2016 guidelines achieved their LDL-C targets.

Those patients treated under the 2019 guidelines had fewer patients meeting their absolute (26/51, (51%)) or relative reduction (11/37, 30%) LDL-C targets when compared to the 2016 cohort. The mean reduction in LDL-C from baseline was 48% (95% CI 37–59%).

Table 2 Lipid lowering therapy at completion of phase 3 of CR in 2019

LLT therapy	2016 (%)	2019 (%)	Cohort total (%)
No LLT	10 (9)	4 (8)	14 (9)
Low intensity statin monotherapy	3 (3)	1 (2)	4 (2)
Moderate intensity statin monotherapy	33 (30)	8 (16)	41 (25)
High intensity statin monotherapy	62 (55)	29 (57)	91 (56)
Moderate intensity statin + ezetimibe	2 (2)	0 (0)	2 (1)
High intensity statin + ezetimibe	2 (2)	0 (0)	2 (1)
Ezetimibe monotherapy	0 (0)	1 (2)	1 (1)
Unknown/unrecorded LLT	0 (0)	8 (16)	8 (5)
Grand total	112	51	163

Table 2 displays the choice of LLT in those patients who completed CR in 2019, stratified by guidelines used Values shown as numbers with percentage of row total shown in brackets

LLT lipid lowering therapy

Missing data

During data collection, there were 4 patients who had no LDL-C data available, either pre- or post-CR.

Choice of LLT was not recorded for 8 patients. Baseline LDL-C was either unavailable or could not be estimated for 45 (28%) patients.

Discussion

Baseline characteristics

The majority of patients who attended cardiac rehabilitation in 2019 had established ASCVD. The majority of those patients without ASCVD were referred following cardiac valve surgery, a diagnosis of heart failure and insertion of implantable cardiac defibrillator (ICD).

Choice of LLT

While the most common choice of LLT, only slightly more than half of our cohorts were prescribed a high intensity statin monotherapy (56%), and only a very small minority were prescribed ezetimibe. As the majority of our cohorts (88%) were considered to be at 'very high risk', this seems to suggest that many patients are being undertreated. This could perhaps be due to intolerance of these medications, therapeutic inertia, or a lack of awareness of available therapeutic strategies. As there were no patients who did not meet their LDL-C target while prescribed ezetimibe in combination with a high intensity statin therapy, no patients met the criteria for a combination therapy with a PCSK9i, as recommended by the ESC.

Prescribing practices

Allowing for the proportion of missing data, those treated under the 2019 ESC guidelines appeared to have been subject

Table 3 Comparison of LLT prescribing practices between those treated under the 2016 and 2019 guidelines

Prescribing practice	2016 ($n=112$)	2019 ($n=51$)	p-value	Total ($n=163$)
No change in LLT	82 (73)	14 (27)	<0.005*	96 (59)
LLT initiated	14 (13)	16 (31)	0.004*	30 (18)
LLT up-titrated	5 (4)	8 (16)	0.014*	13 (8)
LLT down-titrated	3 (3)	1 (2)	0.430	4 (2)
Change of therapy to an equivalent LLT	5 (4)	4 ()	0.098	17 (10)
Unknown/missing	3 (3)	8 (16)	0.009*	3 (2)

Table 3 displays the alterations made to patient LLT during phase 3 of cardiac rehabilitation in 2019, stratified by guidelines used. Values in brackets represent percentages of column total. Column proportions were compared using the chi-squared test for independent samples and the corresponding p-values are shown. Change to equivalent LLT represents a change of agent or combination of agents, with similar expected LDL-C lowering effects

LLT lipid lowering therapy

*p-value is statistically significant <0.05

Table 4 Predicted required LLT for those who completed CR in 2019 ($n=55$)

Moderate intensity statin monotherapy	4 (7)
High intensity statin monotherapy	15 (27)
High intensity statin + ezetimibe	14 (25)
PCSK9i + high intensity statin	9 (16)
PCSK9i + high intensity statin + ezetimibe	13 (24)

Table 4 displays the predicted LLT required for those who failed to meet their absolute LDL-C targets upon completion of CR in 2019. Values are displayed as count with percentage of column total in brackets

to a more aggressive LLT strategy. This may be as a result to changes in practice in response to the new lower targets set out in the 2019 and may account for the lower LDL-C levels seen in those treated under the 2019 ESC guidelines.

LDL-C target achievement

For many of those patients treated under the 2016 guidelines who had not met their absolute LDL-C targets, determining their baseline LDL-C levels found that they achieved-over 50% reduction in LDL-C from baseline, and as such could be said to be treated in accordance with best practice. This resulted in overall greater number of patients meeting their LDL-C targets.

However, given that the 2019 ESC dyslipidaemia guidelines specify that both an absolute and relative target needed to be met for those at high and very high risks, many who met their absolute LDL-C target did not meet their relative reduction from LDL-C baseline. This meant that for this cohort, consideration of their baseline LDL-C levels meant fewer patients were meeting their LDL-C targets.

Table 5 Summary of LDL-C values for those patients who completed CR in 2019, stratified by treatment guidelines and risk category

Risk category	N	Baseline LDL-C available	LDL-C pre-CR	LDL-C post-CR	Absolute LDL-C target met	% LDL-C red. from baseline	> 50% red. LDL-C	Guidelines achieved
2016 Guidelines								
Very high	99	76 (77)	2.72 (2.48 – 2.97)	1.67 (1.52 – 1.82)	61 (62)	61 (56 – 66)	49 (70)	73 (73)
High	2	1 (50)	4.03 (NA*)	4.5 (NA*)	1 (50)	70 (NA*)	1 (100)	1 (50)
Moderate	11		2.69 (1.33 – 4.05)	0.95 ((−0.9) – 2.82)	8 (73)			8 (72)
Low	0							
Subtotal	112	81 (72)	2.70 (2.46 – 2.93)	1.64 (1.49 – 1.79)	70 (63)	61 (56 – 66)	50 (65)	82 (73)
2019 Guidelines								
Very High	43	30 (70)	3.34 (3.01 – 3.66)	2.86 (2.39 – 3.34)	21 (49)	50 (40 – 61)	11 (37)	18 (42)
High	2	2 (100)	2.91 (NA*)	4.81 (NA*)	1 (50)	13.92 (NA*)	0 (0)	0 (0)
Moderate	5		3.45 (1.56 – 5.34)	2.25 (1.01 – 3.48)	3 (60)			3 (60)
Low	1				1 (100)			1 (100)
Subtotal	51	37 (73)	2.83 (2.41 – 3.25)	1.83 (1.41 – 2.25)	26 (51)	48 (37 – 59)	11 (34)	22 (43)
All patients								
Very High	142	108 (76)	2.68 (2.48 – 2.88)	1.60 (1.47 – 1.72)	82 (58)	58 (53 – 63)	68 (67)	91 (64)
High	4	3 (75)	3.28 (1.56 – 5.00)	2.43 (1.02 – 3.84)	2 (50)	32 (NA*)	1 (33)	1 (25)
Moderate	16		3.02 (2.23 – 3.80)	2.43 (1.91 – 2.94)	11 (69)			11 (69)
Low	1				1 (100)			1 (100)
Total	163	118 (72)	2.72 (2.52 – 2.91)	1.69 (1.57 – 1.82)	96 (59)	57 (52 – 62)	61 (52)	104 (64)

Table 5 displays the LDL-C level attainment for those patients who completed CR in 2019, stratified by guidelines used. The number of patients for whom LDL-C data prior to commencement to commencing CR is given, with percentage of row total in brackets. The mean measured LDL-C level prior and following completion of cardiac rehab is given with 95% confidence intervals for the mean in brackets. The number of patients who met their absolute LDL-C category for their specified risk category is displayed with row percentage displayed in brackets. The percentage in reduction of LDL-C from measured or calculated baseline LDL-C is given, with 95% confidence intervals for the mean displayed in brackets. The number of patients who achieved an over 50% reduction in their LDL-C level when compared to their measured or calculated baseline LDL-C level is given with row percentage in brackets. The number of patients who met their LDL-C guidelines as defined by their contemporary guidelines is displayed with row percentage in brackets. For the 2016 cohort, this required achievement of a reduction of LDL-C below an absolute target, and for those at very high and high risks, a relative reduction of at least 50% LDL-C when compared to measured or calculated baseline lipids. For the 2019 cohort, both of these criteria must be satisfied

CR cardiac rehabilitation

[a]Baseline lipids do not refer to 'LDL-C pre-rehab' column, but instead the measured LDL-C level for those not on LLT (or the calculated LDL-C level of a patient, adjusted for LLT effect), prior to commencing CR

Table 6 Comparison of LDL-C target achievement between those who completed CR in 2019 with the EUROASPIRE and DAVINCI studies

Number of 'very high risk' patients (*n*)	Age (SD)*	Female	LDL-C target achieved
CR 2019 (*n* = 142)	62 (10)	40 (25)	96 (59)
2016 Guidelines (*n* = 99)	63 (9)	14 (28)	70 (63)
2019 Guidelines (*n* = 43)	61 (11)	26 (23)	26 (51)
EUROASPIRE V[a] (*n* = 8261)	62.5 (9.6)	62.5 (9.6)	2396 (29)
DAVINCI[a] (*n* = 2039)	68 (10)	68 (10)	795 (39)
Primary care (*n* = 526)			188 (35)
Secondary care (*n* = 1513)			620 (41)

Table 6 compares absolute LDL-C target achievement between those that completed cardiac rehabilitation in 2019 with those examined in the EUROASPIRE V and DAVINCI studies. Unless where otherwise stated, values are given as the number with the percentage of the total sample size in brackets

Primary care = primary care practitioner only. Secondary care = regular attendance with a cardiologist, diabetologist or endocrinologist

*Values are displayed as mean (SD)

[a]Both studies were conducted using the 2016 ESC guidelines

Comparison with international standards

Numerous large international cross-sectional and prospective studies, both European and worldwide, have demonstrated poor risk factor control in those with established ASCVD [4–8]. The proportion of patients who attended CR in 2019 in our centre and reached their absolute LDL-C target compares favourably when compared to large European studies. A survey of 8261 patients with ASCVD from the European Action on Secondary and Primary Prevention Intervention to Reduce Events V (EUROASPIRE V) [9] registry demonstrated that only 29% (2396/8261) of these patients met their LDL-C target. The majority of these patients (> 80%) were under specialist care (Cardiologist, Cardiac ANP, Diabetologist/endocrinologist).

The 'EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care' (DAVINCI) [8] study examined LDL-C compliance in both secondary and primary prevention cohorts, and further stratified these patients as being managed in either primary or secondary care. Of those at 'very high risk', 39% (795/2029) met their absolute LDL-C targets, with fewer patients treated in primary care meeting their LDL-C targets when compared to those under specialist supervision (35% (188/526) vs. 41% (620/1513).

Table 6 compares the results of the current study with both the EUROASPIRE and DAVINCI cohorts.

Estimated required lipid-lowering therapies

It was a notable finding that 13% (22/163) of our cohort would likely require a PCSK9i combination therapy to achieve their absolute LDL-C targets. While none of these patients met the ESC criteria for this combination as they had not been trailed on a high intensity statin and ezetimibe, this finding is likely significant given the cost of these therapies [10] and the strict reimbursement criteria outlined by the Health Services Executive (HSE) in Ireland [11]. The current HSE reimbursement criteria for those with ASCVD require a LDL-C > 4 mmol/L while maintained on a high intensity statin and ezetimibe combination [11]. None of the 22 patients identified in our cohort met the current reimbursement criteria due to either an LDL-C that was already < 4 mmol/L on current therapies (91%; 20/22) or an LDL-C level that would likely fall below 4 mmol/L with up-titration of their LLT to a high intensity statin and ezetimibe combination (9%; 2/22).

As a corollary, the prescription of a high intensity statin to all patients in a 'very high' risk group is estimated to have led to at least an additional 12% (19/163) of patients, who completed CR with LDL-C levels above their recommended level, achieving their absolute LDL-C targets. The addition of ezetimibe to high intensity statin therapy in select patients who were unlikely to meet their targets with a high intensity statin alone is estimated to have led to a further 14 patients meeting their absolute LDL-C targets (14/163; 9%). Combined, these interventions are likely to have led to a further 20% (33/162) of patients to meet their LDL-C targets.

As such, while it is likely that a sizable minority of patients are likely to require a PCSK9i combination to meet the targets outlined by the ESC, increased prescription of high intensity statins and ezetimibe combination therapy may represent a more cost-effective area of focus to ensure a greater number of patients meet their LDL-C targets.

Limitations

The single centre, retrospective design of this study poses several limitations. As there was no systematic protocol in

place for the assessment and recording of LLT compliance or side effects, it is not clear to what degree this may have influenced DL-C target achievement or choice of LLT. Additionally, this may have led to misclassification bias for those who were non-compliant. The sample sizes of the 2016 and 2019 cohorts are unequal, due to the suspension of CR services in Jan. 2020 as a result of the COVID-19 pandemic, which may reduce the statistical power of the study. Information regarding baseline LDL-C, and LLT was missing for a proportion of patients, which may have confounded our results. While a rapid implementation of new ESC guidelines within the CR unit was confirmed, the present study cannot account for improvements in practice that may arise due to increased familiarity practicing within these guidelines. Estimates for the 'predicted required LLT' are based on the average LDL-C lowering effects of each LLT as outlined by the ESC and do not account for the between-person variability of treatment effect.

Conclusion

With the introduction of lower absolute LDL-C targets and the additional requirement for a reduction in LDL-C levels > 50% from baseline, fewer patients attending CR are meeting the LDL-C targets set out in the 2019 ESC dyslipidaemia guidelines. LDL-target achievement following CR in our centre compares favourably with international standards of usual primary or secondary care, and patients likely benefit from specialist input. Both high intensity statin therapy and ezetimibe are under prescribed. Of the minority of patients likely to require PCSK9i combination therapy to meet their LDL-C targets, none currently qualify for reimbursement in Ireland.

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Author contribution All the authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Conor McCaughey, Deepti Ranganathan, Mary Keirins and Gregory Murphy. The first draft of the manuscript was written by Conor McCaughey, and all the authors commented on the previous versions of the manuscript. All the authors read and approved the final manuscript.

Declarations

The requirement for ethical review was waived by the St James Hospital Institutional Review Board (Research and Innovation approval number ref: 6562) due to the retrospective nature of the study and the processing of data in line with routine quality and improvement. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest Not applicable.

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