Frequently asked questions (FAQs) concerning bempedoic acid (Nilemdo®) and in combination with ezetimibe (Nustendi®) for primary care practitioners in South East London

The intended purpose of this document is to support primary care practitioners with clinical decision making when considering initiating and continuing Nilemdo® and Nustendi® therapy in patients requiring lipid lowering therapy to reduce cardiovascular risk in primary and secondary prevention but who cannot tolerate statin therapies

This guidance has been developed and reviewed by the South East London Cardiovascular Medicines Working Group and approved by the South East London Integrated Medicines Optimisation Committee

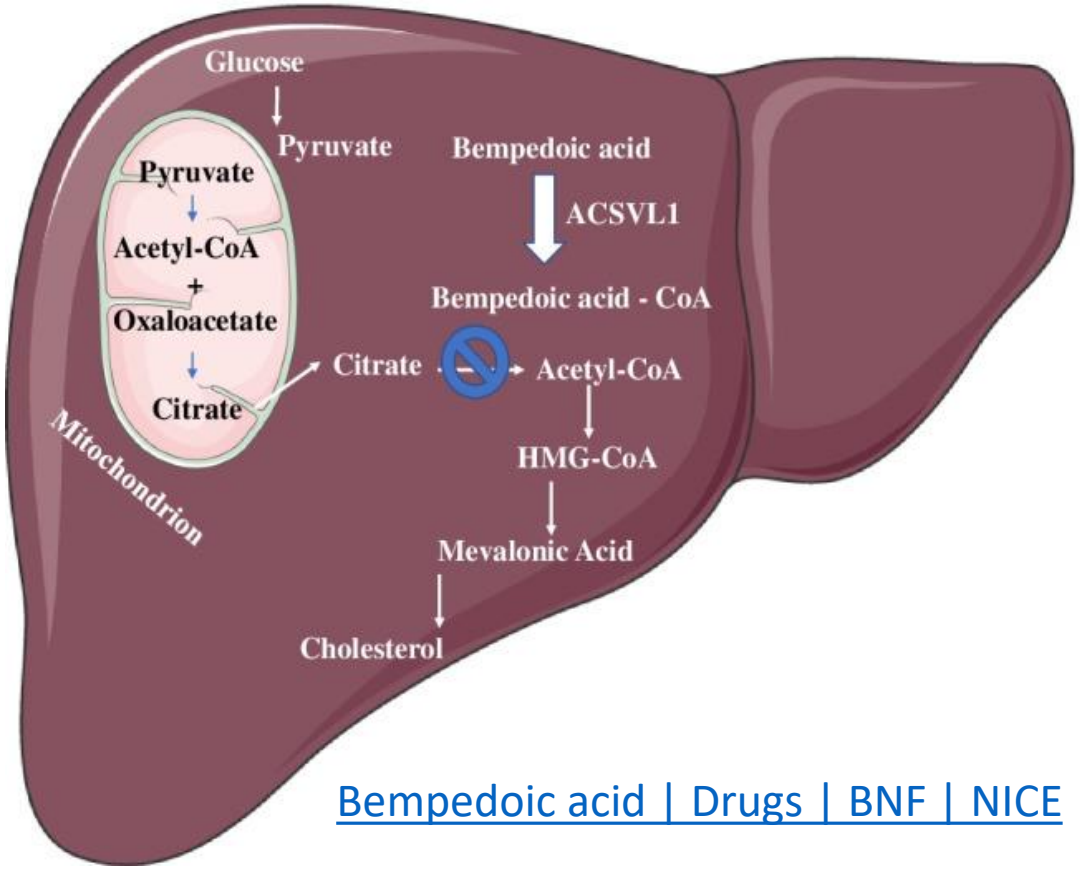
Approval date: December 2023 Review date: December 2025 (or sooner if evidence or practice changes)

South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London: South East London Integrated Care System (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

INDEX FOR FAQs

Q What is bempedoic acid and how does it work?

- Bempedoic acid is an adenosine triphosphate citrate lyase (ACL) inhibitor that inhibits cholesterol synthesis in the liver, thereby lowering LDL-cholesterol
- Bempedoic acid is currently available as a 180mg tablet monotherapy (Nilemdo®) or in fixed combination with ezetimibe 10mg (Nustendi®)
- Bempedoic acid as a monotherapy is associated with a reduction in LDL-C of 21% and additional LDL-C reductions are observed in combination with ezetimibe or statin therapy
- Prescribing of the bempedoic acid/ezetimibe fixed-dose combination is encouraged as this may improve compliance and is more cost effective than prescribing separate dosage forms
- Bempedoic acid is activated in the liver and not in most peripheral tissues, including skeletal muscle, reducing the potential for adverse effects on muscle (and so is of benefit for patients experiencing statin intolerance)



Bempedoic acid | Drugs | BNF | NICE

Q Which patients may be suitable for bempedoic acid according to NICE ?

Bempedoic acid is recommended by NICE TA694 (April 2021) in combination with ezetimibe as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults

It is recommended only if:

•statins are contraindicated or not tolerated

•ezetimibe alone does not control low-density lipoprotein cholesterol well enough

Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination (Nustendi®) **BNF**

In SEL we encourage prescribing of the combination tablet to support adherence and cost effectiveness

Please note: There may be circumstances when bempedoic acid monotherapy is recommended by a lipid specialist for patients intolerant of ezetimibe. This is a licensed indication however is not endorsed by NICE. In SEL the prescribing of bempedoic acid monotherapy is **amber 1**.

Q What are the recommendations for prescribing bempedoic acid in SEL?

Bempedoic acid with ezetimibe is included in the SEL formulary as RAAG status **green** and if prescribed as monotherapy in patients intolerant of ezetimibe it is RAAG **amber 1**

In SEL, bempedoic acid is approved as an addition to ezetimibe for primary hypercholesterolaemia where (see page 7 of the SEL lipid management guideline) in line with NICE guidance :

- statins are contraindicated or not tolerated
- ezetimibe alone does not control low-density lipoprotein cholesterol well enough

As a **"green"** drug, initiation may occur within primary or secondary care.

Where possible, the combination bempedoic acid/ezetimibe should be prescribed to support patient adherence and is more cost-effective

See page 7 of the SEL lipid management guideline (primary and secondary prevention pathways and statin intolerance pathway)

Q. What is the LDL Lowering effect of bempedoic acid vs other lipid lowering agents

Extent of lipid lowering with available therapies

Lipid lowering therapy	5mg	10mg	20mg	40mg	80mg
Simvastatin		27%	32%	37%	42%
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53% ****specialist initiation ****	
Atorvastatin plus ezetimibe		52%	54%	57%	61%
Bempedoic acid 180mg	21% ***amber 1: monotherapy if ezetimibe intolerance***				
Bempedoic acid 180mg with Ezetimibe 10mg	38% ***** green: primary or secondary care initiation***				
Ezetimibe 10mg monotherapy	15 to 22% *green: **primary or secondary care initiation***				
Inclisiran	~ 50% (range 48-52%) ***amber 1 in SEL***				
PCSK9i mAB (evolocumab or alirocumab)	~ 50% (range 25-70%) ***** Red - secondary care prescribing only***				

Medium intensity will produce an LDL-reduction of 31-40%

High intensity will produce an LDL-C reduction of above 40%

	NICE titration threshold for primary and secondary prevention of CVD	JBS3 target for patients with CVD	QOF 23/24 CHOL002
Lipid lowering targets	Intensify therapy if non-HDL-C reduction from baseline is less than 40%	Non-HDL-C < 2.5mmol/L (LDL-C < 1.8mmol/L)	Patients on CVD register with non-HDL-C < 2.5mmol/L (LDL-C < 1.8mmol/L) in previous 12 months

Joint British Societies –JBS3

RAAG status: Green- may be initiated in primary and secondary care Amber 1- can be initiated in primary care after recommendation from an appropriate specialist Amber 2- initiation by a specialist with maintenance prescribing in primary care Red- specialist or hospital only

Q. What is statin intolerance?

- Link: statin-intolerance-pathway-v2.pdf (england.nhs.uk)

- In clinical trials, statins are well tolerated (often with a similar adverse effect (AE) profile to placebo), however in clinical practice up to 75% of people started on a statin will discontinue treatment within 2 years
- Stopping statin therapy is associated with an increased risk of major CV events
- There is growing concern that patients are labelled as 'statin intolerant' too quickly.
- Patient led statin discontinuation is significantly associated with negative media coverage

Definition of Statin Intolerance

- NICE: *the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy*
- Any adverse event (AEs) considered unacceptable by the patient, and/or some laboratory abnormalities, both attributed to statin treatment and leading to its discontinuation

Statin-associated muscle symptoms (SAMS)

- SAMS commonly cause statin non-adherence and/or discontinuation. However, not all muscular symptoms should lead to a label of 'statin intolerance' as this may not be truly statin related muscle toxicity (SRM)
- SAMS resolve on de-challenge of statin and SAMS reappear with re-challenge of statin

Non-Statin related musculoskeletal symptoms (Non SRM)

- If patients report symptoms not typical of SRM (e.g. asymmetric distribution, failure to resolve with de-challenge despite normal CK) consider other musculoskeletal, metabolic, degenerative or inflammatory disorders e.g. Vitamin D deficiency, polymyalgia rheumatica- Check Bone profile, Vitamin D, C-reactive protein

Q At what stage is bempedoic acid considered in SEL lipid management pathways?

Primary prevention (SEL lipid management summary guide):

If statin intolerance

Step 1: follow statin intolerance pathway and rechallenge with low dose alternative statin
Step 2: start ezetimibe 10mg daily
Step 3: initiate bempedoic acid 180mg daily in combination with ezetimibe if confirmed statin intolerance (green)

Secondary prevention (SEL summary link):

If statin intolerance

Step 1: follow statin intolerance pathway and rechallenge with low dose alternative statin
Step 2: start ezetimibe 10mg daily
Step 3: add bempedoic acid 180mg daily to ezetimibe if statin intolerant (green); or consider inclisiran if LDL >2.6mmol/L and *use checklist for A&G* (amber 1)

If your patient is tolerating ezetimibe but not achieving lipid lowering targets after a period of up to 3 months: consider adding **bempedoic acid 180mg** as a combination tablet or inclisiran injection (if the patient has CVD).
A SEL IMOC initiation checklist is available to support A&G discussions concerning inclisiran as this is initiated on the recommendation of a lipid specialist in primary or secondary care settings.
When initiating bempedoic acid in patients already taking ezetimibe, SEL recommendation is to prescribe the fixed combination tablet (Bempedoic acid 180mg /ezetimibe 10mg) for improved compliance and cost-effectiveness.
See the SEL lipid management pathway and NHSE Accelerated Access Collaborative AAC pathway for further information

Q At what stage is bempedoic acid considered in the NHSE/AAC statin intolerance pathway? statin-intolerance-pathway-v2.pdf (england.nhs.uk)

Bempedoic acid has a role in the "polypharmacy" element of the algorithm S.L.A.P. (Switch statins, Lower dose, Alternate day dosing, Polypharmacy) used to manage lipids in the presence of statin intolerance. Please see the SEL lipid management and NHSE/AAC lipid management guidance for more information:

If maximum tolerated dose of statin does not control non-HDL-C/LDL-C well enough after 3 months confirm statin adherence, then consider the following options based on shared decision making with the patient.

If recommended statin is contraindicated or not tolerated – follow SEL lipid management guidance and the NHSE/AAC statin intolerance pathway for advice regarding adverse effects

If statin intolerance is confirmed, consider initiating in primary care:
- Ezetimibe 10mg monotherapy
Assess response after 3 months (TA385)

- **Ezetimibe 10mg/bempedoic acid 180mg** combination when ezetimibe does not control non-HDL-C sufficiently. This may be initiated in primary care.

Ezetimibe 10mg daily. Reassess after 3 months. If non-HDL-C remains >2.5mmol/L; consider injectable therapies- arrange a fasting blood test and assess eligibility according to NICE criteria for inclisiran, evolocumab and alirocumab

Injectable therapies

If non-HDL-C > 2.5mmol/L and the patient has CVD; arrange a fasting blood test to measure LDL-C to assess eligibility according to NICE:

- inclisiran – if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy
-see FAQ for more information

OR

-Refer to specialist lipid clinic for eligibility for PCSK9i (monoclonal antibodies) alirocumab and evolocumab

Q Dosing and administration?

- In adults, the recommended dose of bempedoic acid is one film-coated tablet of 180mg or 180mg/10mg (when used in combination with ezetimibe) once daily (taken orally with or without food)

- No dose adjustment is necessary in patients with mild to moderate renal or hepatic impairment

- There is limited information for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) and clinical studies have not included patients with end stage renal disease (ESRD) on dialysis

- Bempedoic acid has not been studied in patients with severe hepatic impairment (Child-Pugh C)

- Please note, there may be a small number of patients co-prescribed a low dose of a tolerated statin if under a lipid specialist. In this circumstance, when coadministered with simvastatin, simvastatin dose should be limited to 20mg daily (or 40mg daily for patients with severe hypercholesterolaemia and high risk of cardiovascular complications, who have not achieved their treatment goal doses and when the benefits are expected to outweigh the risk)

See the SPC for further information

Q. What are the most common side effects?

- In the CLEAR studies, bempedoic acid was generally well tolerated, but laboratory abnormalities to be aware of are:
- Increases in serum uric acid: a mean increase of 0.8 mg/dL (47.6 micromole/L) in uric acid compared to baseline was observed with bempedoic acid at week 12. The elevations in serum uric acid usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation of treatment. Gout was reported in 1.4% of patients treated with bempedoic acid and 0.4% of patients treated with placebo. In both treatment groups, patients who reported gout were more likely to have a medical history of gout and/or baseline levels of uric acid above the ULN
- Increases in serum transaminases (AST and/or ALT) have been reported with bempedoic acid. The incidence of elevations (≥ 3× ULN) in hepatic transaminase levels was 0.7% for patients treated with bempedoic acid and 0.3% for placebo. These elevations in transaminases were not associated with other evidence of liver dysfunction
- Increase in serum creatinine and BUN: A mean increase of 0.05 mg/dL (4.4 micromole/L) in serum creatinine and a mean increase of 1.7 mg/dL (0.61 mmol/L) in BUN compared to baseline was observed with bempedoic acid at week 12. The elevations in serum creatinine and BUN usually occurred within the first 4 weeks of treatment, remained stable, and returned to baseline following discontinuation of treatment.
- Decreases in haemoglobin were observed in clinical trials with bempedoic acid: A decrease in haemoglobin from baseline of ≥ 20 g/L and < lower limit of normal (LLN) was observed in 4.6% of patients in the bempedoic acid group compared with 1.9% of patients on placebo. Greater than 50 g/L and < LLN decreases in haemoglobin were reported at similar rates in bempedoic acid and placebo groups (0.2% versus 0.2%, respectively). The decreases in haemoglobin usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation of treatment.
- Compared to placebo, bempedoic acid did not increase myalgia and muscle weakness in patients with statin intolerance

These laboratory abnormalities were apparent by week 4, stable over time, and reversible after treatment cessation

Please report any suspected adverse effects reactions via the Yellow Card Scheme . Consult the BNF and SPC for full details.

Symptoms of anaemia (lower numbers of red blood cells), which could include:
- Unusual tiredness
- Headache
- Shortness of breath

Symptoms of increased levels of uric acid/ gout, which could include:
- Sudden severe pain in any joint – usually the big toe, fingers, wrists, elbows, or knees
- Red, hot, or swollen skin over the affected joint

Other common symptoms, which could include:
- Pain in shoulders, legs, or arms
- Blood test results indicating liver abnormalities

Nilemdo 180mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Q. Are there any drug interactions with bempedoic acid?

- The majority of patients prescribed bempedoic acid will be statin intolerant, however there may be some patients under lipid specialists who are prescribed a low dose of tolerated statin with ezetimibe/bempedoic acid to reduce CV risk and lower their lipid profiles

- Bempedoic acid is cautioned with concomitant statin therapy:

- The pharmacokinetic interactions between bempedoic acid and statins (simvastatin, atorvastatin, pravastatin and rosuvastatin) were evaluated in a clinical trial. The co-administration of bempedoic acid and statins resulted in increased statin exposure

- Recommendations are that when bempedoic acid is coadministered with simvastatin, the simvastatin dose should be limited to 20mg daily (or 40mg daily for patients with severe hypercholesterolaemia and high risk for cardiovascular complications)

- Please note, concomitant use with simvastatin > 40mg daily is contraindicated

- The list above is not exhaustive and please consult the BNF and SPC for full details

Q What is the evidence concerning clinical outcomes?

The aim of the CLEAR Outcomes trial was to determine the effects of bempedoic acid on adverse cardiovascular events in a mixed population of patients for whom primary or secondary prevention is clinically indicated but who were unable or unwilling to take guideline-recommended doses of statins- *outcome data is on page 14*

Please note that over the duration of the study among placebo patients 15.6% received additional lipid lowering therapy compared with 9.4% of bempedoic acid patients

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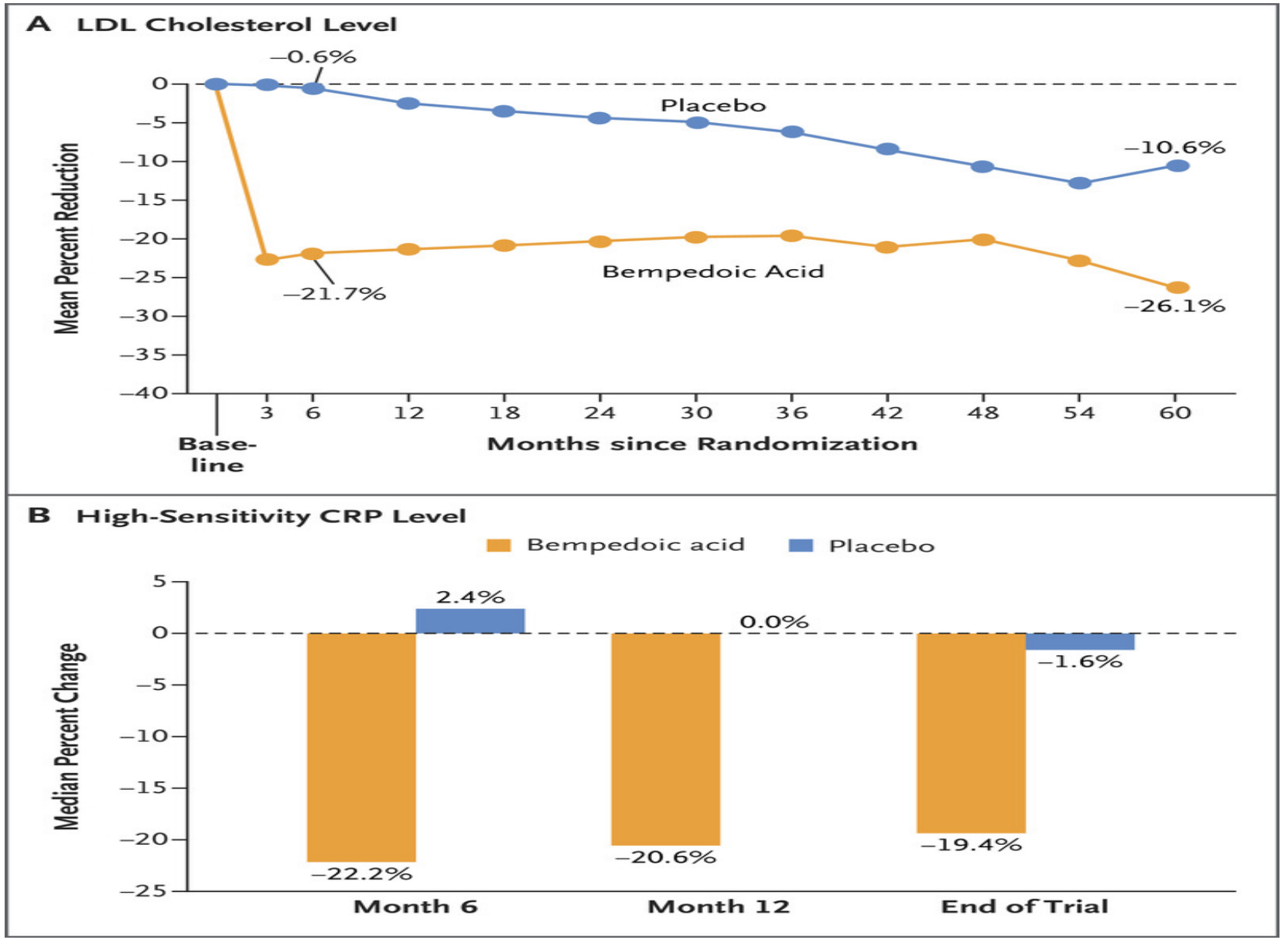

Q What is the evidence concerning clinical outcomes?

Key Secondary Efficacy Outcomes

Time to event outcomes	Bempedoic acid (N=6992)	Placebo (N=6978)	Bempedoic acid vs Placebo	
	Events, n (%)		HR (95% CI)	P-value
3-component MACE*	575 (8.2)	663 (9.5)	0.85 (0.76-0.96)	0.006
Fatal and non-fatal MI	261 (3.7)	334 (4.8)	0.77 (0.66-0.91)	0.002
Coronary revascularisation	435 (6.2)	529 (7.6)	0.81 (0.72-0.92)	0.001
Fatal or non-fatal stroke†	135 (1.9)	158 (2.3)	0.85 (0.67-1.07)	0.16†
Death from CV causes†	269 (3.8)	257 (3.7)	1.04 (0.88-1.24)	NA†
All-cause mortality†	434 (6.2)	420 (6.0)	1.03 (0.90-1.18)	NA†

MACE- major adverse cardiovascular event

CLEAR OUTCOMES trial: Nissen SE, et al. N Engl J Med. 2023 Mar 4 doi: 10.1056/NEJMoa2215024

- primary endpoint was 4-component MACE: nonfatal MI, nonfatal stroke, coronary revascularization or CV death
- Number needed to treat (NNT) was 63

- Adverse effects in the trial:

incidences of gout (3.1% vs. 2.1%) Number needed to harm (NNH) = 100
cholelithiasis (2.2% vs 1.2%) NNH =100
renal impairment (11.5% vs. 8.6%) NNH = 34
elevated hepatic-enzyme level (4.5% vs. 3.0%) NNH=66
hyperuricemia (10.9% vs. 5.6%) NNH=19

- all higher in the bempedoic acid group compared to the placebo group

CLEAR Outcomes study - bempedoic acid and cardiovascular outcomes in statin intolerant patients - General Practice notebook (gpnotebook.com)

Q What monitoring is required at baseline and at 3 months?

- At baseline:
- Ensure there are no contra-indications to therapy SPC and a shared decision with the patient to start bempedoic acid
- Check eGFR (do not start if eGFR <30ml/min)
- Check LFTs (do not start in severe hepatic impairment eg. Child-Pugh C)
- Check uric acid (do not start if active gout) discuss risk:benefit in a patient with a history of gout
- Check FBC (particularly haemoglobin (Hb) level- do not start if existing anaemia) discuss risk:benefit in a patient with a history of anaemia
- Check lipid profile if no result within the last year
- Communicate to primary care/record in patient record: baseline information at initiation

- Patient information: Report any unexplained muscle pain, tenderness or weakness. Report any gout symptoms (usually within the first month of therapy)

- At 3 months: ▼Report any side effects to the yellow card scheme
- Check eGFR- discontinue if eGFR <30ml/min, discontinue and seek specialist advice if sustained eGFR reduction of ≥15 ml/min/1.73m2 within 12 months or a Cr rise of ≥1.5 times from baseline (think kidneys- AKI guidance)
- Check LFTs- discontinue treatment if AST/ALT ≥3x ULN
- Monitor for hyperuricaemia with gout symptoms- if present, discontinue bempedoic acid
- Check FBC, stop if Hb decreases by ≥20g/L from baseline or < lower limit of normal (LLN), investigate other possible causes/refer to appropriate specialist
- Monitor for myopathy symptoms- if present, check creatine kinase (CK >10x ULN confirms myopathy: stop bempedoic acid and statin)- reduce statin dose or change statin/lipid lowering therapy if symptoms persist
- Check lipid profile to determine if the treatment is effective and discuss tolerance/adherence to therapy
- Schedule follow up annually to monitor therapy effects and tolerability as with other lipid lowering therapies

Q How do we ensure shared decision making?…. think overprescribing

Ensure a full and detailed shared-decision making/alternative options are recorded in the primary care record:

- Discuss the risks and benefits of bempedoic acid therapy with your patient
- Consider the evidence of benefits for CV risk reduction with each medicine. See slide 6 for extent of lipid lowering with available therapies
- Consider contra-indications and cautions for bempedoic acid with your patient: Discuss risk:benefit in patients with a history of gout, severe renal and hepatic impairment, anaemia, lactose intolerance and in those who are pregnant/breastfeeding

Consider not prescribing in palliative/end of life patients and those with severe frailty

- The Supportive & Palliative Care Indicator (SPICT™) tool can be used to support decision making

For patients with an intolerance to bempedoic acid ▼

- Ensure any ADRs have been reported via the yellow card system

Consider holistic approaches to lipid lowering/CV risk reduction with lifestyle interventions-there are many resources to support self-management: Heart UK and British Heart Foundation, national support groups, local social prescribing options

Support the patient to review their diet (NHS Eat Well) exercise, smoking cessation, alcohol intake and mental health considerations which are key to lipid management: In dietary intervention studies, CVD events were reduced by 12% over 5 years (NNT=95), and statins/lipid lowering therapies reduce CVD risk by 25% for each year of treatment per 1mmol/L LDL-C reduction -*Lancet 2016 (page 8 of SEL lipid management pathways)*

Q What information could we share with patient to support shared decision making?

Heart UK – The cholesterol charity

Bempedoic acid

Bempedoic acid (Nilemdo) patient leaflet

Patient leaflet (PIL)

Nustendi PIL

Heart UK – Tackling Cholesterol Together

https://www.heartuk.org.uk/tackling-cholesterol-together/home

NHS Live well

Live Well - NHS (www.nhs.uk)

NHS statins- side effects

Statins - Side effects - NHS (www.nhs.uk)

BHF- heart matters magazine

7 cholesterol-lowering alternatives to statins - BHF

REFERENCES

BNF (British National Formulary) | NICE

Overview | Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia | Guidance | NICE

Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance | Journal of the American Heart Association (ahajournals.org)

SEL Lipid Management: Medicines Optimisation Pathway

Nilemdo 180mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy - PubMed (nih.gov)

lipid-management-pathway-v6.pdf (england.nhs.uk)

statin-intolerance-pathway-v2.pdf (england.nhs.uk)

Nilemdo-Short-Patient-Leaflet-BIL210032.pdf (kssahsn.net)