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ORIGINAL RESEARCH

A UK multicentre audit of the management of patients with primary hypercholesterolaemia or mixed dyslipidaemia with bempedoic acid▼ against published lipid-lowering treatment targets

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Abstract

Background: Bempedoic acid, an adenosine triphosphate citrate lyase inhibitor, was introduced to UK practice via a pre-reimbursement access scheme for adults with primary hypercholesterolaemia or mixed dyslipidaemia who are at high risk of cardiovascular disease, in whom statins are either not tolerated or contraindicated, who have not achieved target cholesterol, despite being on ezetimibe therapy, and do not qualify for PCSK9 inhibitor treatment. This retrospective multicentre audit aimed to evaluate the achievement of lipid-lowering targets with bempedoic acid in UK patients based on recommendations in the Joint British Societies (JBS) guidelines for the prevention of cardiovascular disease.

Methods: Pseudo-anonymized medical record data for 221 adults treated with bempedoic acid as part of the UK scheme were entered into a bespoke data collection tool at four UK hospitals. Patient demographics, clinical characteristics, treatment pathways and lipid assessment results (against JBS lipid-lowering targets) were collected against pre-specified criteria.

Results: Overall, 54% (99/184) of patients achieved the JBS2 audit standard (total cholesterol (TC) <5 mmol/L and low-density lipoprotein cholesterol (LDL-C) <3 mmol/L or ≥25% reduction in TC and ≥30% reduction in LDL-C) at 12 weeks post-initiation. At week 12, the mean absolute change in LDL-C was –1.0 mmol/L; the mean percentage reduction from baseline was 22.0%. Additionally, 52% (96/185) of patients had an LDL-C of <3 mmol/L and 10% (18/185) an LDL-C of <1.8 mmol/L at 12 weeks (as per JBS3).

Conclusion: This audit highlights the role of bempedoic acid as part of combination therapy for a population with previously limited treatment options.

Keywords: adenosine triphosphate, bempedoic acid, cholesterol, hydroxymethylglutaryl CoA reductases, hypercholesterolaemia, lipoprotein.

Citation

Ramachandran S, Maarouf A, Mitchell K, Avades T, Smith P, Boulton L, Kelly J, Vekaria N, Hughes E. 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. https://doi.org/10.7573/dic.2024-2-4

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death and morbidity in the United Kingdom and Europe.[1] Patients with hypercholesterolaemia or high levels of low-density lipoprotein cholesterol (LDL-C), which is often accompanied by low levels of high-density lipoprotein cholesterol (HDL-C), have a higher risk of

developing CVD.[2,3] Current non-pharmacological strategies for hypercholesterolaemia and dyslipidaemia management to reduce CVD risk include lifestyle changes such as eating a healthy diet, weight management and regular exercise.[4]

Currently in the UK, statins are recommended by various bodies, such as the National Institute for Health and Care Excellence (NICE) and the Joint British Societies (JBS), as first-line pharmacological treatment to help lower levels of LDL-C[3,4] and have been consistently shown to reduce the absolute risk of cardiovascular events in individuals at high risk.[5] Additionally, the Cholesterol Treatment Trialists' (CTT) Collaboration reports that reduction of LDL-C with lipid-lowering therapy (LLT) reduces the risk of major vascular events by about one-fifth for each 1 mmol/L reduction in LDL-C achieved after 3 years of treatment.[6,7] In clinical practice, it is widely acknowledged that a small proportion of patients treated with statins develop musculoskeletal side-effects such as myalgia or, very rarely, myositis or myopathy.[8,9] Furthermore, many patients are unable to tolerate the recommended therapeutic dose.[10] Therefore, considering the high number of patients who receive treatment, statin intolerance poses a significant challenge for both patients and clinicians and for the wider management of hypercholesterolaemia and dyslipidaemia to reduce CVD risk.[10,11]

Bempedoic acid is an adenosine triphosphate citrate lyase inhibitor, which inhibits cholesterol synthesis in the liver upstream of hydroxymethylglutaryl CoA reductase, therefore, lowering LDL-C.[2,9] Although bempedoic acid, much like statins, reduces cholesterol synthesis, it is not converted to its active form within skeletal muscle and therefore could be a beneficial treatment for patients who might otherwise be unable to tolerate the recommended dose of a statin.[2] From 1 October 2020 (ahead of the NICE approval on 28 April 2021, to 90 days after its approval), bempedoic acid was made available for the treatment of primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet in adults through a pre-reimbursement access scheme to secondary care centres in the UK.

The bempedoic acid pre-reimbursement access scheme addressed an unmet clinical need in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who were considered to be at high or very high risk of developing CVD. The scheme also included those who were intolerant to statins or in whom a statin was contraindicated as well as patients who had not achieved an adequate LDL-C level with ezetimibe, but were not eligible for alirocumab or evolocumab. The efficacy and safety of bempedoic acid were previously studied in phase III randomized controlled trials (RCTs), including the CLEAR trial programme (CLEAR Serenity, CLEAR Tranquillity, CLEAR Wisdom and CLEAR Harmony trials).[12] These RCTs included patients at high and very high risk who required further LDL-C lowering, some of whom were statin intolerant or on maximum tolerated LLT dose. Results for efficacy end points showed a significant reduction in LDL-C during the 12 weeks post-initiation when compared to placebo.[12]

In the UK, there are a number of lipid-lowering recommendations and guidelines available to inform clinical practice and decision-making for CVD. For example, for patients defined to be at high risk (established CVD, those with diabetes and aged >40 years, chronic kidney disease, familial hypercholesterolaemia (FH), a high 10-year CVD risk, or a high lifetime CVD risk where lifestyle changes alone are considered insufficient), the JBS guidelines recommend an intensive cholesterol-lowering treatment strategy to achieve the following targets:[4,13]

- JBS3: non-HDL-C <2.5mmol/L; LDL-C <1.8mmol/L[4]
- JBS2 audit standard: total cholesterol (TC): <5.0 mmol/L or a 25% reduction in TC; LDL-C: <3.0 mmol/L or a 30% reduction in LDL-C[13]
- JBS2 optimal target: TC: <4.0 mmol/L or a 25% reduction in TC; LDL-C: <2.0 mmol/L or a 30% reduction in LDL-C[13]

There is currently limited data as to the extent to which bempedoic acid lowers LDL-C and achieves wider lipid targets in real-world practice. It also remains unclear whether these lipid-lowering targets are being successfully achieved in UK clinical practice for patients receiving LLT.

The overall aim of this retrospective multicentre audit was to evaluate the achievement of lipid-lowering targets with bempedoic acid in UK adult patients with primary hypercholesterolaemia or mixed dyslipidaemia (who received treatment via the pre-reimbursement access scheme) based on lipid management recommendations in the JBS guidelines for the prevention of CVD.

The specific objectives of this study were as follows: to evaluate the achievement of lipid-lowering targets with bempedoic acid in adult patients with primary hypercholesterolaemia or mixed dyslipidaemia based on JBS guidelines; to describe patient demographics and baseline clinical characteristics, and to describe bempedoic acid treatment pathways.

Methods

Study design

This was a retrospective multicentre audit, conducted in four UK secondary care NHS centres. Patients with a diagnosis of primary hypercholesterolaemia or mixed

dyslipidaemia were eligible for inclusion if they were adults (aged ≥18 years at bempedoic acid initiation) who had received bempedoic acid through the pre-reimbursement access scheme from 1 October 2020, to 90 days after the NICE TA 694 published on 28 April 2021. All patients initiated on bempedoic acid had not achieved LDL-C targets according to the guidelines adopted by the clinics. All patients that were included in this audit were initiated on bempedoic acid in line with the recommendations within the Summary of Product Characteristics. There were no audit exclusion criteria; data were collected from all eligible patients at the participating centres. Individual centres selected patients when LDL-C targets were not met in secondary prevention and after discussion with the patient regarding absolute, relative and lifetime risk reduction estimates in primary prevention. A project Steering Committee, composed of clinician representatives from the participating centres, identified the JBS Guidelines (JBS2[13] and JBS3[4]) as the most appropriate source of standards as they were UK-specific and provided measurable benchmarks, although equivalent European lipid modification guidelines (e.g. European Society of Cardiology/European Atherosclerosis Society[14]) were also considered. Both absolute risk reduction and lifetime risk reduction in primary prevention were actively discussed with the patients at the main study centre when discussing treatment options and this was another supporting factor in the choice of JBS targets.

Study collection

A bespoke data collection tool was developed in Microsoft® Excel® for entry of the pre-defined audit dataset. Pseudo-anonymized patient data on demographics, bempedoic acid treatment pathways and lipid assessment results (against JBS lipid-lowering targets) at pre-specified time-points were entered into the data collection tool by a nominated member of the direct care team in a standardized format as pre-specified within the tool. The clinician representative and/or nominated members of the direct care team were instructed to enter the main audit outcome at 12 weeks or the closest result to the 12-week time period based on information recorded in medical records for eligible patients. Since patients may have started LLT many years prior to bempedoic acid, and lipid levels at the time of starting first LLT were often not available, the baseline measurement was defined as the closest measurement prior to the date of bempedoic acid initiation for the purpose of this audit. To preserve patient confidentiality, only anonymized aggregated (as opposed to patient-level) data were transferred outside of the participating centres for further analysis. The primary database was maintained in the NHS secondary care centre.

Data analysis

Centre level analyses were performed automatically in the data collection tool and an aggregated summary report of audit outcomes was produced for each participating centre.

All analyses generated in the data collection tool were descriptive in nature. Continuous (quantitative) outcomes were described by the number of observations (*n*), mean, standard deviation (SD), median, interquartile range (IQR) and range. Distributions were provided for continuous (quantitative) outcomes where appropriate and categorical outcomes were described as the total number and percentage per category.

The final analysis was carried out by OPEN Health using Microsoft® Excel® by combining the aggregated data obtained from all participating centres from the reports (populated table shells) generated by the audit tool. For each of the categorical outcomes, all centres' results were pooled, and an overall summary table was provided. As only aggregated (summary) measures as opposed to patient-level data were available from the centres, for each of the continuous (quantitative) outcomes the overall median and IQR could not be calculated. For continuous (quantitative) outcomes, with the total number of observations provided for each site. Category distributions were pooled and reported where relevant. All percentages were reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding.

Regulatory, ethical and administrative obligations

No research ethics committee approval was required as this was a clinical audit project (i.e. not classified as healthcare research). Participating centres gained approval from the appropriate management/clinical audit office (who all classified the project as an audit) for the conduct of the audit and for release of aggregated (fully anonymized) data to OPEN Health. No patient consent was required as the audit was retrospective and anonymized, and identifiable medical records were accessed only by members of the direct care team at each centre. The audit was performed in accordance with the ethical principles within the Declaration of Helsinki.

Results

Patient demographics and clinical characteristics

The audit included a total of 221 patients across 4 centres (University Hospitals Birmingham NHS Foundation

Trust (*n*=113), University Hospitals Plymouth NHS Trust (*n*=13), Calderdale and Huddersfield NHS Foundation Trust (*n*=31) and Sandwell and West Birmingham Hospitals NHS Trust (*n*=64)). Patient demographics are summarized in Table 1; in the overall cohort, 66% (145/221) of patients were women, 81% (171/210) were of white ethnicity and patients had a mean (SD) body mass index (BMI) of 29.9 (7.5) kg/m^2 (*n*=84). The mean blood pressure at baseline (*n*=67) was 139.2 mmHg (systolic (range, 107.0–210.0 mmHg)) and 83.2 mmHg (diastolic (range: 50.0–126.0 mmHg)).

In total, 5% (12/221) of patients had a documented CVD risk score based on the JBS3 risk calculator[4,15] and 12% (26/221) had a CVD risk score based on an alternative risk scoring algorithm (QRISK: 11%, 24/221; other scoring methods: 1%, 2/221). At baseline, patients presented with hypertension (42%, 93/219), FH (31%, 67/215), diabetes (type 2: 17%, 37/221; type 1: 1%, 2/221), established atherosclerotic CVD (17%, 37/219), a history of cardiovascular events (16%, 35/219), and a history of stroke and/or transient ischaemic attack (6%, 14/217).

Nearly all patients (99%, 218/221) were documented to have received prior LLT (there was no documentation for 3 patients). Patients had been on LLT for a mean (SD) of 5.4 (4.4) years prior to bempedoic acid initiation (*n*=180). At the time of bempedoic acid initiation, 50% (109/218) of patients had documentation in their medical records about another ongoing LLT and, of these, ezetimibe 10 mg (47%, 51/109) was the most common (Table 1). Of the patients who were in receipt of concomitant statin therapy, most (74%, 40/54) were documented to be receiving low-intensity statins (statin intensity was not documented for one patient with ongoing statin treatment; Table 1). Most patients included in this audit were documented to be statin intolerant (93%, 167/180). The most common reason for starting bempedoic acid was statin intolerance (90%, 198/220) followed by inadequate response to previous treatment (8%, 18/220).

At baseline (most recent result prior to bempedoic acid initiation), the mean (SD) lipid levels were: 4.0 (1.2) mmol/L for LDL-C (*n*=209); 5.0 (1.4) mmol/L for non-HDL-C (*n*=218); 6.4 (1.4) mmol/L for total cholesterol (*n*=220) and 2.3 (1.8) mmol/L for triglyceride levels (*n*=213).

Overall, the mean (SD) time from initiation of bempedoic acid to data collection (i.e. total available observation period) was 65.1 (10.8) weeks (*n*=220).

Figure 1 shows the JBS2 (optimal) lipid target attainment at 12 weeks post-bempedoic acid initiation for the overall cohort. At 12 weeks post-bempedoic acid initiation, 44% (80/182) of patients achieved an LDL-C of <2 mmol/L or a reduction of ≥30% in LDL-C from baseline (Figure 1).

Table 1. Patient baseline demographics.

Sex	***n***	**% (*n*=221)**
Men	76	34
Women	145	66
Age (years)	**Mean (SD)**	**Range**
At data collection (*n*=221)	64.1 (10.0)	32.0–86.0
At bempedoic acid initiation (*n*=220)	62.9 (10.0)	30.7–84.7
BMI (kg/m^2) (*n*=84)	**Mean (SD)**	**Range**
	29.9 (7.5)	16.0–64.5
Race/ethnicity	***n***	**% (*n*=210)**
White	171	81
Asian	22	10
Black/African/Caribbean	14	7
Other	3	1
Not stated/Missing	11	–
Smoking status	***n***	**% (*n*=192)**
Current smoker	17	9
Ex-smoker	38	20
Never smoked	137	71
Lipid levels (mmol/L)	**Mean (SD)**	**Range**
LDC-C (*n*=209)	4.0 (1.2)	1.5–9.3
Non-HDL-C (*n*=218)	5.0 (1.4)	1.9–10.0
Total cholesterol (*n*=220)	6.4 (1.4)	3.1–11.3
Triglyceride levels (*n*=213)	2.3 (1.8)	0.3–21.5
Ongoing lipid-lowering therapies[a]	***n***	**% (*n*=109)**
Ezetimibe 10 mg	51	47
Statin + ezetimibe 10 mg	30	28
Statins	25	23
Other treatments	3	3
Recorded concomitant statin therapies[a,b]	***n***	**% (*n*=54)**
Low intensity statins	40	74
Medium intensity statins	7	13
High intensity statins	7	13

[a]As documented in patients' medical records.
[b]One patient with ongoing lipid therapy did not have the intensity recorded.

A total of 34% (68/198) of patients achieved TC of <4 mmol/L or a reduction of ≥25% in TC from baseline. Overall, 29% (54/184) of patients achieved the JBS2 optimal lipid target (TC <4 mmol/L and LDL-C <2 mmol/L)

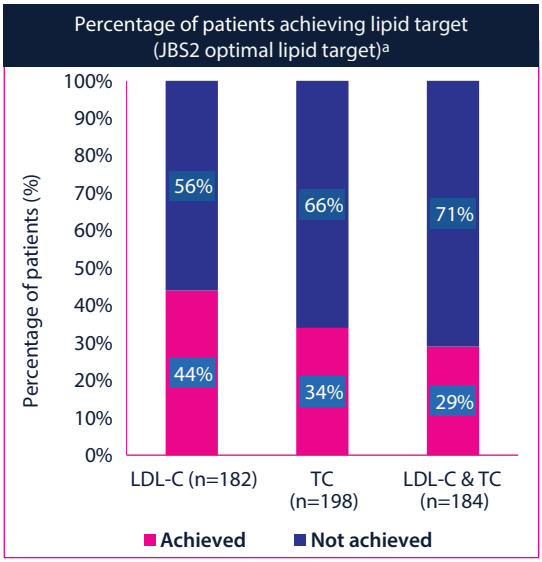
or (≥25% reduction in TC and ≥30% reduction in LDL-C) (Figure 1).

Figure 2 shows the JBS2 (audit standard) lipid target attainment at 12 weeks post-bempedoic acid initiation. At 12 weeks post-bempedoic acid initiation, 62% (113/182) of patients achieved an LDL-C of <3 mmol/L or a reduction of ≥30% in LDL-C from baseline (Figure 2). A total of 58% (115/198) of patients achieved TC of <5 mmol/L or a reduction of ≥25% in TC from baseline (Figure 2). Overall, 54% (99/184) of patients achieved lipid targets based on the JBS2 audit standard (TC <5 mmol/L and LDL-C <3 mmol/L or ≥25% reduction in TC and ≥30% reduction in LDL-C) (Figure 2).

Figure 3 shows the JBS3 lipid target attainment at 12 weeks post-bempedoic acid initiation; 10% (18/185) of patients had an LDL-C of <1.8 mmol/L at 12 weeks post-bempedoic acid initiation, achieving the JBS3 LDL-C target (Figure 3). Furthermore, 6% (11/198) of patients had a non-HDL-C of <2.5 mmol/L at 12 weeks post-bempedoic acid initiation, achieving the JBS3 non-HDL-C target (Figure 3).

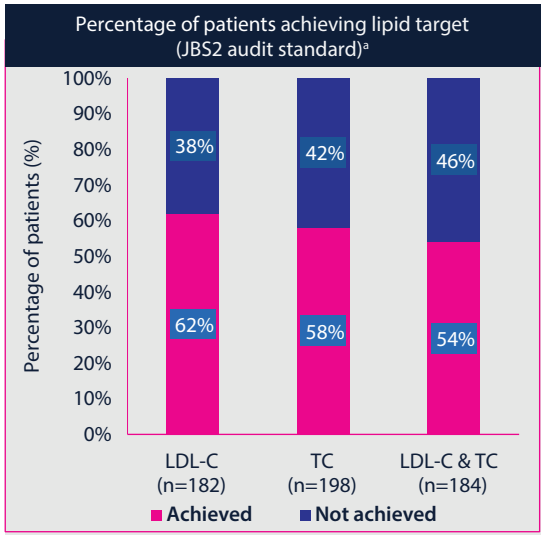
The mean (SD) absolute change in LDL-C from baseline to 12 weeks post-bempedoic acid initiation was −1.0 (0.9) mmol/L (*n*=182) (Figure 4a). The mean (SD) percentage change in LDL-C from baseline to 12 weeks post-bempedoic acid initiation was −22.0% (22.6%) (*n*=182) (Figure 4b). At 12 weeks post-bempedoic acid initiation, the majority (88%, 160/182) of patients had lowered LDL-C from baseline, whilst 10% (19/182) of patients had increased LDL-C and 2% (3/182) had no change in LDL-C from baseline. At 12 weeks post-bempedoic acid initiation, 37% (68/182) of patients had a ≥30% reduction in

Figure 1. Percentage of patients achieving lipid target at 12 weeks (JBS2 optimal lipid target).



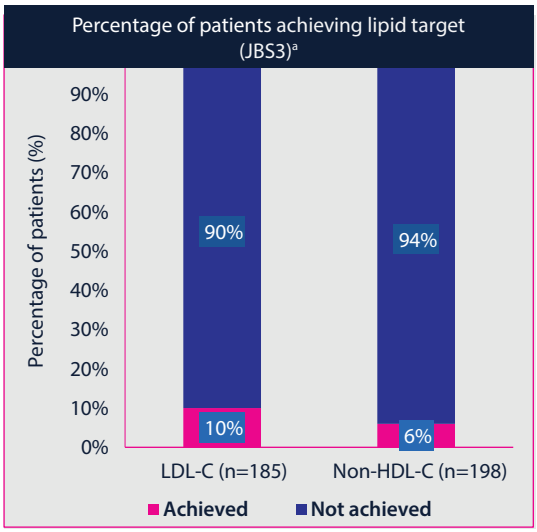
[a]JBS2 optimal target: TC: <4.0 mmol/L; LDL-C: <2.0 mmol/L.
JBS, Joint British Societies; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Figure 2. Percentage of patients achieving lipid target at 12 weeks (JBS2 audit standard).



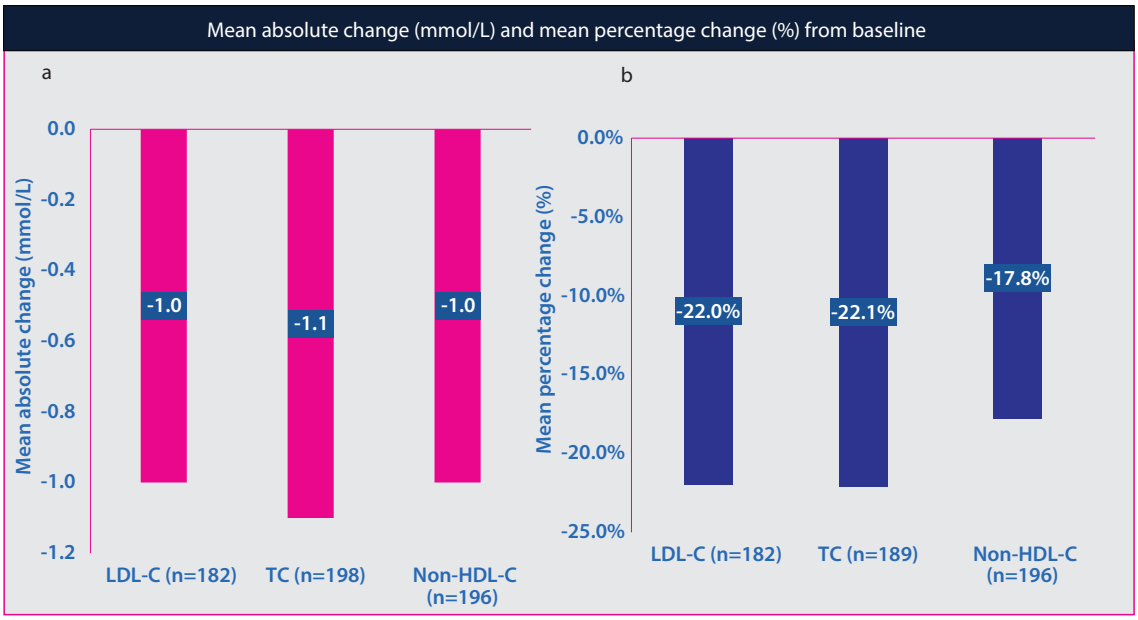
[a]JBS2 audit standard target: TC: <5.0 mmol/L; LDL-C: <3.0 mmol/L.
JBS, Joint British Societies; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Figure 3. Percentage of patients achieving lipid target at 12 weeks (JBS3).



[a]JBS3 target: Non-HDL-C: <2.5 mmol/L; LDL-C: <1.8 mmol/L.
JBS, Joint British Societies; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Figure 4. Absolute and percentage change in LDL-C, total cholesterol and non-HDL-C from baseline to week 12.



LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TC, total cholesterol.

LDL-C from baseline and 52% (96/185) of patients had an LDL-C measurement of <3 mmol/L.

The mean (SD) absolute change in TC from baseline to 12 weeks post-bempedoic acid initiation was −1.1 (1.1) mmol/L (*n*=198) (Figure 4a). The mean (SD) percentage change in TC from baseline to 12 weeks post-bempedoic acid initiation was −22.1% (23.6%, *n*=189) (Figure 4b). At 12 weeks post-bempedoic acid initiation, 31% (61/198) of patients had a ≥25% reduction in TC from baseline. At 12 weeks post-bempedoic acid initiation, 46% (91/198) of patients had a TC measurement of <5 mmol/L.

Furthermore, the mean (SD) absolute change in non-HDL-C from baseline to 12 weeks post-bempedoic acid initiation was −1.0 (1.1) mmol/L (*n*=196) (Figure 4a). The mean (SD) percentage change in non-HDL-C from baseline to 12 weeks post-bempedoic acid initiation was −17.8% (19.7%) (*n*=196) (Figure 4b). At 12 weeks post-bempedoic acid initiation, the majority (85%, 167/196) of patients had lowered non-HDL-C from baseline, whilst 14% (28/196) of patients had increased non-HDL-C and 1% (1/196) had no change in non-HDL-C from baseline.

A total of 33% (69/212) of patients in this audit discontinued bempedoic acid treatment during the observation period. The mean (SD) duration of treatment in patients who discontinued was 22.1 (17.6) weeks (*n*=63) and 72% (50/69) of patients who discontinued bempedoic acid treatment did so due to an adverse event. Other reasons for discontinuing bempedoic acid treatment included patient choice (58%, 40/69), clinician choice (16%, 11/69), lack of efficacy (7%, 5/69), interaction with concomitant medication (1%, 1/69) and other (4%, 3/69); categories for discontinuation were not mutually exclusive as there could be multiple reasons for discontinuation.

Discussion

Summary of patient demographics and clinical characteristics

This audit included 221 (66% women) patients with a mean (SD) age of 62.9 (10.0) years at the time of bempedoic acid initiation. The proportion of women was similar to the bempedoic acid group in the CLEAR Tranquillity trial (60.2% women)[9] but higher than in the CLEAR Harmony trial, in which the majority (73.9%) of patients were men.[16] The audit population had a broader ethnic profile (81% white, 10% Asian, 7% Black/African/Caribbean, 1% 'other' ethnic group) than the bempedoic acid groups in other clinical studies, such as the CLEAR Tranquillity (91.2% white)[9] and CLEAR Harmony (95.6% white)[16] clinical trials, and is therefore likely more reflective of the wider UK population.[17] Most patients in the audit with BMI recorded (*n*=84) were classified as overweight (38%) or obesity (40%) at baseline, and the mean (SD) BMI was 29.9 (7.5) kg/m^2. Only 17% of patients in this audit had established atherosclerotic CVD and 16% had a history of cardiovascular events, whilst the audit eligibility

criteria required that patients were managed in secondary care specialist centres only. These results indicate that, in secondary care settings, the majority of patients (over 80%) were receiving bempedoic acid for primary CVD prevention. Therefore, according to the NHS Accelerated Access Collaborative lipid management clinical pathway,[18,19] these patients may represent a cohort suitable for management in primary care, which would reduce referral into the secondary care setting.

Formal CVD risk scoring was not used (or not documented) in the majority of patients prior to bempedoic acid initiation as only 5% of patients had a documented CVD risk score based on the JBS3 risk calculator and 12% had a CVD risk score using an alternative risk scoring algorithm (primarily QRISK). These findings may suggest that formal risk scoring is reserved for primary care and may also reflect current European guidance recommending that patients deemed to be at 'high risk' should be referred to a specialist lipid clinic. Because this audit took place in a secondary care setting, these patients by nature were likely to be perceived as being at 'high risk' and therefore would not require any further risk assessment as this would have been conducted in primary care. Furthermore, because the audit considered patients who had been treated prior to reimbursement of bempedoic acid, these patients will have been considered as high risk by the very nature of their participation in the pre-reimbursement access scheme. As most patients were at 'high risk', the proportion of patients achieving the secondary prevention targets was evaluated as outlined in the JBS targets (noting that these targets were in line with NICE 2014 targets at the time of the audit).[3,4,13] Moreover, risk scores for patients with FH (who represented approximately one-third of patients in this audit) are not routinely performed in this cohort because they will likely underestimate true CVD risk.

The finding that 31% of patients in this audit had FH is considerably higher than observed in some clinical trials,[16] and is likely due to the classification of patients included in this secondary care cohort as being at high risk. Excluding FH, the most common comorbidities at baseline were hypertension (42%) and diabetes mellitus (18%).

Summary of main results

This audit evaluates real-world data on bempedoic acid and provides valuable insight into the role of bempedoic acid as a treatment option to support lipid target attainment in a UK real-world setting. These data may also provide further opportunities for benchmarking and service improvement within the participating NHS centres as well as providing early insight into the real-world effectiveness of treatment via the pooling of aggregated data from the individual centres. Patients in the audit sample were treated with bempedoic acid as part of a pre-reimbursement access scheme, thus representing a population with high unmet clinical needs and significant previous attempts to reach lipid targets.

At baseline (most recent result prior to bempedoic acid initiation), the mean (SD) lipid levels were: 4.0 (1.2) mmol/L for LDL-C (n=209), 5.0 (1.4) mmol/L for non-HDL-C (n=218) and 6.4 (1.4) mmol/L for TC (n=220). Overall, the majority of patients in the audit had lowered LDL-C (88%) and non-HDL-C (85%) levels at 12 weeks post-initiation.

When considering lipid target attainment at 12 weeks post-initiation in relation to the JBS standards, the results showed that 29% of patients achieved the JBS2 optimal TC/LDL-C target whilst 54% of patients achieved the JBS2 TC/LDL-C audit standard. Attainment of the more stringent JBS3 LDL-C and non-HDL-C targets was lower (10% and 6%, respectively). At week 12, the mean absolute change in LDL-C was −1.0 mmol/L, which generally corresponds to the results observed in the CLEAR RCTs in a similar population. However, it is important to note that this audit was not designed to directly compare with RCT data, given the variation between the trials in terms of the characteristics of the patients, degrees of statin intolerance and background treatments, which could potentially affect the interpretation.[20] For instance, the CLEAR Tranquility trial, which had similarities to this audit, also included patients with a history of statin intolerance, and one-third were receiving a low or very low dose of statin at baseline. In this study, there was a 28.5% reduction in LDL-C observed at week 12 in patients treated with bempedoic acid compared to placebo.[9]

Furthermore, the mean (SD) percentage reduction in LDL-C from baseline to 12 weeks post-bempedoic acid initiation in this audit was −22.0% (22.6%), whilst the mean (SD) percentage reduction in TC was −22.1% (23.6%). The results from this largely statin-intolerant cohort also generally align with the average percentage change from baseline observed across pooled data from four bempedoic acid RCTs, whereby the LDL-C level percentage change from baseline with bempedoic acid was −17.8% overall but −24.5% for patients intolerant to statins.[20]

The data also provide insight into the real-world persistence of patients on bempedoic acid. The discontinuation rate of 33% was much higher than in the RCTs (which were approximately 11% for patients on bempedoic acid and 8% for patients in the placebo group).[12] However, these discrepancies can be partially explained by differences in the follow-up period: for instance, the discontinuation rate was only measured for up to 12 and 24 weeks in the CLEAR Tranquility[9] and CLEAR Serenity[20] RCTs, respectively, whereas the follow-up duration is much greater in this audit (~60 weeks). The high-risk nature of

this secondary care cohort also means that the patients are likely to have previously discontinued other LLTs and may be more likely to report treatment intolerance. Further investigation in a future research study would be required to determine the cause of this.

Overall, this audit provides valuable new insight as to the real-world outcomes of patients initiated on bempedoic acid in a clinical setting, including the proportion of patients within real-world practice who are actually attaining the stringent JBS targets. However, the results also open up questions as to the appropriateness of these targets and the practicalities associated with their implementation and interpretation for patients at higher risk who have already received LLT on several occasions. For instance, it is important to consider the targets and the associated findings in the context of the baseline characteristics of patients who are likely to be initiated on bempedoic acid within clinical practice. Moreover, JBS targets were intended as a treatment goal for patients beginning their pharmacological treatment journey on statins. The JBS guidelines do not currently make distinctions to account for factors such as statin intolerance, baseline LLT levels or the number of prior therapies, and state that one should expect to see the full effect of (statin) treatment within 6–8 weeks after initiation or titration of the dose.[4,15] It is therefore notable that, in the current audit, 218 (99%) patients had a documented history of LLT before initiating bempedoic acid, and the mean duration of prior LLT was 5.4 years.

In this audit, the baseline measurement was defined as the most recent measurement prior to the initiation of bempedoic acid, irrespective of prior LLT. Yet, the original targets are initially intended for patients naive to LLT, with an emphasis on early treatment. Absolute lipid lowering will partially reflect the baseline levels, with the magnitude of change likely to be lower for those with lower versus higher lipid levels at baseline – a factor that may impact the interpretation of these results. Furthermore, approximately a third of patients in this cohort had FH. Additionally, 93% of patients in this audit were described as 'statin intolerant' and 90% of patients started bempedoic acid due to statin intolerance, though a considerable number of patients (51% of those with ongoing LLT) remained on statins. Those that remained on statins were most likely on the lowest dose of statin, either alone or combined with ezetimibe 10 mg.

Definitions of statin intolerance vary within clinical practice and associated guidance; for instance, the 2022 National Lipid Association scientific statement on statin intolerance defined intolerance as either partial or complete, taking into consideration the ability to achieve therapeutic targets on maximally tolerated statin dosing.[21] However, in clinical practice, the term 'statin intolerant' may be used to describe an inability to tolerate statins at the recommended dose to provide optimal LDL-C reductions as opposed to a complete intolerance of statins that results in discontinuation. Further research may therefore be required to consider lipid target attainment within different sub-groups of patients within UK clinical practice.

Limitations

The project was designed and implemented as a descriptive, retrospective audit with the aim to evaluate lipid target attainment achieved with bempedoic acid both across and between the participating UK centres; it was not a formal healthcare research study designed to assess treatment effects (i.e. efficacy or effectiveness). As such, the project did not include certain design elements (e.g. power calculation, control of bias and confounding, source data verification, ethics review) that would have been required for healthcare research. However, the specific nature of this cohort, who had received bempedoic acid as part of the pre-reimbursement access scheme in the UK, is the strength of this audit and the sample size of n=221 are appropriate for early real-world data from this region. Additionally, the audited use of bempedoic acid was not biased by the subsequent usage guidance. Subsequent to the audit, inclisiran (TA733)[22] became available in secondary prevention when LDL-C after statin treatment was >2.6 mmol/L. In primary prevention, PCSK9 inhibitors are utilized in FH if LDL-C >5.0 mmol/L and in secondary prevention if LDL-C >3.5 mmol/L or 4.0 mmol/L (depending on single-bed/multi-bed CVD). In both primary and secondary prevention, bempedoic acid should be used in patients with statin intolerance (as defined in the national guidance document for primary and secondary prevention of CVD), or for whom statins are contraindicated, after ezetimibe 10 mg monotherapy and PCSK9 inhibitors (when funding is available).[23] Bempedoic acid would subsequently be used after maximum statin/ezetimibe treatment with evolocumab (TA394)[24] and alirocumab (TA393)[25] (which would be chosen clinically if within the NICE guidelines because of superior efficacy). The main audit outcome (lipid target attainment) was measured at 12 weeks post-bempedoic acid initiation; overall target attainment during bempedoic acid treatment (i.e. exceeding the post-12-week period) may be higher.

As with any retrospective data collection project, the quality of the data collected relies on the completeness and accuracy of information recorded in patient hospital medical records. It should be noted that many of the sites did not have access to patient information, such as carotid ultrasound findings and coronary calcium scores, to inform subsequent prescription of bempedoic acid and thus the information was not available for the

purposes of this audit. Patient-level data was also not received; therefore, analysis within sub-groups (such as sex and ethnicity) was not conducted. Furthermore, individual-level data would have been essential to understand specific patient benefits, such as whether patients with the highest baseline LDL-C may experience the greatest benefit in LDL-C lowering.

Because appointment scheduling in real-world practice can vary, data may not always be available at pre-specified study time points. There were missing data at week 12 for a significant proportion of patients in the audit. The ability of centres to carry out repeat phlebotomy at 12 weeks was also further hindered due to COVID-19 restrictions in place at the time of the audit. It is important to acknowledge the wider implications of the timing of this audit in relation to the COVID-19 pandemic, and the fact the audit took place at a time when many patients were moving from virtual consultations back to face-to-face; therefore, they may not have had access to the same levels of support and clinicians may not have had the chance to build up the same level of rapport with their patients than in the past.

Whilst the JBS targets were the standards selected by the investigators for the purpose of this audit, the cholesterol-specific thresholds may not always form the basis of actual decision-making in practice. Indeed, the wider audit findings suggested that these JBS targets are not widely adopted to inform decisions (based on information documented in medical records). Other guidelines, for example, those based on the American College of Cardiology/American Heart Association (ACC/AHA),[26] the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) 2019 (ref.[14]) and NICE guidance CG181 (ref.[3]) are often the preferred sources of decision-making. However, it should be noted that target attainment in relation to these was not the purpose of this audit. Further work would be needed to assess cholesterol target attainment in the United Kingdom in relation to other guidelines.

Contributions: SR supported audit design, data collection, data interpretation, and drafting/approval of manuscript. AM, EH, TA, KM, PS, LB and NV performed audit design, data collection, data interpretation, and drafting/approval of manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: SR has received research grants, travel grants and speakers' honoraria from Besins Healthcare, Daiichi Sankyo, Novartis, and Amarin. EH is a trustee of HEARTUK and Dinwoodie Charity, received payment from Daiichi Sankyo UK Ltd., Amarin, Amgen, ACCEA and Novartis, and received funding from Sanofi and Amarin. TA has received funding and honoraria from Daiichi Sankyo UK Ltd. PS is an employee of Daiichi Sankyo UK Ltd. LB, NV and JK are former employees of Daiichi Sankyo UK Ltd. AM and KM have no conflicts of interest to declare. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2024/07/dic.2024-2-4-COI.pdf

Acknowledgements: Data analysis was conducted by Mano Andiappan of OPEN Health, and medical writing support was provided by Angie Bonsu, Will Cottam, and Fiona Glen of OPEN Health, funded by Daiichi Sankyo UK Ltd.

Funding declaration: This audit was funded by Daiichi Sankyo UK Ltd. Daiichi Sankyo UK Ltd initiated the audit and provided input into the audit design, report and manuscript. The company Daiichi Sankyo Europe GmbH are marketing authorisation holders of bempedoic acid and the bempedoic acid/ezetimibe combination in the UK, European Economic Area and Switzerland.

Article URL: https://www.drugsincontext.com/a-uk-multicentre-audit-of-the-management-of-patients-with-primary-hypercholesterolaemia-or-mixed-dyslipidaemia-with-bempedoic-acid-against-published-lipid-lowering-treatment-targets

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Provenance: Submitted; externally peer reviewed.

Submitted: 29 February 2024; **Accepted:** 20 May 2024; **Published:** 8 August 2024.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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References

1. Bilitou A, Were J, Farrer A, et al. Prevalence and patient outcomes of adult primary hypercholesterolemia and dyslipidemia in the UK: longitudinal retrospective study using a primary care dataset from 2009 to 2019. *CEOR*. 2022;14:189–203. https://doi.org/10.2147/CEOR.S347085
2. Pinkosky SL, Newton RS, Day EA,. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun*. 2016;7:13457. https://doi.org/10.1038/ncomms13457
3. National Institute for Health and Care Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline [CG181]. http://www.nice.org.uk/Guidance/CG181. Accessed December 2023.
4. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart*. 2014;100(Suppl. 2):ii1–ii67. https://doi.org/10.1136/heartjnl-2014-305693
5. Tramacere I, Boncoraglio GB, Banzi R, et al. Comparison of statins for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. *BMC Medicine*. 2019;17(1):67. https://doi.org/10.1186/s12916-019-1298-5
6. Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. *Eur Heart J*. 2018;39(27):2540–2545. https://doi.org/10.1093/eurheartj/ehx450
7. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670–1681. https://doi.org/10.1016/S0140-6736(10)61350-5
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):215–224. https://doi.org/10.1080/1744666X.2018.1440206
9. Ballantyne CM, Banach M, Mancini GBJ, 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. https://doi.org/10.1016/j.atherosclerosis.2018.06.002
10. Mesi O, Lin C, Ahmed H, Cho LS. Statin intolerance and new lipid-lowering treatments. *CCJM*. 2021;88(7):381–387. https://doi.org/10.3949/ccjm.88a.20165
11. National Institute for Health and Care Excellence (NICE). Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694). https://www.nice.org.uk/guidance/ta694/resources/bempedoic-acid-with-ezetimibe-for-treating-primary-hypercholesterolaemia-or-mixed-dyslipidaemia-pdf-82609440519877. Accessed December 2023.
12. Chaplin S. Bempedoic acid for primary hypercholesterolaemia. *Prescriber*. 2021;32(1):29–31. https://doi.org/10.1002/psb.1888

13. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91(Suppl. 5):v1–v52. https://doi.org/10.1136/hrt.2005.079988
14. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111–188. https://doi.org/10.1093/eurheartj/ehz455
15. JBS3 Risk Calculator. https://www.jbs3risk.co.uk/pages/lifetime_risk.htm. Accessed December 2023.
16. 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):1022–1032. https://doi.org/10.1056/NEJMoa1803917
17. Population of England and Wales. https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest. Accessed December 8, 2022.
18. Accelerated Access Collaborative (AAC). https://www.nice.org.uk/aac. Accessed January 5, 2023.
19. NHS Accelerated Access Collaborative. https://www.england.nhs.uk/aac/. Accessed January 5, 2023.
20. Banach M, Duell PB, Gotto AM Jr, et al. Association of bempedoic acid administration with atherogenic lipid levels in phase 3 randomized clinical trials of patients with hypercholesterolemia. *JAMA Cardiol*. 2020;5(10):1124–1135. https://doi.org/10.1001/jamacardio.2020.2314
21. Gaine SP, Kulkarni A, Dixon DL, Patel P. NLA 2022 definition of statin intolerance. American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2022/08/08/12/27/nla-2022-definition-of-statin-intolerance. Accessed December 2023.
22. National Institute for Health and Care Excellence (NICE). Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733). NICE; 2021. https://www.nice.org.uk/guidance/TA733. Accessed May 2, 2024.
23. NHS Accelerated Access Collaborative. Summary of national guidance for lipid management. https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed April 24, 2024.
24. National Institute for Health and Care Excellence (NICE). Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA394). NICE; 2016. https://www.nice.org.uk/guidance/ta394. Accessed May 1, 2024.
25. National Institute for Health and Care Excellence (NICE). Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA393). NICE; 2016. https://www.nice.org.uk/guidance/ta393. Accessed May 1, 2024.
26. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2019;74(10):e177–e232. https://doi.org/10.1016/j.jacc.2019.03.010