Lipid Lowering Therapies

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Declarations

Pharmaceutical and other medical companies for which you have attended an Advisory Board in the past 3 years	EASD attendance 2024 – sponsorship from Daiichi Sankyo ADA virtual attendance 2023 – sponsorship from Lilly EASD attendance 2023 – sponsorship from Daiichi Sankyo ADA virtual attendance 2022 – sponsorship from Lilly EASD in person attendance 2022- sponsorship from Novonordisk EASD virtual attendance 2021 – sponsorship from Novonordisk Since joining Leeds CCG and now Leeds Health and Care Partnership/West Yorkshire Health and Care partnership no personal payments have been made to myself from pharmaceutical companies for advisory boards. I am part of an advisory board for Leeds/Manchester University for the Aster AKI Study. No payment received to me personally. I am part of an advisory board for Astra Zeneca, looking at implementation of NG28. No payment received. I have participated in the public policy projects webinars. No payment received.
Pharmaceutical and other medical companies for which you have delivered or received sponsored education in the past 3 years	Since joining Leeds CCG and now Leeds Health and Care Partnership/West Yorkshire Health and Care Partnership no personal payments have been made to myself from pharmaceutical companies for education. I have done unpaid education linked to: Kings fund, i2i, CPPE, DPC, SPS, Newcastle University, PM Management, PCDS, Amgen, Lilly, Daiichi Sankyo, Sunderland University, Astra Zeneca, Leeds University, DSN Forum, RPS, PCDE, DUK, Cardiology Professional Care, PCPA, Sanofi, PITSTOP, BHS, BCS, UKKW
Roles that you hold a professional contract with (i.e. for which you earn a salary/fee)	Consultant Pharmacist for West Yorkshire and Leeds Health and Care Partnership Tutor for Warwick university MSC in Diabetes
Professional non-financial roles	Co-chair of Diabetes UK Council of Healthcare Professionals Member of the UKCPA Diabetes and Endocrinology Committee Trustee of the Primary Care Diabetes Society Member of Royal Pharmaceutical Society Chair of the Expert Reference Group for Cardio-Renal and Metabolic Medicine at Leeds Health and Care Partnership Chair for the Diabetes Steering Group at Leeds Health and Care partnership
Other relevant potential conflicts of interest	I am working with Kidney Research UK and Ashridge Business School to understand opportunities around a leadership course for CaReMe in the UK. Currently exploratory.

Meet Melvin ….

65 years old
Lives alone

PMHx
Type 2 Diabetes since 2010
Foot ulcer 2021
CKD – G3aA2

Medications
Metformin 1g bd
Dapagliflozin 10mg od
Aspirin 75mg od
Amlodipine 5mg od
Gabapentin 300mg tds
Ezetimibe 10mg od

Observations
BMI = 38kg/m2
BP=128/77mmHg

Results
HbA1c= 80mmol/mol
LDL-C = 2.5 mmol/L
Triglycerides = 1.2mmol?/L
Non-HDLC = 3.2mmol/L
UACR = 22mg/mmol
eGFR = 55ml/min/1.73m2
Retinal screening – normal

Initial Approach

01

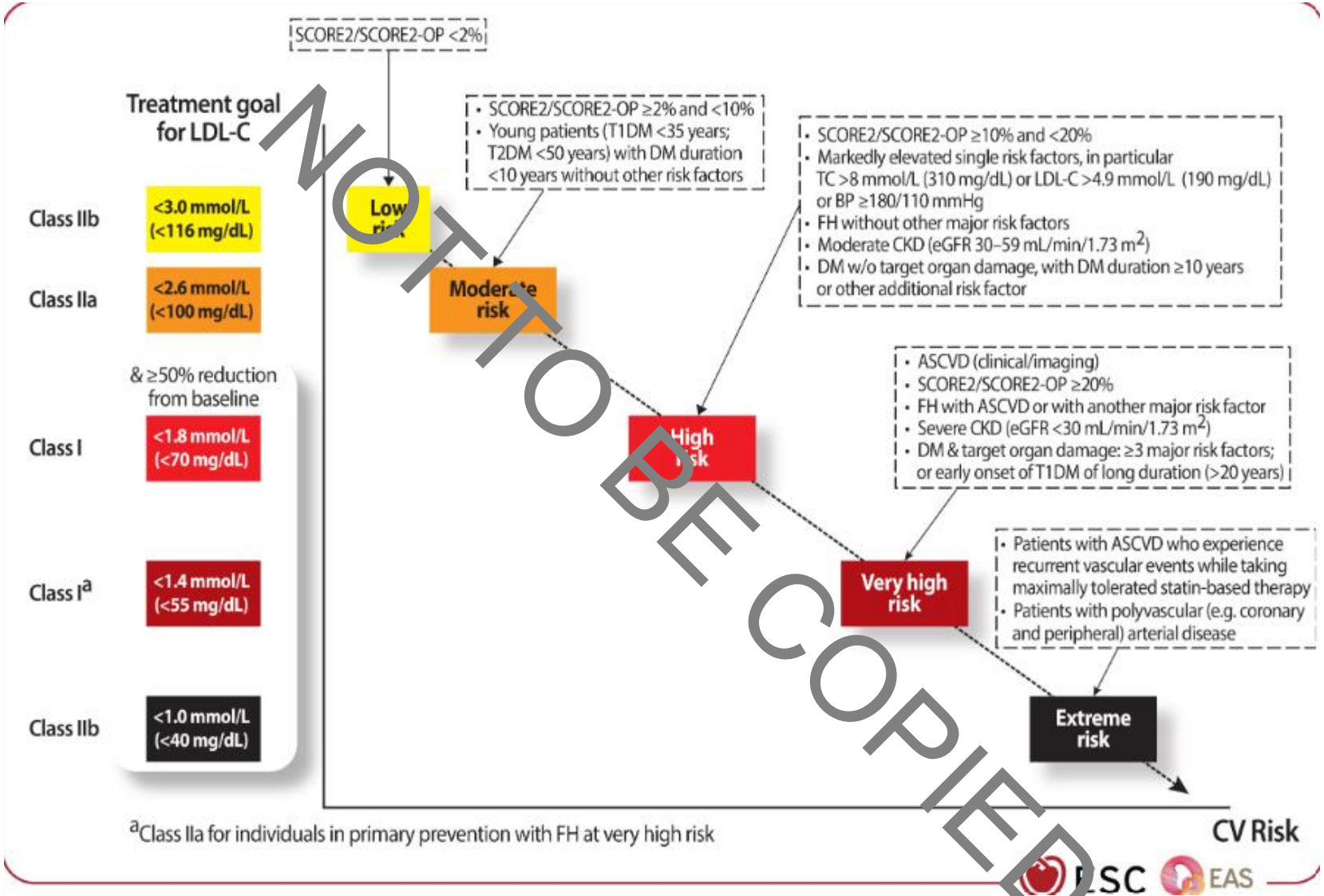
We need to understand Melvins level of cardiovascular risk to choose the right treatment options.. Does he have PVD ? Is this secondary prevention ?

02

The LDL lowering effect statins have is a class effect and this gives us different options for treatment based on your level of cardiovascular risk and your treatment goals. What has Melvin tried before ?

03

Adjustment of doses may be needed in the future and addition of other cholesterol lowering medications can be considered if needed.



François Mach, Konstantinos C Koskinas, Jeanine E Roeters van Lennep, Lale Tokgözoğlu, Lina Badimon, Colin Baigent, Marianne Benn, Christoph J Binder, Alberico L Catapano, Guy G De Backer, Victoria Delgado, Natalia Fabin, Brian A Ference, Ian M Graham, Ulf Landmesser, Ulrich Laufs, Borislava Mihaylova, Børge Grønne Nordestgaard, Dimitrios J Richter, Marc S Sabatine, ESC/EAS Scientific Document Group , 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), *European Heart Journal*, 2025;, ehaf190, https://doi.org/10.1093/eurheartj/ehaf190

Lifestyle Options

	Magnitude of the effect	Level
Lifestyle interventions to reduce TC and LDL-C levels		
Avoid dietary trans fats	++	A
Reduce dietary saturated fats	++	A
Increase dietary fibre	++	A
Use functional foods enriched with phytosterols	++	A
Use red yeast rice nutraceuticals	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B

François Mach, Colin Baigent, Alberico L Catapano, Konstantinos C Koskinas, Manuela Casula, Lina Badimon, M John Chapman, Guy G De Backer, Victoria Delgado, Brian A Ference, Ian M Graham, Alison Halliday, Ulf Landmesser, Borislava Mihaylova, Terje R Pedersen, Gabriele Riccardi, Dimitrios J Richter, Marc S Sabatine, Marja-Riitta Taskinen, Lale Tokgozoglu, Olov Wiklund, ESC Scientific Document Group , 2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), *European Heart Journal*, Volume 41, Issue 1, 1 January 2020, Pages 111–188, https://doi.org/10.1093/eurheartj/ehz455

Further information…

Melvin does have PVD and was seen by the vascular team at the time when he had his foot ulcer. This was not coded on the clinical system. This means we are treating secondary cardiovascular disease.

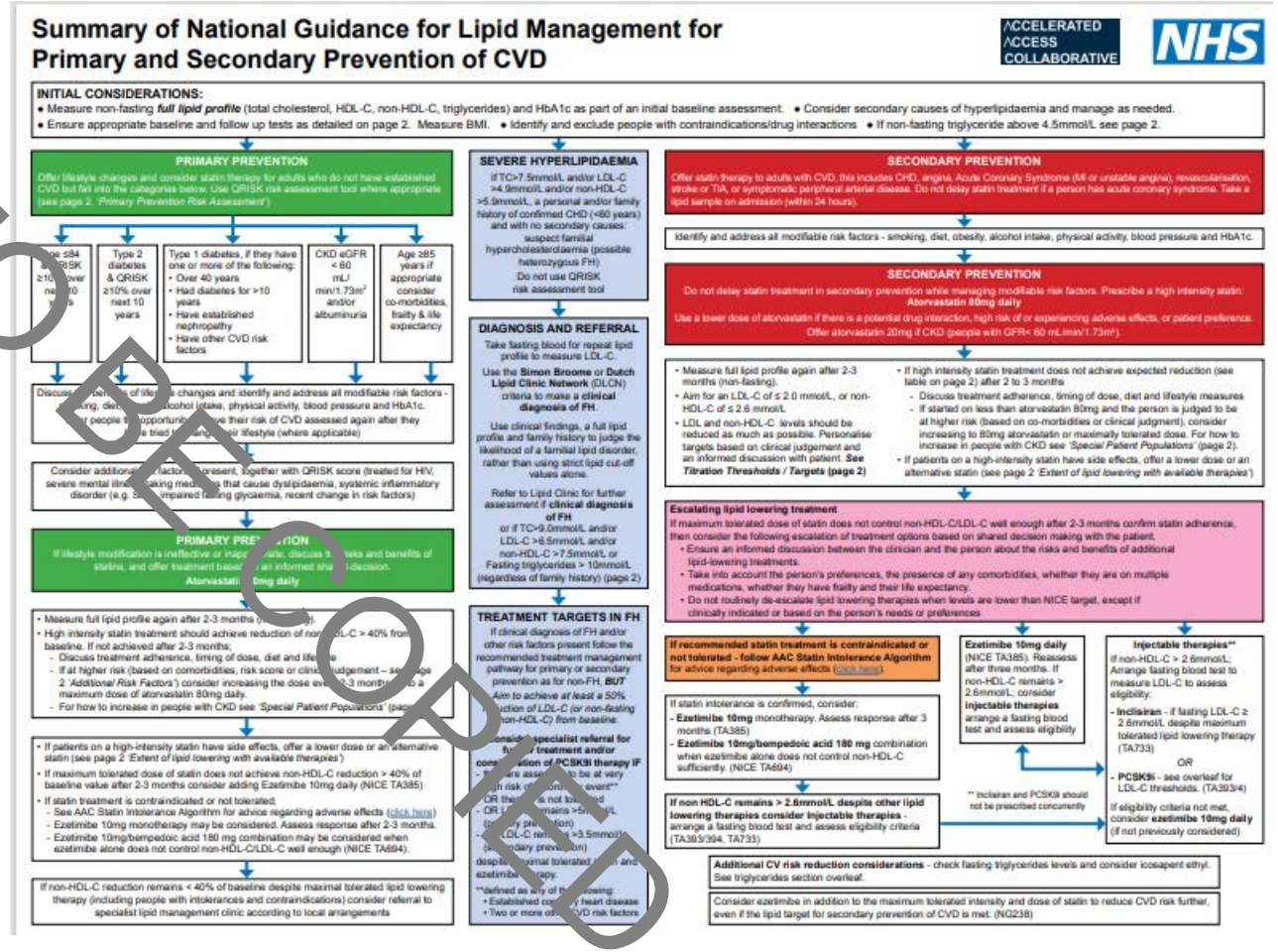
Melvin also has CKD

Melvin has only ever tried Atorvastatin 40mg once daily (confirmed by his records) and had severe muscle pain with this. The muscle pain resolved on discontinuation of the medication. He doesn't remember any blood tests being taken at the time (also confirmed by his records).

He was subsequently tried on Ezetimibe 10mg od which he has had no issues with

Guidelines

- Statins are first line therapy in the management of primary and secondary hyperlipidaemia
- Dose recommended depends on the level of risk a person carries



Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD

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INITIAL CONSIDERATIONS:

- Measure non-fasting *full lipid profile* (total cholesterol, HDL-C, non-HDL-C, triglycerides) and HbA1c as part of an initial baseline assessment.
- Consider secondary causes of hyperlipidaemia and manage as needed.
- Ensure appropriate baseline and follow up tests as detailed on page 2. Measure BMI.
- Identify and exclude people with contraindications/drug interactions
- If non-fasting triglyceride above 4.5mmol/L see page 2.

PRIMARY PREVENTION

Offer lifestyle changes and consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate (see page 2 *'Primary Prevention Risk Assessment'*)

- Type 2 diabetes & QRISK ≥10% over next 10 years
- Type 1 diabetes, if they have one or more of the following:
  - Over 40 years
  - Had diabetes for >10 years
  - Have established nephropathy
  - Have other CVD risk factors
- CKD eGFR < 60 mL/min/1.73m² and/or albuminuria
- Age ≥85 years if appropriate consider co-morbidities, frailty & life expectancy

Discuss benefits of lifestyle changes and identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c. For people with opportunistic CVD risk their risk of CVD assessed again after they have tried to improve their lifestyle (where applicable)

Consider additional risk factors if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors)

PRIMARY PREVENTION

If lifestyle modification is ineffective or inappropriate, discuss the risks and benefits of statins, and offer treatment based on an informed shared decision.

Atorvastatin 10mg daily

- Measure full lipid profile again after 2-3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 2-3 months:
  - Discuss treatment adherence, timing of dose, diet and lifestyle
  - If at higher risk (based on comorbidities, risk score or clinical judgement – see page 2 *'Additional Risk Factors'*) consider increasing the dose every 2-3 months up to a maximum dose of atorvastatin 80mg daily.
  - For how to increase in people with CKD see *'Special Patient Populations'* (page 2)
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*)
- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value after 2-3 months consider adding Ezetimibe 10mg daily (NICE TA385)
- If statin treatment is contraindicated or not tolerated:
  - See AAC Statin Intolerance Algorithm for advice regarding adverse effects (click here)
  - Ezetimibe 10mg monotherapy may be considered. Assess response after 2-3 months.
  - Ezetimibe 10mg/bempedoic acid 180 mg combination may be considered when ezetimibe alone does not control non-HDL-C/LDL-C well enough (NICE TA694).

If non-HDL-C reduction remains < 40% of baseline despite maximal tolerated lipid lowering therapy (including people with intolerances and contraindications) consider referral to specialist lipid management clinic according to local arrangements

SEVERE HYPERLIPIDAEMIA

If TC>7.5mmol/L and/or LDL-C >4.9mmol/L and/or non-HDL-C >5.9mmol/L, a personal and/or family history of confirmed CHD (<60 years) and with no secondary causes: suspect familial hypercholesterolaemia (possible heterozygous FH)

Do not use QRISK risk assessment tool

DIAGNOSIS AND REFERRAL

Take fasting blood for repeat lipid profile to measure LDL-C.

Use the **Simon Broome** or **Dutch Lipid Clinic Network** (DLCN) criteria to make a **clinical diagnosis of FH.**

Use clinical findings, a full lipid profile and family history to judge the likelihood of a familial lipid disorder, rather than using strict lipid cut-off values alone.

Refer to Lipid Clinic for further assessment if **clinical diagnosis of FH** or if TC>9.0mmol/L and/or LDL-C >6.5mmol/L and/or non-HDL-C >7.5mmol/L or Fasting triglycerides > 10mmol/L (regardless of family history) (page 2)

TREATMENT TARGETS IN FH

If clinical diagnosis of FH and/or other risk factors present follow the recommended treatment management pathway for primary or secondary prevention as for non-FH, ***BUT*** *Aim to achieve at least a 50% reduction of LDL-C (or non-fasting non-HDL-C) from baseline.*

Consider specialist referral for further treatment and/or consideration of PCSK9i therapy IF

- [illegible] are assessed to be at very high risk of [illegible] event**
- OR the [illegible] is not tolerated
- OR if [illegible] remains >5mmol/L (secondary prevention)
- OR LDL-C remains >3.5mmol/L (secondary prevention)

despite maximal tolerated [illegible] and ezetimibe therapy.

**defined as any of the following:
- Established cardiovascular heart disease
- Two or more other CVD risk factors

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes CHD, angina, Acute Coronary Syndrome (MI or unstable angina), revascularisation, stroke or TIA, or symptomatic peripheral arterial disease. Do not delay statin treatment if a person has acute coronary syndrome. Take a lipid sample on admission (within 24 hours).

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

SECONDARY PREVENTION

Do not delay statin treatment in secondary prevention while managing modifiable risk factors. Prescribe a high intensity statin: **Atorvastatin 80mg daily**

Use a lower dose of atorvastatin if there is a potential drug interaction, high risk of or experiencing adverse effects, or patient preference. Offer atorvastatin 20mg if CKD (people with GFR< 60 mL/min/1.73m²).

- Measure full lipid profile again after 2-3 months (non-fasting).
- Aim for an LDL-C of ≤ 2.0 mmol/L, or non-HDL-C of ≤ 2.6 mmol/L
- LDL and non-HDL-C levels should be reduced as much as possible. Personalise targets based on clinical judgement and an informed discussion with patient. ***See Titration Thresholds / Targets* (page 2)**
- If high intensity statin treatment does not achieve expected reduction (see table on page 2) after 2 to 3 months
  - Discuss treatment adherence, timing of dose, diet and lifestyle measures
  - If started on less than atorvastatin 80mg and the person is judged to be at higher risk (based on co-morbidities or clinical judgment), consider increasing to 80mg atorvastatin or maximally tolerated dose. For how to increase in people with CKD see *'Special Patient Populations'* (page 2).
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*)

Escalating lipid lowering treatment

If maximum tolerated dose of statin does not control non-HDL-C/LDL-C well enough after 2-3 months confirm statin adherence, then consider the following escalation of treatment options based on shared decision making with the patient.

- Ensure an informed discussion between the clinician and the person about the risks and benefits of additional lipid-lowering treatments.
- Take into account the person's preferences, the presence of any comorbidities, whether they are on multiple medications, whether they have frailty and their life expectancy.
- Do not routinely de-escalate lipid lowering therapies when levels are lower than NICE target, except if clinically indicated or based on the person's needs or preferences

If recommended statin treatment is contraindicated or not tolerated - follow AAC Statin Intolerance Algorithm for advice regarding adverse effects (click here)

If statin intolerance is confirmed, consider:

- **Ezetimibe 10mg** monotherapy. Assess response after 3 months (TA385)
- **Ezetimibe 10mg/bempedoic acid 180 mg** combination when ezetimibe alone does not control non-HDL-C sufficiently. (NICE TA694)

If non HDL-C remains > 2.6mmol/L despite other lipid lowering therapies consider injectable therapies - arrange a fasting blood test and assess eligibility criteria (TA393/394, TA733)

Ezetimibe 10mg daily (NICE TA385). Reassess after three months. If non-HDL-C remains > 2.6mmol/L; consider **injectable therapies** arrange a fasting blood test and assess eligibility

** Inclisiran and PCSK9i should not be prescribed concurrently

Injectable therapies**

If non-HDL-C > 2.6mmol/L, Arrange fasting blood test to measure LDL-C to assess eligibility:

- **Inclisiran** - if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy (TA733)

OR

- **PCSK9i** - see overleaf for LDL-C thresholds. (TA393/4)

If eligibility criteria not met, consider **ezetimibe 10mg daily** (if not previously considered)

Additional CV risk reduction considerations - check fasting triglycerides levels and consider icosapent ethyl. See triglycerides section overleaf.

Consider ezetimibe in addition to the maximum tolerated intensity and dose of statin to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is met. (NG238)

[lipid-management-pathway-v7.pdf]

What is their effect on the main lipid parameters?

LDL-C	Triglycerides	HDL-C
Effect is dose-dependent and varies between the different statins (and response can vary between individuals). A high intensity regimen reduces LDL-C by >40%; moderate-intensity therapy is defined as the dose expected to reduce LDL-C by 30-40%. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM Jr, Ridker PM, Grundy SM, Kastelein JJ. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 2014;64:485494 Recommendations | Cardiovascular disease: risk assessment and reduction, including lipid modification | Guidance | NICE	Statins usually reduce TG levels by 10-20% from baseline values. More potent statins (e.g. atorvastatin and rosuvastatin) demonstrate robust lowering of TG levels, especially at high doses. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. Nutr Metab Cardiovasc Dis 2013;23:794807	Statins can cause elevation in HDL-C levels, but the response is varied and dose dependent. Elevations ranged from 1-10%. Effect of this rise on lowering CV risk is difficult to elucidate given the confounding LDL-C lowering. Barter PJ, Brandrup-Wognsen G, Palmer MK, Nicholls SJ. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. J Lipid Res 2010;51:15461553.

Cardiovascular Risk Reduction

- In the Cholesterol Treatment Trialists (CTT) meta-analysis of individual participant data (IPD) from >170 000 participants in 26 RCTs of a statin vs. control or a more vs. less intensive statin regimen
- For each 1 mmol/L reduction in LDL-C, statin/more statin reduced over a 5-year period:
  - major vascular events (MI, CAD death, or any stroke or coronary revascularization) by 22%
  - major coronary events by 23%
  - CAD death by 20%
  - total stroke by 17%
  - total mortality by 10%

  There was no increased risk for any non-CV cause of death, including cancer, in those allocated statin

Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a metaanalysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:16701681.

Can we eliminate anything that may have caused side effects with statins ?

Risk Factors for Statin Intolerance and SAMS (Statin Associated Muscle Symptoms)

Exogeneous Factors

- Female gender
- Advanced age (> 75 yrs)
- Frailty (reduced lean body mass)
- History of muscle disorder or high CK
- Impaired renal or hepatic function – take baseline monitoring
- Personal or family history of intolerance to lipid-lowering therapies, consider taking some baseline CK levels
- Hypothyroidism – take baseline monitoring

Endogenous factors

- Excessive alcohol intake
- High intensity exercise
- Dehydration
- Drug interactions with statins (including herbal medicines)
- Vitamin D deficiency

Consider starting on lower doses in these groups

statin-intolerance-pathway-v2.pdf

SRM(Statin Related Muscle Toxicity)

Rhabdomyolysis	Myopathy	SAMS (Statin Associated Muscle Symptoms)
SRM 5	SRM 3 and 4	SRM 1 and 2
most severe form of statin-induced muscle damage and needs inpatient management	SRM 3 (CK <10x ULN) manage through statin intolerance pathway, SRM 4(CK >10x ULN but <50 ULN) refer to outpatients if no renal impairment.	Non-severe, manage through statin intolerance pathway
characterized by severe muscular pain, muscle necrosis, and myoglobinuria potentially leading to renal failure and death	Complete resolution on de-challenge	Characterised by non-severe muscular pain and tenderness (myalgia), completely resolved on de-challenge
In rhabdomyolysis, creatine kinase (CK) levels are elevated by >10 times, and often >50 times, the upper limit of normal (ULN).	CK >4 x ULN and <50 x ULN	Minimal (<4xULN) or No rise in CK
The frequency of rhabdomyolysis has been estimated to represent 0.1-8.4 cases/100 000 patient-years.	0.11% or 5 cases/100,000 patient years	10-15% of people taking statins
*ULN= upper limit of normal		

Remember that the most common cause is medication related

Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgozoglu L, Nordestgaard BG, Bruckert E, De Backer G, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, Marz W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN; European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36:10121022. 235. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:52C60C. 236. Bruckert E, Hayem G

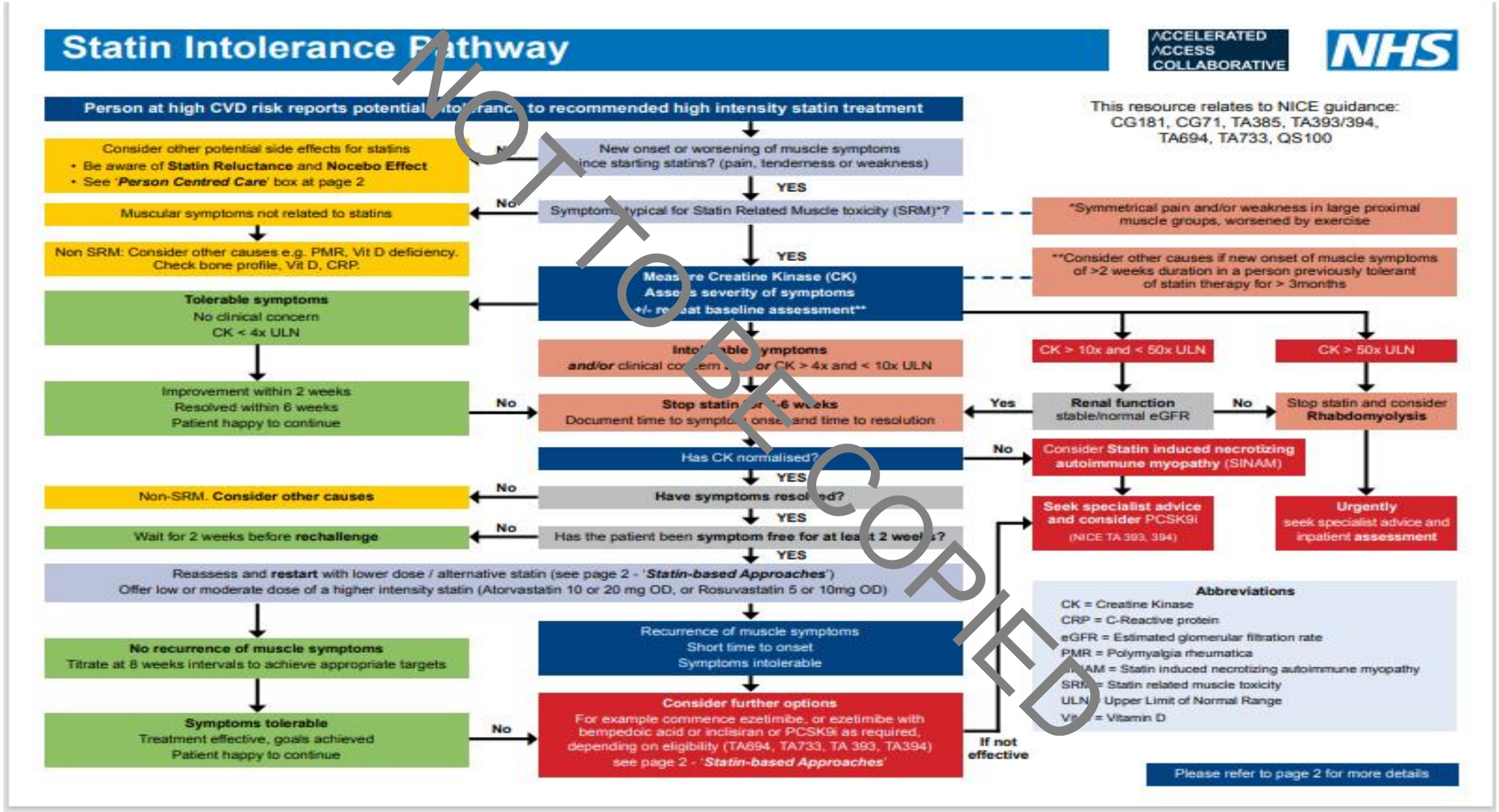
Drug interactions with statins

- Most statins are metabolised by a group of isoenzymes in the liver and intestines called CYP isoenzymes.
- Some drugs interfere with the CYP isoenzymes (being either enzyme inducers or inhibitors), this can then impact on statin metabolism and risk of side effects.

Anti-infective agents	Calcium channel blockers	Others
Itraconazole	Verapamil	Ciclosporin
Ketoconazole	Diltiazem	Danazol
Erythromycin	Amlodipine	Amiodarone
Clarithromycin		Ranolazine
HIV protease inhibitors		Grapefruit juice
		Gemfibrozil
*this is not an exhaustive list but some examples		

Egan A, Colman E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. N Engl J Med 2011;365:285287. 258. Wiklund O, Pirazzi C, Romeo S. Monitoring of lipids, enzymes, and creatine kinase in patients on lipid-lowering drug therapy. Curr Cardiol Rep 2013;15

Statin Intolerance



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Differential Diagnosis of Non-Statin Related Musculoskeletal Symptoms (non-SRM)

If the following is true :

- Asymmetric distribution
- Failure to resolve with de-challenge
- Normal CK

Consider other causes of musculoskeletal symptoms such as:

- Metabolic
- degenerative e.g. check bone profile
- inflammatory

Consider to check bone profile, Vitamin D deficiency, polymyalgia rheumatica, Vit D, CRP.

statin-intolerance-pathway-v2.pdf

Let's retry Melvin on statins...

Different Characteristics of Statins

- Statins differ in their absorption, bioavailability, plasma protein binding, excretion, and lipophilicity.
- These different characteristics have led to different potency and effects in the body
- Evening administration is usually recommended.

Statin dose mg/day	5	10	20	40	80
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42% (NOT RECOMMENDED)
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	
Atorvastatin+ Ezetimibe 10mg		52%	54%	57%	61%

Low intensity	
Medium intensity	
High intensity	

lipid-management-pathway-v7.pdf
Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM Jr, Ridker PM, Grundy SM, Kastelein JJ. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 2014;64:485494.

Stroke Risk

- Melvin read in the daily mail that statins can increase strokes.
- His father had a stroke and he is not sure he wants to take something that will give him increased risk in this area.

Haemorrhagic Stroke

- Poor quality evidence base in this area.
- Observational studies have associated reduced total cholesterol with haemorrhagic stroke
- The CTT meta-analysis, there was a 21% relative increase per mmol/L lower LDL cholesterol in haemorrhagic stroke.
- Other meta-analyses have yielded conflicting findings
- The overall benefit on other stroke subtypes greatly outweighs this small (and uncertain) risk

McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke 2012;43:21492156. 252. Hackam DG, Woodward M, Newby LK, Bhatt DL, Shao M, Smith EE, Donner A, Mamdani M, Douketis JD, Arima H, Chalmers J, MacMahon S, Tirschwell DL, Psaty BM, Bushnell CD, Aguilar MI, Capampangan DJ, Werring DJ, De Rango P, Viswanathan A, Danchin N, Cheng CL, Yang YH, Verdel BM, Lai MS, Kennedy J, Uchiyama S, Yamaguchi T, Ikeda Y, Mrkobrada M. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. Circulation 2011;124:22332242

Alternate Day dosing

- There is compelling evidence that there is still a considerable LDL-C-lowering effect when using alternative dosing, such as every other day or twice a week, with atorvastatin or rosuvastatin.
- It should be noted that there are no clinical endpoint trials however for those at high risk this may be a good option to ensure LDL-C lowering where possible.

Keating AJ, Campbell KB, Guyton JR. Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. Ann Pharmacother 2013;47:398404

Follow -Up

- Refresh Melvins memories about adverse effects associated with statin therapy
- Advise patients to contact you if they experience muscle symptoms
- Discuss the importance of adherence to get the cardiovascular benefits from statin therapy

Monitoring for Lipid lowering Therapies

Baseline	Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Renal Function : eGFR, creatinine Glucose tolerance : HbA1c Thyroid function : T4 and TSH Liver Function : ALT (or ASP), albumin
3 months	Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Liver Function : ALT (or ASP)
6-9 months	If <40% non-HDL-C reduction, up titration required. Repeat full lipid profile and ALT (or AST)within 3 months of each up-titration of statin dose or addition of Ezetimibe as required Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Liver Function : ALT (or ASP)
12 months	Lipid profile : LDL-C, HDL-C, TC, N-HDLC, triglycerides Liver Function : ALT (or ASP)
As needed	CK if unexplained muscle pain

Adapted from : lipid-management-pathway-v7.pdf

Hepatic side effects

- ALT (alanine aminotransferase) is a good marker of hepatocellular damage.
- Mild elevation of ALT occurs in 0.5-2.0% of patients on statin treatment and as might be expected this is related more commonly with potent statins or high doses.
- A clinically relevant ALT elevation would be three times the ULN, and a repeat sample would be needed if an elevation was detected.
- Given that mild elevation of ALT has not been shown to be associated with true hepatotoxicity or changes in liver function and progression to liver failure is exceedingly rare routine monitoring of ALT during statin treatment is no longer recommended beyond monitoring recommended on initiation. See table.
- In patients already experiencing ALT elevations due to steatosis, there is no evidence that statins worsen liver disease.

	AST monitoring
Baseline	Yes
2-3 months	Yes
6-9 months	If person is not optimised then to titrate as agreed and repeat AST after 2-3 months (do this on each titration and on addition of ezetimibe)
12 monthly	Yes
Annually	Not needed unless clinically indicated

Marcum ZA, Vande Griend JP, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. Am J Geriatr Pharmacother 2012;10:264271. 244. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004;126:12871292. 245. Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, Maggioni M, Kakela P, Wiklund O, Mozzi E, Grimaudo S, Kaminska D, Rametta R, Craxi A, Fargion S, Nobili V, Romeo S, Pihlajamaki J, Valenti L. Statin use and nonalcoholic steatohepatitis in at risk individuals. J Hepatol 2015;63:705712. 246. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. Am J Med Sci 2005;329:6265

Renal Function

- More research is needed to understand if statins have a clinically significant beneficial or adverse effect on renal function.
- Evidence around rosuvastatin has linked increased proteinuria to statin use:
  - With a high dose of 80 mg, a frequency of 12% was reported.
  - With the approved doses <40mg the frequency is much lower and in line with the frequency for other statins.
  - The proteinuria induced by statins is of tubular origin, usually transitory, and is believed to be due to reduced tubular reabsorption and not to glomerular dysfunction.

Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev 2014;1:CD005019. 254.
Agarwal R. Effects of statins on renal function. Am J Cardiol 2006;97:748755. 255.
Sidaway JE, Davidson RG, McTaggart F, Orton TC, Scott RC, Smith GJ, Brunskill NJ. Inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase reduce receptor-mediated endocytosis in opossum kidney cells. J Am Soc Nephrol 2004;15:22582265.

Melvin still has not tolerated his statin …What other options do we have ?

Reasons for Adding in non-statin therapy

- Patients who cannot tolerate the recommended intensity of a statin because of adverse effects
- those who do not reach their therapeutic goals with statins alone

Ideally non-statin therapy would be added to maximally tolerated statin therapy.

Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, Kopecky SL, Baccara-Dinet MT, Du Y, Pordy R, Gipe DA; ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. J Clin Lipidol 2015;9:758769. 198.

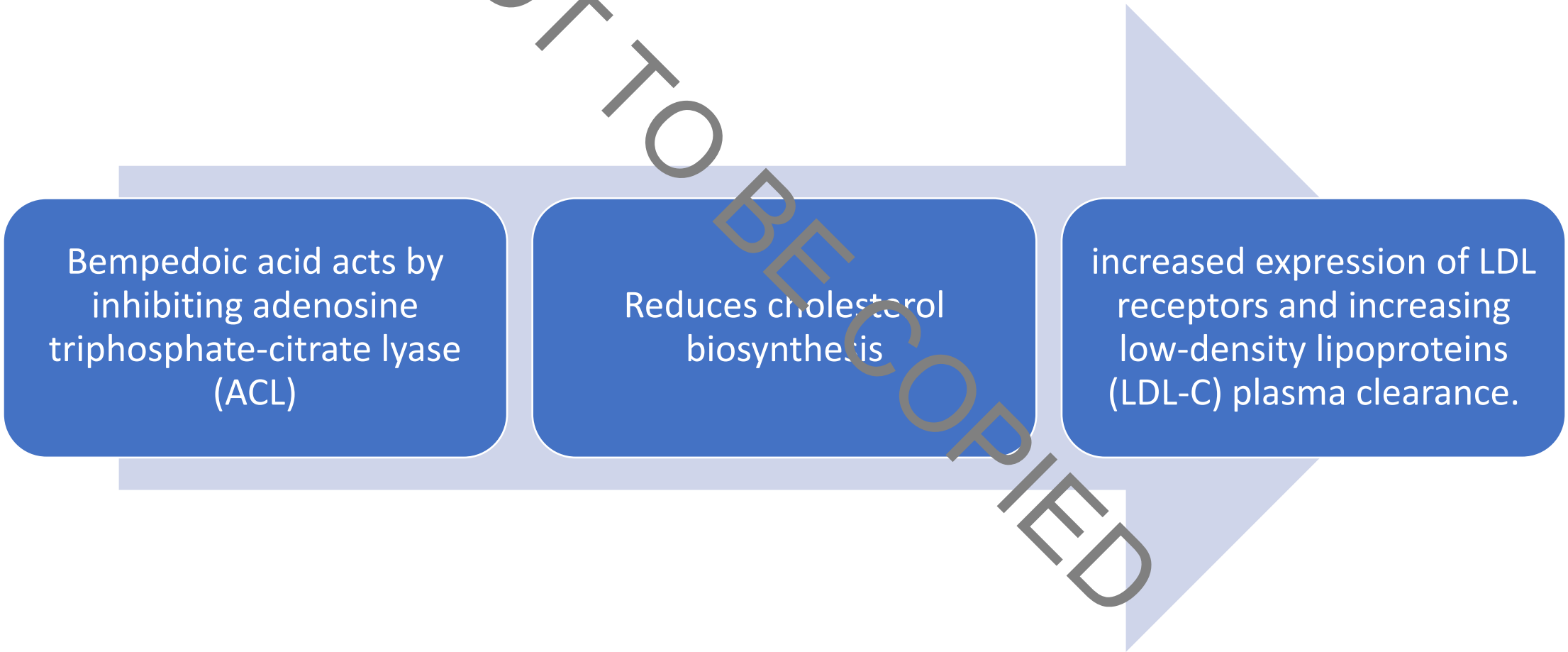
Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, Bruckert E, Cho L, Dent R, Knusel B, Xue A, Scott R, Wasserman SM, Rocco M; GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol 2014;63:25412548.

Melvin is already taking .. Ezetimibe 10mg once daily – Effects on Lipids

LDL-C	Triglycerides	HDL-C
As monotherapy Ezetimibe reduces LDL-C in by 15-22% (NB relatively high interindividual variation). A meta-analysis (2700 people) showed an 18.5% reduction in LDL-C as compared with placebo. Ezetimibe added to ongoing statin therapy reduces LDL-C levels by an additional 21-27% compared with placebo. In statin naiive patients, ezetimibe and statin combination therapy has resulted in around a 15% greater reduction in LDL-C when compared with the same statins and doses in monotherapy. Stain in addition to Ezetimibe has also significantly improved reductions in LDL-C levels when compared with doubling of the statin dose (13-20%).	As monotherapy significant 8% reduction in TGs	As monotherapy there was a significant 3% increase in HDL-C

Phan BA, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. Vasc Health Risk Manag 2012;8:415427. 262.
Pandor A, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A, Durrington PN, Chilcott J. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. J Intern Med 2009;265:568580. 263.
Morrone D, Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, Shah AK, Tershakovec AM. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis 2012;223:251261.

Bempedoic Acid – Mechanism of Action



Masana Marín L, Plana Gil N. Bempedoic acid. Mechanism of action and pharmacokinetic and pharmacodynamic properties. Clin Investig Arterioscler. 2021 May;33 Suppl 1:53-57. English, Spanish. doi: 10.1016/j.arteri.2021.02.012. PMID: 33966814.

Licence and NICE TA – Bempedoic Acid

Licence	NICE TA
indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults: - in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.	Bempedoic acid **with** ezetimibe is recommended 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 and •the company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement.

Bempedoic Acid can be taken with or without food

Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination.

https://www.medicines.org.uk/emc/product/11743/smpc

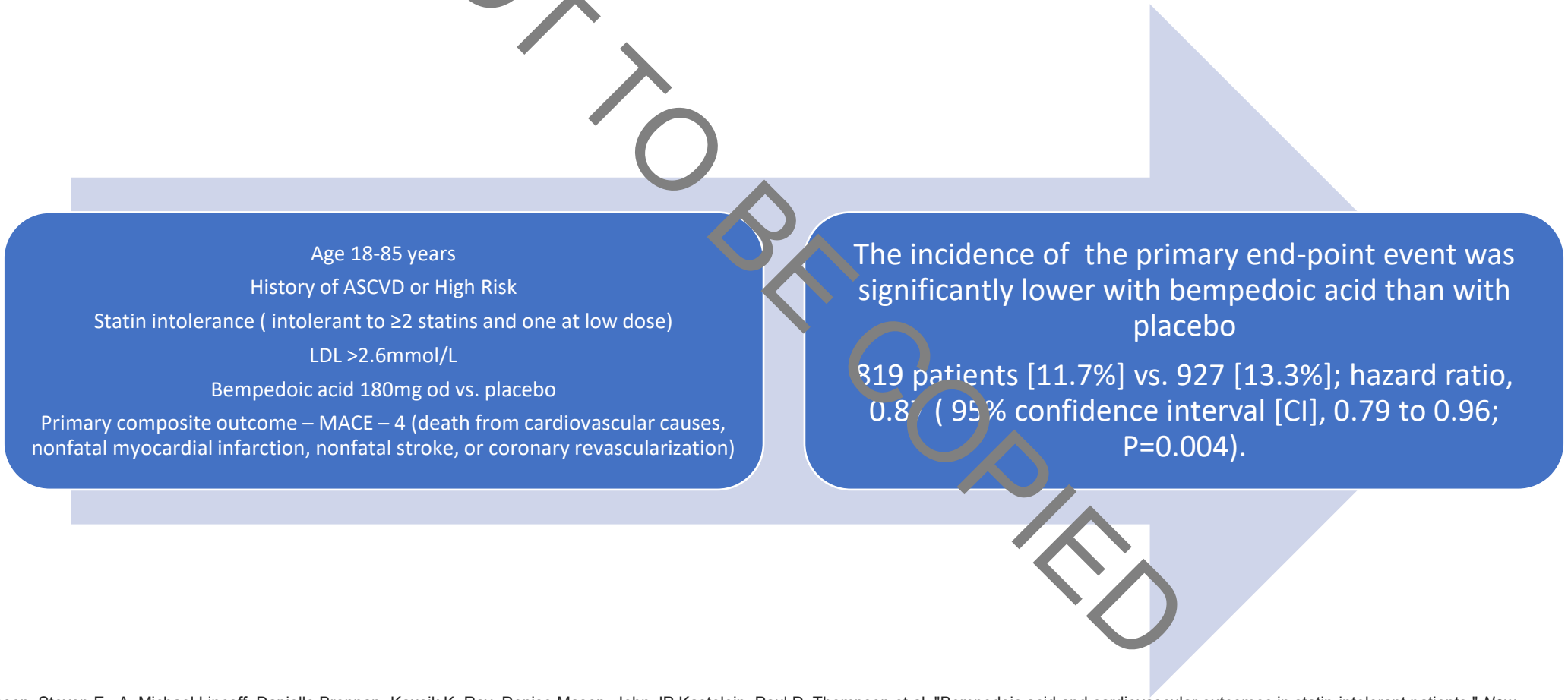
1 Recommendations | Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia | Guidance | NICE

Effect on Lipids – CLEAR Harmony

Lipid Parameters	Difference between Bempedoic Acid and Placebo (% change)
LDL-Cholesterol	-18.1%
Non-HDL Cholesterol	-13.3%
Total Cholesterol	-11.1%

Ray, Kausik K., Harold E. Bays, Alberico L. Catapano, Narendra D. Lalwani, LeAnne T. Bloedon, Lulu R. Sterling, Paula L. Robinson, and Christie M. Ballantyne. "Safety and efficacy of bempedoic acid to reduce LDL cholesterol." *New England Journal of Medicine* 380, no. 11 (2019): 1022-1032.

Cardiovascular Mortality – CLEAR Outcomes



Nissen, Steven E., A. Michael Lincoff, Danielle Brennan, Kausik K. Ray, Denise Mason, John JP Kastelein, Paul D. Thompson et al. "Bempedoic acid and cardiovascular outcomes in statin-intolerant patients." *New England Journal of Medicine* 388, no. 15 (2023): 1353-1364.

Adverse Effects and Interactions

- Bempedoic acid is a prodrug for oral administration with intracellular activation. It is activated in liver cells and to a lesser extent in kidney cells. Its absence in adipose tissue and muscle cells means that unlike statins, its potential myotoxic effect is very limited.
- Increases in serum transaminases (AST and/or ALT) have been reported with bempedoic acid, monitoring of LFTs would be recommended just as you would with statins
- Increases in serum uric acid were observed in clinical trials with bempedoic acid possibly related to inhibition of renal tubular transporter of uric acid (OAT2)
  - elevations in serum uric acid usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation
  - 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 are elevated, this should be asked about prior to initiation and consideration could be given to baseline screening.
  - Bempedoic acid has been shown to increase serum creatinine, this effect needs to be considered when interpreting changes in estimated creatinine clearance in patients on bempedoic acid treatment. This is particularly important in people needing regular renal screening e.g. patients with CKD.
  - Decreases in haemoglobin were observed in clinical trials with bempedoic acid.

https://www.medicines.org.uk/emc/product/11743/smpc

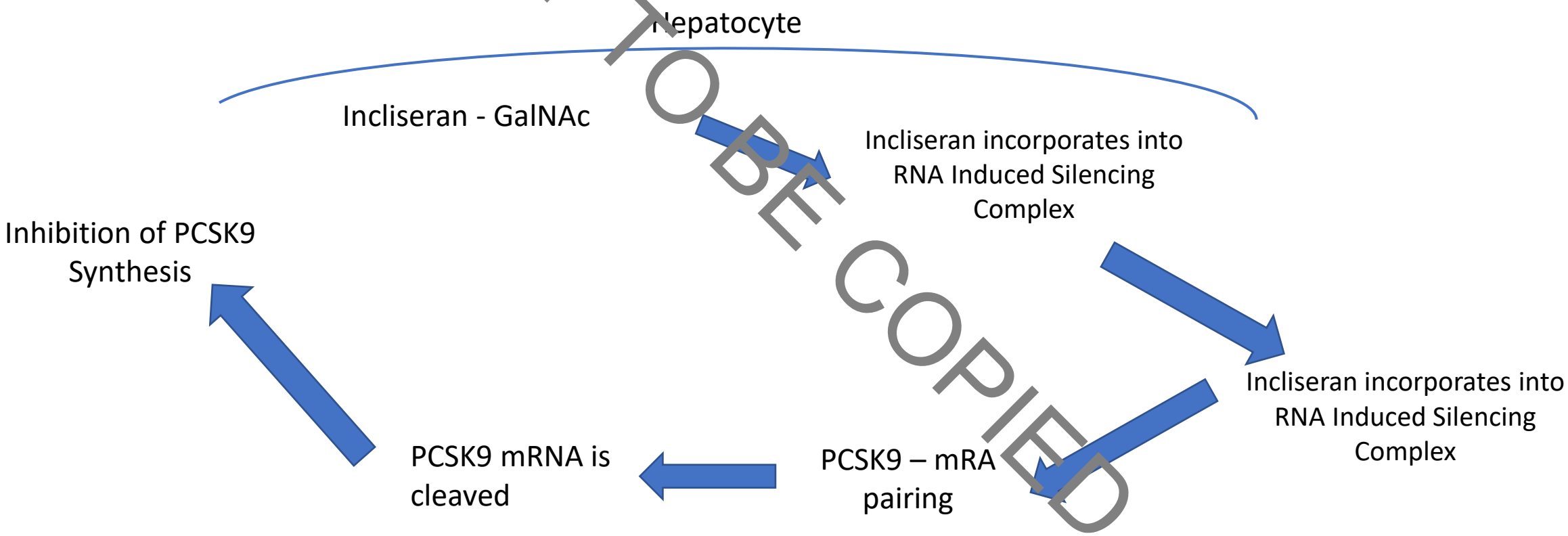
Guidelines – Eligibility Criteria for PCSK9i

	Without CVD	With CVD	
		High risk (ACS, coronary or other arterial revascularisation, PAD, stroke/TIA, CKD)	Very high risk (multiple CV events or events in multiple different vascular beds)
Primary non-FH or mixed dyslipidaemia		LDL-C>4.0mmol/L	LDL-C > 3.5mmol/L
Primary heterozygous FH	LDL-C .5.0mmol/L	LDL-C.3.5mmol/L	

Overview | Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia | Guidance | NICE
Overview | Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia | Guidance | NICE

Incliseran

- Small interfering RNA(siRNA) targeting to PCSK9



François Mach, Colin Baigent, Alberico L Catapano, Konstantinos C Koskinas, Manuela Casula, Lina Badimon, M John Chapman, Guy G De Backer, Victoria Delgado, Brian A Ference, Ian M Graham, Alison Halliday, Ulf Landmesser, Borislava Mihaylova, Terje R Pedersen, Gabriele Riccardi, Dimitrios J Richter, Marc S Sabatine, Marja-Riitta Taskinen, Lale Tokgozoglu, Olov Wiklund, ESC Scientific Document Group , 2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), *European Heart Journal*, Volume 41, Issue 1, 1 January 2020, Pages 111–188, https://doi.org/10.1093/eurheartj/ehz455

Eligibility and Administration

- Subcutaneous injection
- Initially 284 mg for 1 dose, followed by 284 mg after 3 months for 1 dose, then 284 mg every 6 months.
- Avoid in severe renal or hepatic impairment
- If a dose is more than 3 months delayed, then start from initiation again.

NICE TA 733

Recommended 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 there is a history of any of the following cardiovascular events:

- acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
- coronary or other arterial revascularisation procedures
- coronary heart disease
- ischaemic stroke or
- peripheral arterial disease

and

low-density lipoprotein cholesterol (LDL-C) concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, that is:
maximum tolerated statins with or without other lipid-lowering therapies or,
other lipid-lowering therapies when statins are not tolerated or are contraindicated

and

the company provides inclisiran according to the commercial arrangement.

Efficacy and Safety

- In the ORION 3 trial - the inclisiran-only arm, LDL cholesterol was reduced by 47·5% (95% CI 50·7–44·3) at day 210 and sustained over 1440 days.
- The 4-year averaged mean reduction of LDL-C cholesterol was 44·2% (95% CI: 47·1–41·4), with reductions in PCSK9 ranging from 62·2% to 77·8%.
- Adverse events at the injection site were reported in 14 % of participants
- The incidence of treatment-emergent serious adverse events possibly related to the study drug was 1%

Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial Ray, Kausik K et al.The Lancet Diabetes & Endocrinology, Volume 11, Issue 2, 109 - 119

ORION-4 trial - Ongoing

- Set up to interrogate CV outcomes and safety of the medication
- To randomise >15000 participants ages >55 years old with pre-existing CV disease for a median of 5 years
- Pre-existing CV disease – MI, ischaemic stroke, PAD (with revascularisation/aortic aneurysm repair)
- LDL-C - >4mmol/L to proceed (point of care testing)
- Aim for average LDL <2.6mmol/L
- Looking at Primary composite outcome – MACE – CHD death, MI, fatal/non-fatal ischaemic stroke, urgent coronary revascularisation.
- Central appointments made harnessing NHS digital data - feasibility information looking at areas with high CV outcomes

https://www.orion4trial.org/homepage-uk

Out of the Box thinking … what about incretin therapy ?

- Melvin has a high HbA1c and needs additional therapy
- If we look at adding SGLT2i to a GLP-1 , we get the following NNTs (5 year) :
  - MI, Stoke, CVD – 22
  - HF- 14
  - Renal Fx decline – 9
- Average LDL-C reduction with GLP-1 receptor agonist therapies is modest, typically ranging from 4% to 8% of baseline LDL-cholesterol levels; dual GIP/GLP-1 agonists may achieve even greater reductions of about 7% to 12%

Hasegawa Y, Hori M, Nakagami T, Harada-Shiba M, Uchigata Y. Glucagon-like peptide-1 receptor agonists reduced the low-density lipoprotein cholesterol in Japanese patients with type 2 diabetes mellitus treated with statins. J Clin Lipidol. 2018 Jan-Feb;12(1):62-69.e1. doi: 10.1016/j.jacl.2017.11.006. Epub 2017 Nov 21. PMID: 29217412.
Chae Y, Kwon SH, Nam JH, Kang E, Im J, Kim HJ, Lee EK. Lipid profile changes induced by glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a systematic review and network meta-analysis. Expert Rev Clin Pharmacol. 2024 Aug;17(8):721-729. doi: 10.1080/17512433.2024.2363838. Epub 2024 Jun 6. PMID: 38832475.

In the future what might be available for treatment of lipids for Melvin …

- next-generation PCSK9-targeted therapies are emerging, such as oral inhibitors, vaccines, and gene editing applications using CRISPR-Cas9, which may revolutionize lipid management but are still in the developmental stages
- Other antisense oligonucleotides are directed at molecules such as apolipoprotein C3, angiopoietin-like protein 3, and lipoprotein(a) (Lp(a)); examples include pelacarsen and olpasiran, which show promise for genetically driven dyslipidemias and particularly for lowering Lp(a), a difficult-to-treat risk factor
- Obicetrapib, a new CETP inhibitor, has demonstrated significant LDL-C reduction as well as improvement in HDL cholesterol and other apolipoproteins, and is positioned to be a next-step therapy after statins and ezetimibe. Investigational strategies to enhance HDL functionality and ApoA1 also continue, though clinical efficacy remains under study

Capuozzo M, Ottaiano A, Cinque C, Farace S, Ferrara F. Cardiovascular risk management beyond statins: review of new therapies available in Italy. Egypt Heart J. 2025 Jul 1;77(1):[illegible]8. doi: [illegible]0.1186/s43044-025-00660-0. PMID: 40593368; PMCID: PMC12214137.
Advances in lipid management: current challenges and new horizons | Medicine Today
Massimiliano Ruscica, Alessandra Bertoletti, Cecilia Gobbi, Cesare R Sirtori, Stefano Carugo, Alberto Corsini, Lipid-lowering approaches to manage statin-intolerant patients, *European Heart Journal Supplements*, Volume 26, Issue Supplement_1, April 2024, Pages i56–i59, https://doi.org/10.1093/eurheartjsupp/suae007
Lipid-lowering therapy. What comes after the standard treatment? (Statin/Ezetimibe/PCSK9)
Banach M, Surma S, Toth PP; endorsed by the International Lipid Expert Panel (ILEP). 2023: The year in cardiovascular disease - the year of new and prospective lipid lowering therapies. Can we render dyslipidemia a rare disease by 2024? Arch Med Sci. 2023 Nov 2;19(6):1602-1615. doi: 10.5114/aoms/174743. PMID: 38058712; PMCID: PMC10696981.

Thank you

Any Questions ?