www.directivepublications.org

Journal of Cardiovascular Diseases

ISSN 2831-3437

Research Article

Use of Bempedoic Acid in an Out-Patient Setting: an Assessment of Efficacy Heterogeneity.

Amro Maarouf[1], Manjit K Shergill[1], Alan F Jones[1], John Marriott[2], Sudarshan Ramachandran[1].

[1] *Department of Clinical Biochemistry, University Hospitals Birmingham NHS Foundation Trust, West Midlands, United Kingdom.*

[2] *Institute of Clinical Sciences, University of Birmingham, Birmingham, United Kingdom.*

Running title: *Assessment of bempedoic acid efficacy heterogeneity.*

Abstract

Objectives: We describe decreases in total cholesterol (TC), non-high density lipoprotein-cholesterol (non-HDL-C) and low density lipoprotein-cholesterol (LDL-C) following bempedoic acid treatment in an out-patient setting and compare the results to those observed in phase 3 efficacy trials.

Design: We analysed a cohort of 113 patients not achieving LDL-C targets commenced on bempedoic acid after previous treatment with statins and ezetimibe using an intention-to-treat approach.

Methods: We compared pre and post bempedoic acid treatment lipids (3-months) in the total cohort using paired t-tests. Baseline patient characteristics associated with LDL-C decrease was established via linear/multiple regression analyses.

Results: Following bempedoic acid treatment absolute reduction (mean ± SD) in TC, non-HDL-C, and LDL-C values were 1.1 ± 1.0mmol/L, 1.0 ± 1.0mmol/L, and 1.0 ± 0.9mmol/L, respectively, whilst percentage reductions (mean ± SD) were 16.4 ± 14.1%, 18.8 ± 17.2%, and 23.2 ± 20.5%, respectively. Significant decreases in lipids were observed in every subgroup studied. The LDL-C decrease following bempedoic acid was independently greater in ex-smokers, individuals on ezetimibe at baseline, and those with higher baseline LDL-C values.

Conclusions: Our results show that the LDL-C decrease seen with bempedoic acid was comparable to that observed in the phase 3 (CLEAR) efficacy trials. However, efficacy heterogeneity was observed in some of the subgroups studied such as patients on ezetimibe monotherapy or with higher LDL-C at baseline, the latter in accordance with the Wilder principle. The use of effect scores for identified patient subgroups might predict treatment response, enabling optimisation of lipid lowering efficacy.

Keywords: Bempedoic acid, cardiovascular disease, hypercholesterolaemia, low density lipoprotein cholesterol, Wilder principle.

INTRODUCTION

The World Health Organisation in 2021 estimated that atherogenic cardiovascular disease (CVD) annually accounted for around 17.9 million deaths [1]. Many prospective studies have shown dyslipidaemia to be a predictive factor of CVD [2]. Low density lipoprotein-cholesterol (LDL-C) lowering has been an important aspect of CVD risk reduction strategy since the pivotal Scandinavian Simvastatin Survival Study in 1994 [3], this based on the lipid hypothesis [2,4]. The Cholesterol Treatment Trialist' (CTT) collaboration analysed 5 trials including 39,612 patients which compared greater vs lesser efficacious statins and, 21 trials including 129,526 patients which compared statins vs placebo [5]. When the results of all 26 randomised controlled trials (RCT) were pooled, a 1.0 mmol/L LDL-C reduction was associated with a 22% relative risk reduction (RRR) of CVD (Rate Ratio (RR) = 0·78, 95% Confidence Interval (CI) = (0.76, 0.80); p<0·0001) [5]. Additionally non-statin lipid lowering agents such as ezetimibe and Proprotein Convertase Subtilisin/Kexin Type-9 (PCSK9) inhibitors [2] have been shown to lower CVD in accordance with the findings of the CTT collaboration [5].

The Dyslipidaemia/Metabolic clinics run by the University Hospitals Birmingham NHS Foundation Trust have used the LDL-C targets set by the European Society of Cardiology and European Atherosclerosis Society since 2019 [6]. The current treatment pathway used in our clinics to reduce LDL-C include statins, ezetimibe, bempedoic acid (prescribed since October 2020), PSCK9 inhibitors (prescribed since 2016) and inclisiran (prescribed since 2022). Bempedoic acid inhibits adenosine

***Corresponding Author:** **Sudarshan Ramachandran,** Department of Clinical Biochemistry, University Hospitals Birmingham NHS Foundation Trust, Good Hope Hospital, Rectory Road, Sutton Coldfield, West Midlands B75 7RR, United Kingdom. **Tel:** +44-121-424 7246, **Fax:** +44-121-311 1800, **Email:** sud.ramachandran@uhb.nhs.uk, **Orcid:** https://orcid.org/0000-0003-2299-4133.

Received: 18-October-2025, Manuscript No. JOCD-5198 **; Editor Assigned:** 21-October-2025 **; Reviewed:** 03-November-2025, QC No. JOCD-5198 **; Published:** 13-November-2025, **DOI:** 10.52338/jocd.2025.5198.

Citation: Sudarshan Ramachandran. Use of bempedoic acid in an out-patient setting: an assessment of efficacy heterogeneity. Journal of Cardiovascular Diseases. 2025 November; 14(1). doi: 10.52338/jocd.2025.5198.

triphosphate (ATP) citrate lyase, an enzyme found upstream of HMG-CoA reductase, resulting in reduced availability of Acetyl-CoA for hepatic synthesis of cholesterol [7]. Moreover, bempedoic acid is a prodrug requiring hepatic activation by very long chain-chain acyl-CoA synthetase 1 (ACSVL1) and since this enzyme is not found in skeletal muscle, bempedoic acid is less likely to cause myotoxicity, potentially offering an alternative therapeutic strategy in patients not reaching the assigned LDL-cholesterol targets because of statin discontinuation or dose reduction [7-10]. The Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) study programme comprising 4 RCTs (CLEAR Serenity, CLEAR Tranquillity, CLEAR Wisdom and CLEAR Harmony) evaluated lipid lowering efficacy and safety of bempedoic acid [9,11-13]. The mean LDL-C decreases in the treatment (bempedoic acid) arms after 12-weeks ranged between 15% and 24% (CLEAR Serenity - 24%, baseline LDL-C = 4.1mmol/L, CLEAR Tranquillity - 24%, baseline LDL-C = 3.3mmol/L, 15%, CLEAR Wisdom - baseline LDL-C = 3.1mmol/L, and CLEAR Harmony - 17%, baseline LDL-C = 2.7mmol/L) [10]. The CLEAR Outcomes RCT including 13,970 (6992 - bempedoic acid, 6978 – placebo) patients at high CVD risk with a median follow-up of 40.6 months, showed bempedoic acid being associated with significantly (hazard ratio = 0.87, 95% CI = (0.79, 0.96), p=0.004) lower major adverse cardiovascular events; a composite of death from CVD, non-fatal myocardial infarction and non-fatal stroke or coronary revascularisation [14].

Bempedoic acid was made available to the Dyslipidemia/ Metabolic clinics at Good Hope and Birmingham Heartlands Hospitals (part of University Hospitals Birmingham NHS Foundation Trust) between 01.10.2020 and 28.04.2021, prior to the National Institute for Health and Care Excellence (NICE) technology appraisal guidance (TAG) being published [15] via a pre-reimbursement access scheme. The aim of this audit was to evaluate the efficacy of bempedoic acid in the total cohort and selected subgroups, comparing against the efficacy observed in the CLEAR RCTs [9,11-14] as well as establish predictors of LDL-C change that may account for efficacy heterogeneity.

MATERIALS AND METHODS

This study is part of an ongoing lipid clinic audit programme carried out by the Department of Clinical Biochemistry at Good Hope and Birmingham Heartlands Hospitals (University of Birmingham NHS Foundation Trust) to evaluate the efficacy of lipid lowering agents. Previously, audits on fibrates, statins, and ezetimibe and PCSK9 inhibitor therapy had been completed and published [16-21]. More recently, our group were part of a UK wide multicenter audit that assessed treatment efficacy of bempedoic acid [22]. Approval for the current audit was received from University Hospitals Birmingham NHS Foundation Trust (Ref: CARMS-17932). A list of all 113 patients started on bempedoic acid between 01.10.2020 and 28.04.2021 had been maintained and clinical and lipid profile data were obtained from the hospital electronic patient records. The mean age ± standard deviation (SD) of the 113 patients started on bempedoic acid was 62.5 ± 10.6 years. All patients commenced on bempedoic acid had not achieved their LDL-C targets based on the guidelines adopted by the clinics [6]. Statin intolerance was evident in 100 (88.5%) of the patients. The cohort characteristics regarding sex, ethnicity, diabetes/smoking/CVD status, details of ongoing lipid lowering therapy and baseline LDL-C are shown in Table 1. All patients attended the consultant led specialist Dyslipidemia/ Metabolic Clinics (a minimum of 4 clinics/week) carried out at Good Hope Hospital (consultant: SR) and Birmingham Heartlands Hospital (consultant: AFJ) taking referrals from primary care mainly in the West Midlands, Staffordshire, and Warwickshire (counties in the Midlands of the UK) as well as secondary care (Cardiology, Stroke and Vascular Medicine). It was usual practice to initially establish LDL-C targets based on evidence and guidelines and then decide on the treatment pathway [6]. The clinics would usually consider statins initially, considering pharmacokinetic characteristics of the drug. Atorvastatin would usually be first line with rosuvastatin substituted in intolerant patients. If both statins led to clinical adverse effects, simvastatin, pravastatin and fluvastatin were considered. Ezetimibe was initiated as second line in patients not achieving LDL-C targets. Following statins and ezetimibe, other lipid lowering agents such as PCSK9 inhibitors (depending on funding requirements being met) [20,21] or bempedoic acid would be commenced. Fibrates were used mainly in patients with hypertriglyceridemia [16-19]. Statin and ezetimibe (both these agents would have been usually tried prior to the initiation of bempedoic acid) intolerance was high as shown in Table 1; only 25 (22.1%) patients were on a statin/ezetimibe combination when bempedoic acid was initiated. This could have been due to bempedoic acid being commenced only in patients not achieving LDL-C targets, thus our cohort would arguably demonstrate high statin and ezetimibe intolerance.

Within the audit period, 41 (36.3%) of the patients discontinued bempedoic acid and a lipid profile check/clinic appointment was arranged as soon as possible. In the 72 (63.7%) individuals continuing bempedoic acid, lipid profiles at or close to 12-weeks post-bempedoic acid initiation were conducted just prior to the follow-up appointment. The median (inter quartile range) follow-up was 3.3 (2.3 - 5.1) months. No other changes to lipid lowering therapy took place during the audit period. Total cholesterol (TC), HDL-C and triglycerides (TG) measurements were carried out on the Abbott Alinity c system using the supplied kit reagents. LDL-C was calculated via the Friedwald algorithm [23], as was the

case in the CLEAR RCTs [9,11,13]. Analytical performance of the Abbott Alinity c system has previously been extensively evaluated and reported [24,25].

Statistical analysis

Baseline TC, non-HDL-C and LDL-C were normally distributed (skewness kurtosis test, p>0.05), hence paired and unpaired t-tests were used to compare intra- and intergroup changes in TC, non-HDL-C and LDL-C following bempedoic acid in the total cohort and subgroups stratified by baseline characteristics. Statistical analyses were performed on the entire cohort and not just on the individuals who continued with the treatment. No differences (p>0.05, using logistic regression) in baseline characteristics were observed between individuals continuing or stopping bempedoic acid regarding sex, ethnicity, diabetes/smoking/CVD status, ongoing lipid lowering therapy and LDL-C.

1. Comparison of pre and post bempedoic acid lipid values: Paired t-tests were used to determine if changes in TC, non-HDL-C and LDL-C were significant in the total cohort and subgroups stratified by sex, ethnicity, diabetes/smoking/CVD status, ongoing lipid lowering therapy, and baseline LDL-C levels stratified by the median value of 3.65mmol/L.

2. Factors associated with LDL-C changes following bempedoic acid treatment: Linear regression analysis was performed to establish factors that predicted LDL-C decrease, and all the significant independent variables were included in a single multivariate regression model. For non-continuous independent variables, a single characteristic of the variable was chosen as the reference category and the other characteristics of that variable were compared to the reference category (factorisation) regarding associations with the selected dependent variable. Stata version 14 (College Station, TX) was used for all the statistical analysis.

RESULTS

Bempedoic acid treatment led to a significant decrease (paired t-test) in TC, non-HDL-C and LDL-C in the total cohort and the various subgroups as shown in **Table 1**. The principal analyses were conducted on an intention-to-treat basis, hence the efficacy values seen in **Table 1** could be considered conservative as indicated by the decreases in TC, non-HDL-C and LDL-C (mean ± SD) being significantly lower (TC = 0.8 ± 0.8, n=39, non-HDL-C = 0.7 ± 0.8, n=38, LDL-C = 0.7 ± 0.9, n=37) in the individuals discontinuing bempedoic acid compared to their counterparts (TC = 1.3 ± 1.0, n=71, non-HDL-C = 1.2 ± 1.0, n=70, LDL-C = 1.2 ± 0.8, n=68) who continued the medication; unpaired t-test: p<0.0034, 0.0099, and 0.0034 for changes in TC, non-HDL-C, and LDL-C, respectively.

Table 1. Changes in TC, non-HDL-C and LDL-C following bempedoic acid in the total cohort and patients stratified by baseline characteristics.

Patient groups	Pre-bempedoic acid (mean ± SD)			Post-bempedoic acid (mean ± SD)			Decrease in lipids (mean ± SD), (n), p (paired t-test)		
	TC (mmol/L)	Non-HDL-C (mmol/L)	LDL-C (mmol/L)	TC (mmol/L)	Non-HDL-C (mmol/L)	LDL-C (mmol/L)	TC (mmol/L)	Non-HDL-C (mmol/L)	LDL-C (mmol/L)
Total cohort	**6.2 ± 1.5 (n=113)**	**4.8 ± 1.5 (n=111)**	**3.9 ± 1.3 (n=111)**	**5.1 ± 1.1 (n=110)**	**3.8 ± 1.1 (n=110)**	**2.9 ± 1.6 (n=106)**	**1.1 ± 1.0 (n=110), p<0.0001**	**1.0 ± 1.0 (n=108), p<0.0001**	**1.0 ± 0.9 (n=105), p<0.0001**
Stratification by baseline discrete variables									
Sex									
Males	5.9 ± 1.6 (n=35)	4.8 ± 1.6 (n=33)	3.7 ± 1.3 (n=33)	4.8 ± 1.1 (n=33)	3.8 ± 1.1 (n=33)	2.7 ± 0.9 (n=31)	1.2 ± 0.9 (n=33), p<0.0001	1.1 ± 0.8 (n=31), p<0.0001	1.0 ± 0.8 (n=30), p<0.0001
Females	6.3 ± 1.5 (n=78)	4.9 ± 1,5 (n=78)	3.9 ± 1.3 (n=78)	5.2 ± 1.1 (n=77)	3.9 ± 1.2 (n=77)	3.0 ± 1.1 (n=75)	1.1 ± 1.0 (n=77), p<0.0001	1.0 ± 1.0 (n=77), p<0.0001	1.0 ± 0.9 (n=75), p<0.0001
Ethnicity									
White caucasian	6.2 ± 1.5 (n=86)	4.9 ± 1.4 (n=85)	3.9 ± 1.3 (n=85)	5.1 ± 1.1 (n=83)	3.7 ± 1.1 (n=83)	2.8 ± 1.0 (n=80)	1.2 ± 1.0 (n=83), p<0.0001	1.1 ± 1.0 (n=82), p<0.0001	1.1 ± 0.9 (n=80), p<0.0001
Non-white caucasian	6.2 ± 1.7 (n=27)	4.8 ± 1.8 (n=26)	3.9 ± 1.5 (n=26)	5.2 ± 1.2 (n=27)	4.1 ± 1.4 (n=27)	3.2 ± 1.2 (n=26)	1.0 ± 0.9 (n=27), p<0.0001	0.8 ± 0.8 (n=26), p<0.0001	0.7 ± 0.7 (n=25), p=0.0001
Diabetes status									
T2DM	6.0 ± 1.9 (n=19)	4.6 ± 1.8 (n=19)	3.7 ± 1.6 (n=19)	4.8 ± 1.5 (n=18)	3.6 ± 1.4 (n=18)	2.7 ± 1.3 (n=18)	1.2 ± 1.1 (n=18), p=0.0004	1.0 ± 1.0 (n=18), p=0.0005	1.0 ± 0.9 (n=18), p=0.0002
No T2DM	6.3 ± 1.4 (n=94)	4.9 ± 1.4 (n=92)	3.9 ± 1.3 (n=92)	5.2 ± 1.0 (n=92)	3.9 ± 1.1 (n=92)	2.9 ± 1.0 (n=88)	1.1 ± 1.0 (n=92), p<0.0001	1.0 ± 0.9 (n=90), p<0.0001	1.0 ± 0.9 (n=87), p<0.0001

Smoking status									
Non-smokers	6.2 ± 1.5 (n=80)	4.8 ± 1.5 (n=79)	3.9 ± 1.3 (n=79)	5.2 ± 1.0 (n=77)	3.9 ± 1.2 (n=77)	3.0 ± 1.1 (n=73)	1.0 ± 1.0 (n=77), p<0.0001	0.9 ± 1.0 (n=76), p<0.0001	0.9 ± 0.9 (n=73), p<0.0001
Ex-smokers	5.8 ± 1.7 (n=16)	4.5 ± 1.6 (n=16)	3.5 ± 1.3 (n=16)	4.6 ± 1.1 (n=16)	3.7 ± 1.0 (n=16)	2.3 ± 0.8 (n=16)	1.2 ± 1.0 (n=16), p=0.0003	1.1 ± 0.9 (n=16), p=0.0002	1.2 ± 1.0 (n=16), p=0.0003
Current-smokers	6.8 ± 1.3 (n=17)	5.4 ± 1.3 (n=16)	4.3 ± 1.1 (n=16)	5.2 ± 1.2 (n=17)	4.0 ± 1.2 (n=17)	3.0 ± 1.0 (n=17)	1.6 ± 1.0 (n=17), p<0.0001	1.5 ± 0.9 (n=16), p<0.0001	1.4 ± 0.7 (n=16), p<0.0001
CVD status									
Primary prevention	6.5 ± 1.4 (n=93)	5.1 ± 1.5 (n=91)	4.1 ± 1.3 (n=91)	5.3 ± 1.0 (n=90)	4.0 ± 1.1 (n=90)	3.0 ± 1.0 (n=86)	1.2 ± 1.0 (n=90), p<0.0001	1.1 ± 1.0 (n=88), p<0.0001	1.1 ± 0.9 (n=85), p<0.0001
Secondary prevention	4.8 ± 1.0 (n=20)	3.7 ± 1.0 (n=20)	2.8 ± 0.9 (n=20)	4.1 ± 0.9 (n=20)	3.0 ± 0.9 (n=20)	2.1 ± 0.9 (n=20)	0.7 ± 0.9 (n=20), p=0.0013	0.7 ± 0.8 (n=20), p=0.0030	0.7 ± 0.8 (n=20), p=0.0010
Ongoing lipid lowering agents									
None	7.0 ± 1.4 (n=37)	5.6 ± 1.4 (n=36)	4.5 ± 1.3 (n=36)	5.7 ± 1.1 (n=37)	4.5 ± 1.1 (n=37)	3.4 ± 1.1 (n=37)	1.2 ± 1.0 (n=37), p<0.0001	1.1 ± 1.0 (n=36), p<0.0001	1.1 ± 0.9 (n=36), p<0.0001
Ezetimibe	6.3 ± 1.1 (n=24)	4.8 ± 1.1 (n=24)	3.8 ± 1.1 (n=23)	4.8 ± 0.9 (n=22)	3.5 ± 0.9 (n=22)	2.4 ± 9.8 (n=19)	1.5 ± 1.0 (n=22), p<0.0001	1.3 ± 0.9 (n=22), p<0.0001	1.4 ± 0.9 (n=19), p<0.0001
Statins and Ezetimibe	5.3 ± 1.4 (n=25)	4.0 ± 1.4 (n=24)	3.2 ± 1.1 (n=25)	4.6 ± 0.8 (n=25)	3.3 ± 0.8 (n=25)	2.6 ± 0.8 (n=25)	0.7 ± 0.9 (n=25), p=0.0014	0.6 ± 1.0 (n=24), p=0.0036	0.6 ± 0.8 (n=25), p=0.0017
Statins	6.0 ± 1.7 (n=27)	4.6 ± 1.6 (n=27)	3.7 ± 1.4 (n=27)	4.9 ± 1.2 (n=26)	3.7 ± 1.2 (n=26)	2.8 ± 1.1 (n=25)	1.1 ± 1.1 (n=26), p<0.0001	1.0 ± 0.9 (n=26), p<0.0001	0.9 ± 0.7 (n=25), p<0.0001
Stratification by median LDL-C (3.65mmol/L)									
LDL-C < 3.65mmol/L	5.0 ± 0.9 (n=56)	3.7 ± 0.8 (n=55)	2.8 ± 0.4 (n=56)	4.4 ± 0.8 (n=54)	3.2 ± 0.8 (n=54)	2.3 ± 0.8 (n=53)	0.6 ± 0.7 (n=54), p<0.0001	0.5 ± 0.7 (n=53), p<0.0001	0.5 ± 0.6 (n=52), p<0.0001
LDL-C ≥ 3.65mmol/L	7.4 ± 1.1 (n=55)	6.0 ± 1.1 (n=55)	4.9 ± 0.9 (n=55)	5.7 ± 1.0 (n=54)	4.5 ± 1.0 (n=54)	3.5 ± 0.9 (n=52)	1.7 ± 1.0 (n=54), p<0.0001	1.5 ± 0.9 (n=54), p<0.0001	1.5 ± 0.8 (n=53), p<0.0001

Table 2 shows subgroups based on baseline characteristics that predicted bempedoic acid efficacy (change in LDL-C) using separate linear regression models; ex-smokers (compared to non-smokers) – Model 5, statin monotherapy (compared to those on ezetimibe monotherapy) Model 7, and lower levels of LDL-C that were significantly associated with decreased LDL-C lowering – Models 8 & 9. The LDL-C decrease was greater (coefficient (c) = 0.46, 95% CI = (0.0222, 0.89), p=0.040) in individuals on ezetimibe monotherapy compared to the remaining participants (no lipid lowering therapy, statin monotherapy and statin and ezetimibe treated) combined as the reference group. In view of the above findings, we did not study efficacy in the patient cohort stratified by single, dual, or triple therapies. When the patients were stratified by the median baseline LDL-C value of 3.65mmol/L, patients with LDL-C ≥3.65mmol/L were associated with a significantly greater LDL-C decrease than individuals with LDL-C <3.65mmol/L (reference) – Model 9.

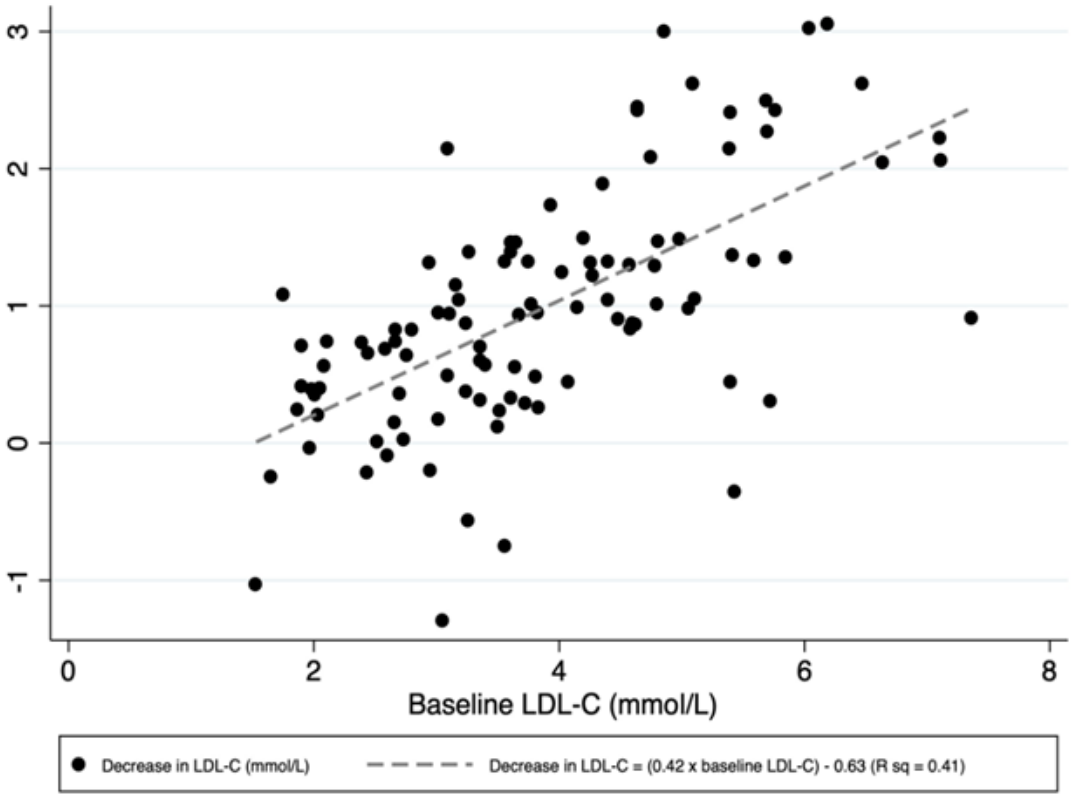
Multiple regression analysis (Model 10) with LDL-C decrease as the dependent variable was then performed with baseline LDL-C, smoking status and lipid lowering therapy at baseline included as independent variables, i,e. factors that reached statistical significance in Models 1-8. LDL-C stratified by the median were omitted and LDL-C was used as a continuous variable. Higher baseline LDL-C, ex-smokers and ezetimibe monotherapy independently showed significantly greater LDL-C reduction following bempedoic acid treatment – Model 10. Months of follow-up was not associated with LDL-C change (c=0.037, 95% CI = (-0.051, 0.13), p=0.40). We could not carry out meaningful statistics in patients with higher than median LDL-C and ezetimibe monotherapy at baseline in view of modest patient numbers (9 patients); LDL-C decrease (mean ± SD): 1.9 ± 0.8mmol/L.

Table 2: Baseline factors associated with LDL-C decrease in patients treated with bempedoic acid; individual factors analysed via linear regression models (1-9) followed by a multiple regression model (10) including all significant factors from the earlier models.

Independent Variable	Dependent variable (outcome): decrease in LDL-C (mmol/L)		
(at baseline)	**Model**	**c (95% CI), p**	**R-squared**
Age (years)	Model 1	-0.0042 (-0.021, 0.012), p=0.61	0.00
Males Females	Model 2	0.073 (-0.31, 0.45), p=0.70 reference	0.00
Non-white caucasians White caucasians	Model 3	-0.25 (-0.77, 0.27), p=0.34 reference	0.01
T2DM No T2DM	Model 4	-0.0096 (-0.46, 0.44), p=0.97 reference	0.00
Current smokers Ex-smokers Non-smokers	Model 5	0.32 (-0.16, 0.79), p=0.19 0.52 (0.048, 1.00), p=0.031 reference	0.05
Secondary prevention Primary prevention	Model 6	-0.39 (-0.82, 0.042), p=0.079 reference	0.30
No lipid lowering agents Statin monotherapy Statins and ezetimibe Ezetimibe monotherapy	Model 7	-0.23 (-0.71, 0.25(, p=0.34 -0.79 (-1.30, -0.27), p=0.003 -0.46 (-0.97, 0.054), p=0.079 reference	0.10
LDL-C (mmol/L)	Model 8	0.42 (0.32, 0.52), p<0.001	0.41
LDL-C ≥ 3.65mmol/L LDL-C < 3.65mmol/L	Model 9	0.99 (0.71, 1.27), p<0.001 reference	0.32
Multiple regression model including significant independent variable from Models 1 - 9.			
LDL-C (mmol/L) Current smokers Ex-smokers Non-smokers No lipid lowering agents Statin monotherapy Statins and ezetimibe Ezetimibe monotherapy	Model 10	0.43 (0.33, 0.54), p<0.001 0.27 (-0.083, 0.63), p=0.13 0.48 (0.12, 0.83), p=0.009 reference -0.51 (-0.88, -0.14), p=0.007 -0.46 (-0.86, -0.068), p=0.022 -0.43 (-0.82, -0.042), p=0.030 reference	0.50

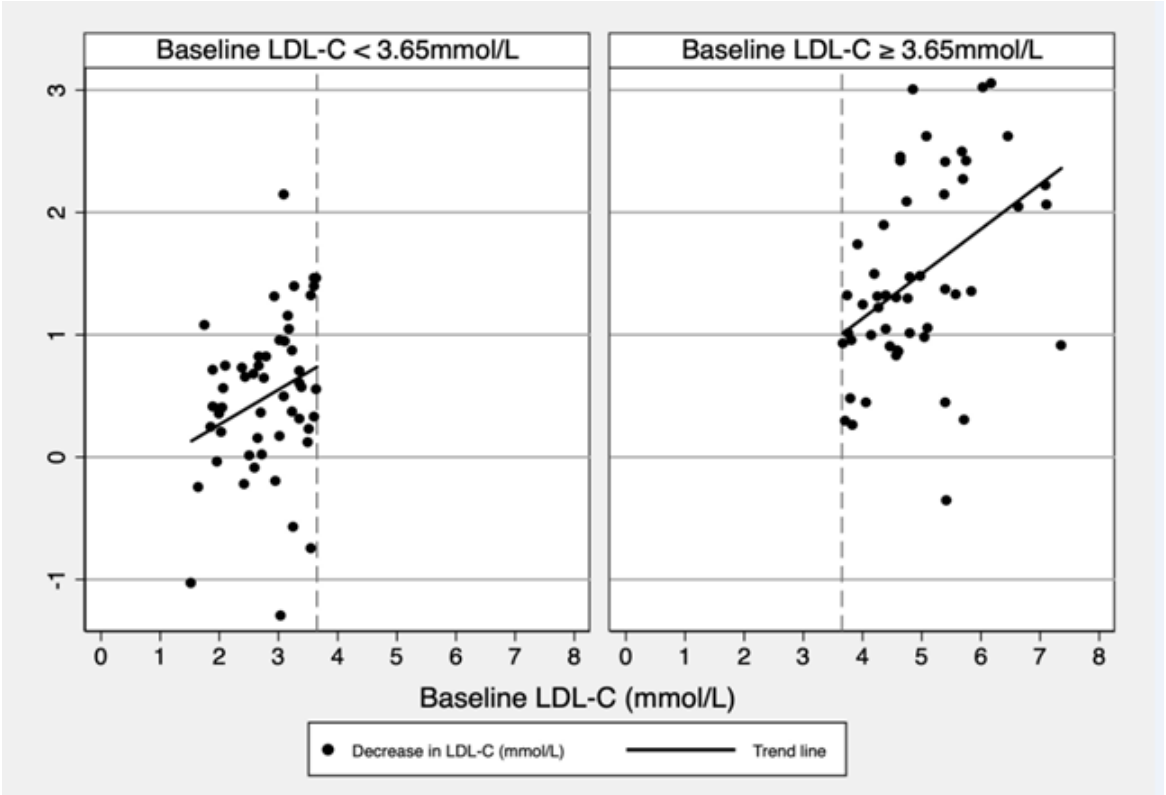
Models 8 and 9 (**Table 2**) indicated that pre-treatment LDL-C values were associated with LDL-C decrease following bempedoic acid initiation; higher baseline LDL-C concentrations were related to greater LDL-C decreases. This is evident in **Figure 1** where LDL-C (x-axis) was plotted against the decrease in LDL-C (y-axis) following bempedoic acid treatment. We then wished to determine whether these effects were due to a fixed percentage decrease in LDL-C following bempedoic acid therapy (this could also show the above pattern). Importantly, baseline LDL-C was also significantly associated with percentage changes in LDL-C (c=4.92, 95% CI = (2.11, 7.74), p=0.001). Baseline LDL-C was also associated with a change in LDL-C when the patients were stratified by the median LDL-C of 3.65mmol/L (**Figure 2** and footnote). This was followed by further study of the association (**Table 3**) between baseline LDL-C (independent variable) and change in LDL-C (dependent variable) using linear regression models. **Table 3** shows that change in LDL-C was also evident for all of the subgroups stratified by the other baseline characteristics, apart from current smokers (p=0.057, n=16). Interestingly, baseline LDL-C was significantly associated with bempedoic acid related LDL-C decrease in, both patients who tolerated the drug (c=0.47, 95% CI = (0.36, 0.58), p<0.001, n=68) and those who discontinued it (c=0.35, 95% CI = 0.19, 0.52), p<0.001, n=37).

Figure 1. A plot of the association between baseline LDL-C and the decrease in LDL-C following bempedoic acid.



Footnote: The trend-line is based on the regression analysis seen in Model 8 (Table 2)

Figure 2. A plot of the association between baseline LDL-C and the decrease in LDL-C following bempedoic acid in patients stratified by the median baseline LDL-C (3.65mmol/L).



Footnote: Regression analyses (dependent variable: decrease in LDL-C (mmol/L), independent **variable:** baseline LDL-C (mmol/L)
LDL-C < 3.65mmol/L: c=0.29, 95% CI = (0.0045, 0.57), p=0.047, n=53
LDL-C ≥ 3.65mmol/L: c=0.37, 95% CI = (0.14, 0.59), p=0.002, n=52

Table 3. Associations between baseline LDL-C and decrease in LDL-C carried out via linear regression in the various patient subgroups stratified by baseline characteristics.

Linear regression models (LDL-C vs decrease in LDL-C) in subgroups		
(at baseline)	**c (95% CI), p**	**n**
Males	0.46 (0.32, 0.60), p<0.001	30
Females	0.40 (0.28, 0.53), p<0.001	75
Non-white caucasians	0.30 (0.13, 0.46), p=0.001	25
White caucasians	0.47 (0.35, 0.58), p<0.001	80
T2DM	0.31 (0.068, 0.56), p=0.016	18
No T2DM	0.45 (0.34, 0.56), p<0.001	87
Current smokers	0.32 (-0.011, 0.65), p=0.057	16
Ex-smokers	0.61 (0.36, 0.85), p<0.001	16
Non-smokers	0.40 (0.29, 0.51), p<0.001	73
Secondary prevention	0.39 (0.020, 0.76), p=0.040	20
Primary prevention	0.45 (0.34, 0.56), p<0.001	85
No lipid lowering agents	0.40 (0.19, 0.61), p<0.001	36
Statin monotherapy	0.32 (0.17, 0.48), p<0.001	25
Statins and ezetimibe	0.52 (0.30, 0.74), p<0.001	25
Ezetimibe monotherapy	0.57 (0.28, 0.86), p=0.001	19

DISCUSSION

This was a real-world study of 113 out-patients treated with bempedoic acid prior to the NICE TAG in April 2021.

Comparison of outcomes with previous RCTs

Following bempedoic acid treatment, absolute reduction (mean ± SD) in TC, non-HDL-C, and LDL-C values were 1.1 ± 1.0mmol/L, 1.0 ± 1.0mmol/L, and 1.0 ± 0.9mmol/L, respectively, whilst percentage reductions (mean ± SD) were 16.4 ± 14.1%, 18.8 ± 17.2%, and 23.2 ± 20.5%, respectively. The mean LDL-C reduction in the present study was similar to the mean decreases observed in the CLEAR Tranquility (24%) and CLEAR Serenity (24%) treatment arms and higher than in the CLEAR Wisdom (15%) and CLEAR Harmony (17%) treatment arms [10]. This could be due to baseline characteristics (including baseline LDL-C values and co-therapies) as seen in Table 2 leading to efficacy heterogeneity. Our findings, if validated, suggest that an understanding of cohort characteristics is essential to interpret differences in study outcomes.

Significant decreases in the lipid values were observed in every subgroup that we studied (Table 1). LDL-C reduction is currently the cornerstone of lipid lowering regarding CVD prevention [2,4,6]. The results from the CTT collaboration suggests a RRR in CVD of 22% per 1mmol/L decrease in LDL-C [4,5]. The lipid hypothesis is based on agents such as resins, statins, ezetimibe, PCSK9 inhibitors and bempedoic acid use being associated with lowering of CVD [2,14]. Absolute risk reduction (ARR) is a function of absolute risk (AR) and RRR, hence we can hypothesize that bempedoic acid treatment in our patients tolerating the drug (mean ± SD = 1.2 ± 0.8mmol/L) would have yielded a significant ARR in CVD, especially in patients with high AR [4].

The LDL-C decrease following bempedoic acid was independently greater in certain subgroups; ex-smokers, individuals on ezetimibe at baseline, and those with higher baseline LDL-C values. We can offer no explanation for the increased bempedoic acid efficacy in ex-smokers. Smoking cessation, whilst increasing HDL-C levels does not appear to change LDL-C values [26.27]. The LDL-C lowering efficacy of bempedoic appeared greater in patients on ezetimibe monotherapy compared to individuals not on lipid lowering agents, statin monotherapy and statin/ezetimibe combination (Table 2). We speculate that this could be due to ezetimibe up-regulating cholesterol synthesis [28]. Sudhop et al. demonstrated that cholesterol synthesis significantly increased by 89% in patients on ezetimibe [28]. Since bempedoic acid acts to decrease cholesterol synthesis by inhibiting ATP citrate lyase [7], it is feasible that the LDL-C lowering efficacy of the drug could perhaps be greater in individuals with an increased rate of cholesterol synthesis. The rate of synthesis would be reduced when statins are added to ezetimibe, hence the LDL-C lowering efficacy of bempedoic acid would perhaps be attenuated in patients also on statin and ezetimibe [29].

Impact of the Wilder Effect (principle of initial value)

Baseline LDL-C values were associated with both an absolute and percentage change in LDL-C following bempedoic acid treatment (higher baseline LDL-C led to greater decrease in LDL-C). The association between baseline LDL-C and change in LDL-C is in accordance with the Wilder principle which suggests that the response to an intervention is dependent on the baseline values [31]. It was also observed in most of the subgroups (Table 3). Previous audits from our centre have also demonstrated this phenomenon [16,18,19]. This

observation has clinical significance as high LDL-C levels are associated with greater AR of CVD and a more pronounced LDL-C reduction would lead to increased RRR [4]. Thus, ARR is perhaps even greater in patients with high baseline LDL-C values. As percentage decrease in LDL-C was also associated with baseline LDL-C, it is likely that it is a real effect and not a statistical abberation, although potential mechanisms have not been elucidated.

Strengths and weaknesses

There are a range of strengths and weaknesses in the present study. It was a real-world single arm longitudinal study with a small sample size with relatively short follow-up. This study contributed 113 patients to a national audit including 221 patients commenced on bempedoic acid which assessed the attainment of lipid targets [22]. The mean efficacy results from the multi-center audit were identical to that observed in our audit; TC: -1.1mmol/L, Non-HDL-C: -1.0mmol/L and LDL-C: -1.0mmol/L. However, these results would have been influenced by our efficacy as our study group (113 patients) comprised nearly half (51.1%) of the multi-center audit cohort of 221 patients.

In this analysis we studied efficacy patterns prior to the NICE TAG being issued (which introduced extra selection criteria such as statin intolerance as a pre-requisite) as this would have introduced selection bias [15]. Thus, all patients started on bempedoic acid were included with no sample size calculation based on previously reported efficacy. The take up rate over a near 7-month period may be considered slow for a new pharmaceutical agent; the coronavirus lockdowns in the UK could have had an impact (https://www.instituteforgovernment.org.uk/sites/default/files/timeline-lockdown-web.pdf). The CLEAR Outcomes trial was also conducted during the COVID-19 pandemic and the excess mortality observed during this period, attributed to cardiovascular death, may have blunted the effect of bempedoic acid on primary cardiovascular endpoints [30]. However, in our study, the intention was to compare the lipid lowering results with published efficacy outcomes at 3 months. Regression towards the mean is possible, although the observed Wilder phenomenon may counter this [31]. The patient numbers were modest, as we wished to evaluate efficacy in patients not achieving LDL-C targets prior to the NICE technology assessment being published, as that could have reshaped the cohort characteristics. The small cohort affected the depth of subgroup analyses and study of interactions. We would have liked to study efficacy in patients with higher baseline LDL-C and ezetimibe monotherapy, but patient numbers were modest. Thus, it is essential to conduct a further study with a larger cohort and longer follow-up to verify the efficacy heterogeneity observed.

CONCLUSIONS

In summary, our findings demonstrated that mean reduction in LDL-C observed 12 weeks following bempedoic acid initiation was comparable to the reductions reported in the CLEAR Serenity and CLEAR Tranquility studies [9,11]. Novel findings emerging from this study include; i) Baseline characteristics predict likelihood of bempedoic acid efficacy, with those taking ezetimibe monotherapy observed to have greater reduction in LDL-C. This would underscore the therapeutic value of combination therapy with ezetimibe and bempedoic acid. ii) Higher pre-treatment LDL-C was associated with greater reduction in LDL-C in accordance with the Wilder principle; a phenomenon whereby the initial value determines, to a large extent, the magnitude of treatment response [31]. These findings need validation through further trials of larger cohort size, but the importance of heterogeneity of treatment effects is summed up in a recent publication by Wang et al [32]. They propose the use of model-derived predictions, so-called effect scores, relating to various patient subgroups to predict the likely treatment response [32]. It would be interesting if this approach was adopted to optimize lipid lowering efficacy of all the therapeutic agents prescribed, thus resulting in maximal CVD prevention.

Author contributions

Conception – SR, AM
Data collection – SR, AM, MKS
Analysis – SR, AM, JM
Manuscript preparation – SR, AM, MKS, JM, AFJ

Statements and declarations

Ethical considerations

Approval for the collection, analysis and publication of this retrospectively obtained data was received from University Hospitals Birmingham NHS Foundation Trust (Ref: CARMS-17932). Furthermore, since the data was anonymised, the Institutional Review Board Statement confirmed that no patient consent was required and therefore ethics approval was not needed.

Consent to participate

Not applicable

Consent for publication

Not applicable

Declaration of conflicting interest

SR has received research grants, travel grants and speakers' honoraria from Daiichi Sankyo UK Ltd

AM, MKS, AFJ and JM declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Funding statement

The authors received no financial support for the research, authorship, and/or publication of this article.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Cardiovascular diseases (CVDs) – World Health Organisation [online] 2021 https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1 (accessed 28.02.2024).

2. Ramachandran S, Bhartia M, König CS. The Lipid Hypothesis: From Resins to Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors. Front. Cardiovasc. Med. Volume 5. 2020 Oct 2;5:1-35.

3. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). The Lancet. 1994;344(8934):1383-9. doi.org/10.1016/S0140-6736(94)90566-5

4. König CS, Mann A, McFarlane R, Marriott J, Price M, Ramachandran S. Age and the Residual Risk of Cardiovascular Disease following Low Density Lipoprotein-Cholesterol Exposure. Biomedicines. 2023;11(12):3208. doi: 10.3390/biomedicines11123208.

5. Baigent C, Blackwell L, Emberson J et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. The Lancet. 2010;376(9753):1670-81. doi: 10.1016/S0140-6736(10)61350-5.

6. Mach F, Baigent C, Catapano AL et al. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019;290:140-205. doi: 10.1016/j.atherosclerosis.2019.08.014.

7. Strikic D, Begic Z, Radman I, Zlopasa F, Mateljic J, Zec I, Titlic M, Sliskovic AM, Pecin I, Reiner Z, Mercep I. Reshaping Dyslipidaemia Treatment with Bempedoic Acid-A Narrative Review. Biomedicines. 2025 Jun 13;13(6):1460. doi: 10.3390/biomedicines13061460.

8. Selva-O'Callaghan A, Alvarado-Cardenas M, Pinal-Fernández I et al. Statin-induced myalgia and myositis: an update on pathogenesis and clinical recommendations. Expert Rev Clin Immunol. 2018;14(3):215-24. doi: 10.1080/1744666X.2018.1440206.

9. Ballantyne CM, Banach M, Mancini GJ et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis. 2018;277:195-203. doi: 10.1016/j.atherosclerosis.2018.06.002.

10. Chaplin S. Bempedoic acid for primary hypercholesterolaemia. Prescriber. 2021;32(1):29-31.

11. Laufs U, Banach M, Mancini GJ et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc. 2019;8(7):e011662. doi: 10.1161/JAHA.118.011662.

12. Goldberg AC, Leiter LA, Stroes ES et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR wisdom randomized clinical trial. JAMA. 2019;322(18):1780-8 doi: 10.1001/jama.2019.16585.

13. Ray KK, Bays HE, Catapano AL et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med. 2019;380(11):1022-32. doi: 10.1056/NEJMoa1803917.

14. Nissen SE, Lincoff AM, Brennan D et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med. 2023;388(15):1353-64. doi: 10.1056/NEJMoa2215024.

15. National Institute for Health and Care Excellence (NICE). Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia. National Institute for Health and Care Excellence (NICE); 2021 ISBN-13:978-1-4731-4099-8.

16. Ramachandran S, Abbas A, Saraf S, Raju J, Jewkes C, Jones AF. Significant increase in high-density lipoprotein cholesterol with fibrates is associated with low pretreatment high-density lipoprotein cholesterol: findings from an outpatient clinic setting. Metab Syndr Relat Disord. 2012;10(3):189-94. doi: 10.1089/met.2011.0112.

17. Abbas A, Saraf S, Ramachandran S, Raju J, Ramachandran S. Fibrates and estimated glomerular filtration rate: observations from an outpatient clinic setting and

clinical implications. Postgrad Med J. 2012;88(1043):503-6. doi: 10.1136/postgradmedj-2011-130594.

18. Gandhi N, Lenton R, Bhartia M, Abbas A, Raju J, Ramachandran S. Effect of fibrate treatment on liver function tests in patients with the metabolic syndrome. Springerplus. 2014;3:1-7. doi: 10.1186/2193-1801-3-14.

19. Collins MW, König CS, Abbas A, Jewkes C, Jones AF, Ramachandran S. Association between triglyceride and high-density lipoprotein cholesterol change following fibrate therapy. Diabetes Metab Syndr. 2014;8(4):212-5. doi: 10.1016/j.dsx.2014.09.004.

20. Groves C, Shetty C, Strange RC, Waldron J, Ramachandran S. A study in high-risk, maximally pretreated patients to determine the potential use of PCSK9 inhibitors at various thresholds of total and LDL cholesterol levels. Postgrad Med J. 2017;93(1098):205-8. doi: 10.1136/postgradmedj-2016-134062.

21. Ramachandran S, Bhartia M, Jones A, Strange RC. PCSK9 Inhibitors in diabetic dyslipidaemia. RSSDI Diabetes Update 2018:374 - 378. Jaypee Brothers Medical Publishers Ltd (ISBN: 978-93-5270-618-1).

22. Ramachandran S, Maarouf A, Mitchell K, Avades T, Smith P, Boulton L et al. A UK multicentre audit of the management of patients with primary hypercholesterolaemia or mixed dyslipidaemia with bempedoic acid against published lipid-lowering treatment targets. Drugs Context. 2024;13: 2024-2-4. doi: 10.7573/dic.2024-2-4.

23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun 1;18(6):499-502. PMID: 4337382.

24. Westgard S, Petrides V, Schneider S, Berman M, Herzogenrath J, Orzechowski A. Assessing precision, bias and sigma-metrics of 53 measurands of the Alinity ci system. Clin Biochem. 2017;50(18):1216-21. doi: 10.1016/j.clinbiochem.2017.09.005.

25. Kanani FZ, Haider Kazmi A, Kaleem B. Sigma metrics of Alinity ci system–a study on thirty-nine clinical chemistry and immunoassay parameters. Adv Lab Med. 2021;2(2):267-75. doi: 10.1515/almed-2021-0001.

26. van der Plas A, Antunes M, Pouly S, de La Bourdonnaye G, Hankins M, Heremans A. Meta-analysis of the effects of smoking and smoking cessation on triglyceride levels. Toxicol Rep. 2023;10:367-75. doi: 10.1016/j.toxrep.2023.03.001.

27. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. Prev Med 2003;37(4):283-90. doi: 10.1016/s0091-7435(03)00110-5.

28. Sudhop T, Lütjohann D, Kodal A et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation. 2002;106(15):1943-8. doi: 10.1161/01.cir.0000034044.95911.dc.

29. Duan Y, Gong K, Xu S, Zhang F, Meng X, Han J. Regulation of cholesterol homeostasis in health and diseases: from mechanisms to targeted therapeutics. Signal Transduct Target Ther. 2022;7(1):265. doi: 10.1038/s41392-022-01125-5.

30. Singh A, Laffin LJ, Sarraju A, Michael Lincoff A, Nicholls SJ, Bloedon L, Sasiela WJ, Li N, Robinson P, Kelly S, Mason D, Nissen SE. Impact of the COVID-19 Pandemic on Conduct and Results of CLEAR Outcomes Trial. Clin Cardiol. 2024 Aug;47(8):e24328. doi: 10.1002/clc.24328.

31. Messerli FH, Bangalore S, Schmieder RE. Wilder's principle: pre-treatment value determines post-treatment response. Eur Heart J. 2015;36(9):576-9. doi: 10.1093/eurheartj/ehu467.

32. Wang G, Heagerty PJ, Dahabreh IJ. Using effect scores to characterize heterogeneity of treatment effects. JAMA. 2024;331(14):1225-6. doi: 10.1001/jama.2024.3376.