Health Innovation Manchester

Inclisiran education webinar

Webinar contents

1 PCSK9 and cholesterol

2 How inclisiran works

3 Safety, efficacy & side effects

4 Inclisiran guidelines

5 Practical prescribing: administration, ordering & payment

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PCSK9 and cholesterol

Proprotein convertase subtilisin/ kexin type 9 (PCSK9) and cholesterol

- PCSK9 is made in the liver and controls cholesterol levels, it is a protease so breaks down other proteins.
- PCSK9 breaks down LDL receptor, reducing LDL receptors on the liver cell. Consequently, less LDL is cleared by the liver, increasing LDL concentration in the blood (Figure 1)

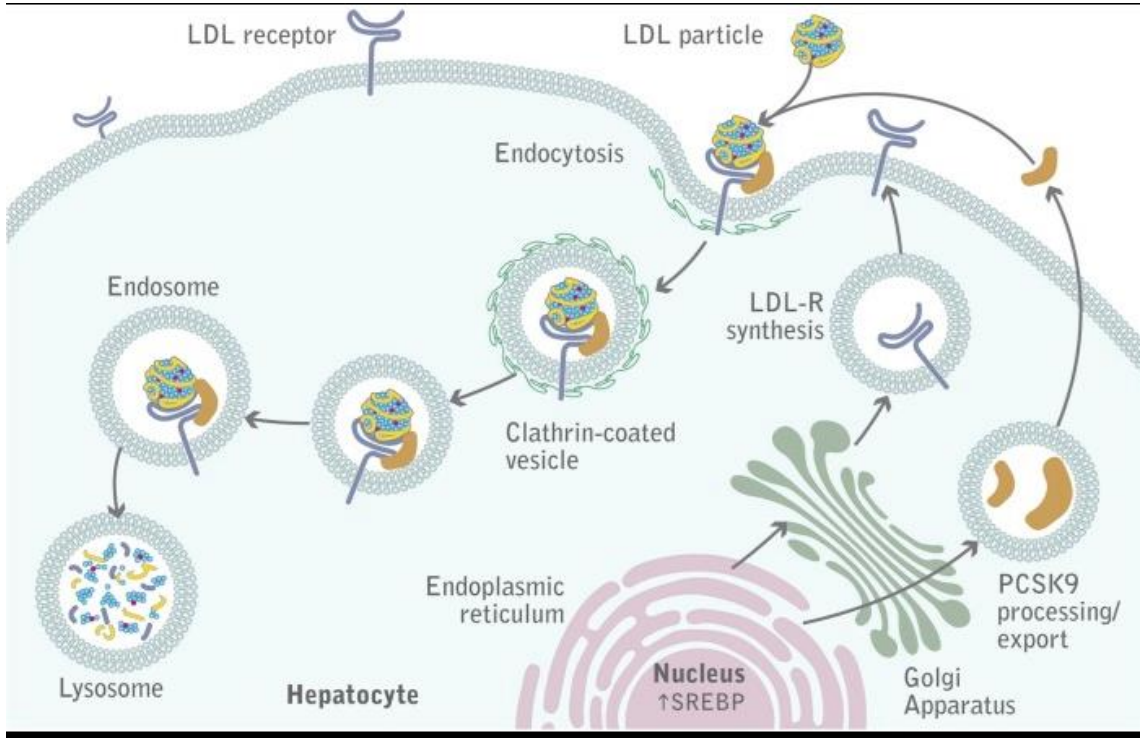
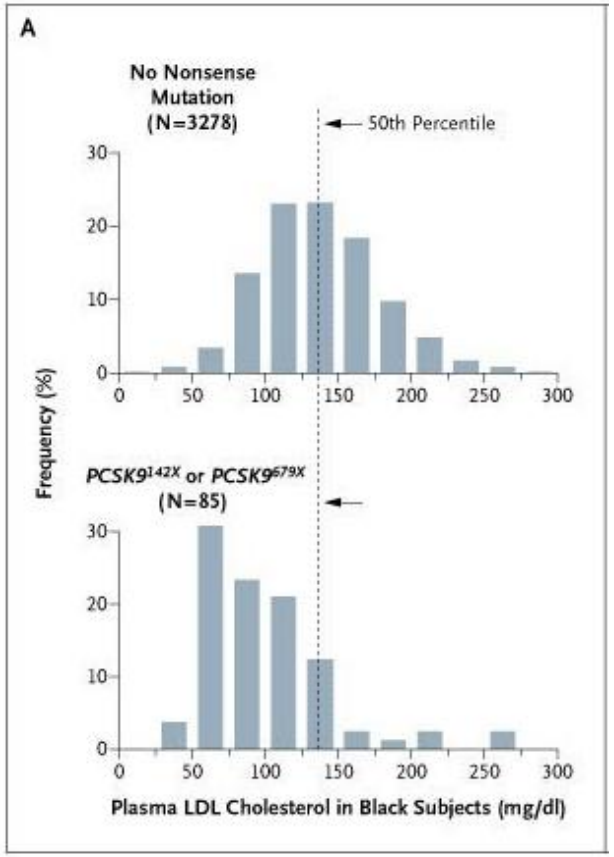


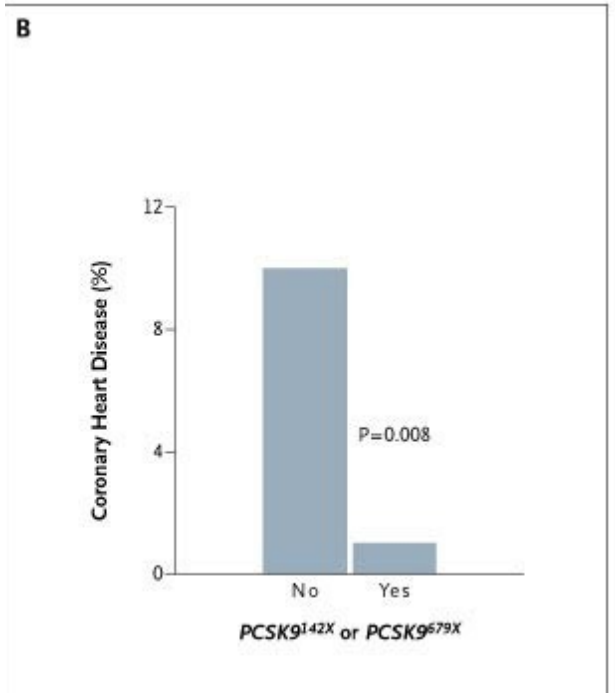
Figure 1: PCSK9-mediated degradation of LDL receptor, J Lipid Res 2012;53:2515

Proprotein convertase subtilisin/ kexin type 9 (PCSK9) and cholesterol

- Loss of function mutations of PCSK9 reduces LDL receptor degradation, so there are more LDL receptors on the liver cell, lowering LDL cholesterol in the blood and reducing risk of CHD (Cohen et al NEJMed 2006;354:1264)



Panel A: the distribution of plasma LDL cholesterol levels for subjects with wild type PCSK9 (top) compared with the distribution of levels among subjects who had PCSK9 loss of function mutation (bottom).



Panel B: the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

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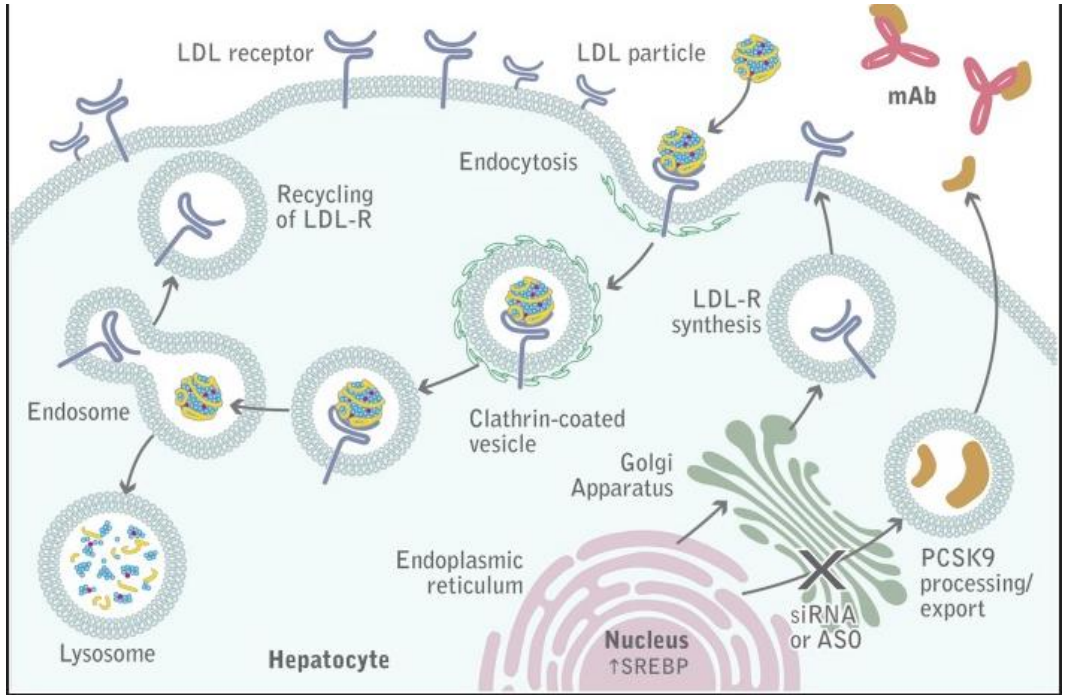
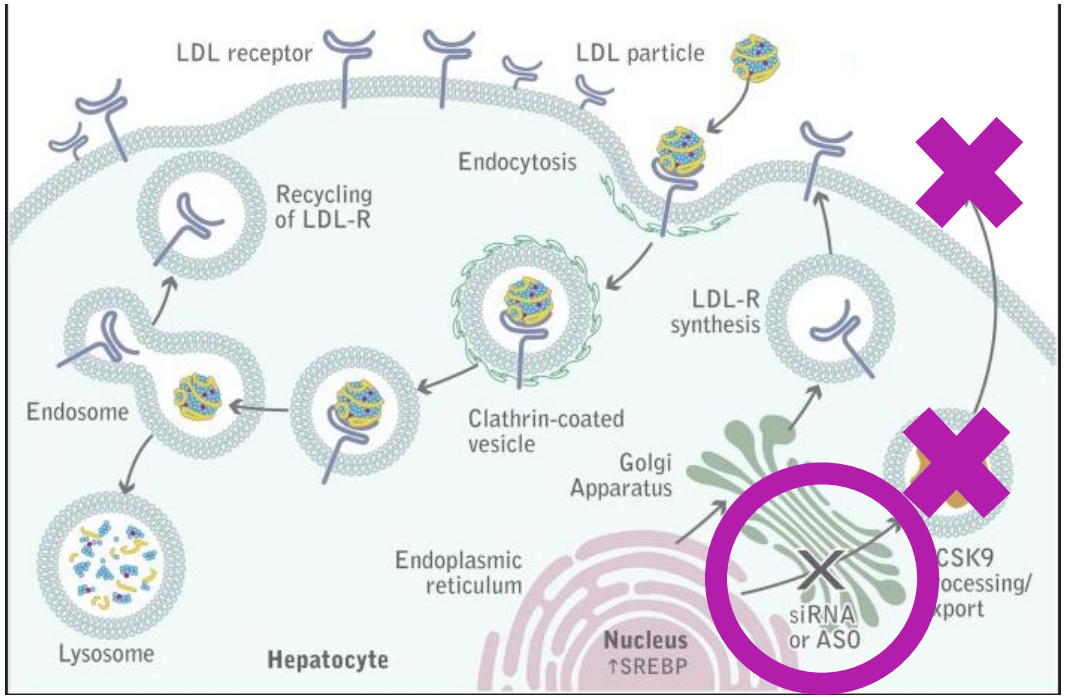
How inclisiran works

How inclisiran works-
PCSK9 inhibitors vs inclisiran mechanism of action

PCSK9 inhibitors are monoclonal antibodies which bind to PCSK9 and inhibit its function



Inclisiran blocks the production of PCSK9 protein production at mRNA source in the liver cell



Inclisiran is the first and only therapy that uses the small interfering RNA (siRNA) mechanism of action to lower LDL-C

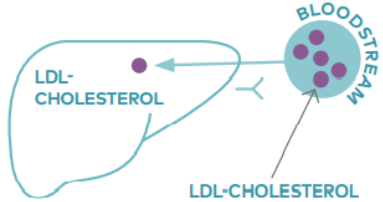
References: [1] Stoekenbroek RM et al. Future Cardiol 2018;14(6):433-442. [2] Leqvio Summary of Product Characteristics.. Available at: https://www.medicines.org.uk. [3] Klinovski M et al. Inclisiran: A Small Interfering RNA Molecule for Treating Hypercholesterolemia. In: CADTH Issues in Emerging Health Technologies. 180;2019

How inclisiran works

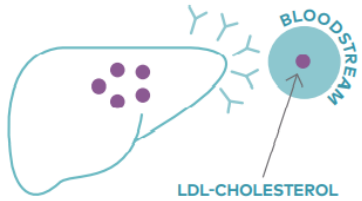
Inside the liver inclisiran prevents production of the protein, PCSK9

This increases the lifespan of the LDL receptors that sit on the surface of liver cells by preventing degradation by PCSK9

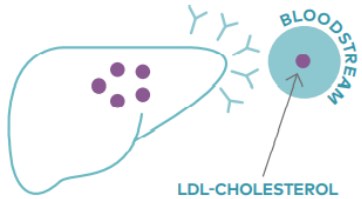
LDL receptors allow LDL-cholesterol to move from the blood to the inside of the liver to be broken down



More LDL receptors on the surface of the liver means more LDL-cholesterol can be let inside the liver, where it is broken down and removed from the body.



This means there is less LDL-cholesterol in the blood and the risk of build up in the arteries is reduced



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Safety, efficacy & side effects

Safety and efficacy

Study inclusion criteria

ORION 10 [1]

- Patients ≥ 18 years
- History of ASCVD, which was defined as CHD, CVD, or PAD
- LDL-C ≥ 70 mg/dL
- Fasting TG < 400 mg/dL
- Lipid-lowering therapies: statin and/or ezetimibe
- If on statin, patient must have been receiving the maximally tolerated dose (MTD)
- If not already on a statin, patient must have shown intolerance to all doses of ≥ 2 statins
- Relevant exclusion criteria: Any major CV event ≤ 3 months before study, uncontrolled severe HTN (> 180/110) despite treatment, PCSK9 inhibitor treatment

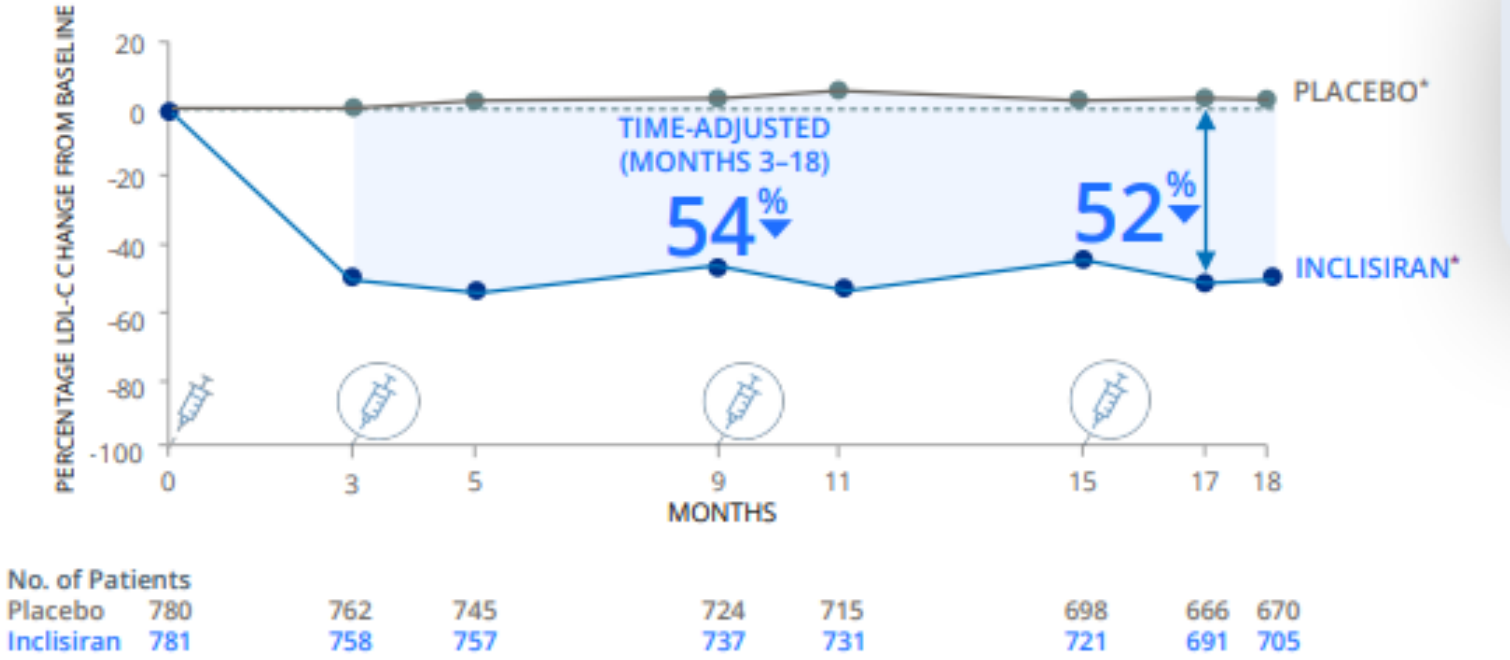
ORION 11 [1]

- Patients ≥ 18 years
- History of ASCVD, which was defined as CHD, CVD, or PAD
- ASCVD-risk equivalents: T2DM, FH, and patients with a 10-year risk of a CV event (Framingham Risk)
- LDL-C ≥ 70 mg/dL
- Fasting TG < 400 mg/dL
- Lipid-lowering therapies: statin and/or ezetimibe
- If on statin, patient must have been receiving the maximally tolerated dose (MTD)
- If not already on a statin, patient must have shown intolerance to all doses of ≥ 2 statins
- Relevant exclusion criteria: Any major CV event ≤ 3 months before study, uncontrolled severe HTN (> 180/110) despite treatment, PCSK9 inhibitor treatment

References: [1] Ray KK et al. N Engl J Med 2020;382(16):1507-1519.

Efficacy- primary endpoints ORION-10

- ORION-10 in combination with a maximally tolerated statin, inclisiran delivered effective and sustained LDL-C reduction in patients with ASCVD1
- In patients with ASCVD on a maximally tolerated statin in ORION-10, inclisiran: [1,2]
  - Reduced LDL-C by 52% relative to placebo at Month 17, as compared with baseline (95% CI: −55.7 to −48.8; P<0.0001)

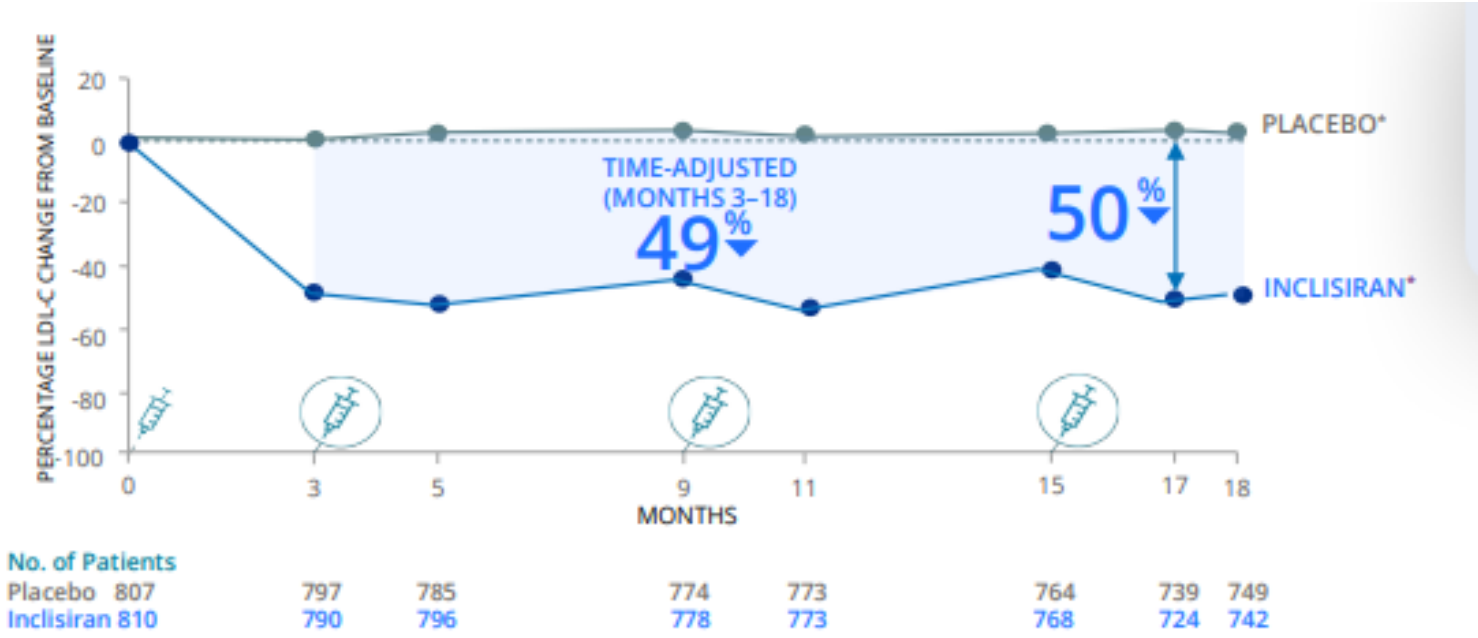


* Reductions were achieved on top of a maximally tolerated statin and/or other lipid-lowering therapies. Adapted from Ray KK et al. N Engl J Med 2020[1]

References: [1] Ray KK et al. N Engl J Med 2020;382(16):1507-1519. [2] Leqvio Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/12039/smpc#gre

Efficacy- primary endpoints ORION-11

- In combination with a maximally tolerated statin, inclisiran delivered effective and sustained LDL-C reduction in patients with ASCVD1
- In patients with ASCVD (or risk equivalents) on a maximally tolerated statin in ORION-11, inclisiran: [1,2]
- Reduced LDL-C by 50% relative to placebo at Month 17, as compared with baseline (95% CI: −53.1 to −46.6; P<0.0001)



*Reductions were achieved on top of a maximally tolerated statin and/or other lipid-lowering therapies. Adapted from Ray KK et al. N Engl J Med 2020[1]

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Efficacy- primary endpoints ORION-11

ORION-10:[1]

As compared with baseline:	**Absolute change in LDL-C at Month 17:** −1.40 mmol/L relative to placebo (95% CI: −1.48 to −1.32; P<0.001)	Improvement relative to placebo in other key secondary endpoints at Month 17 including **lower levels of total cholesterol, non-HDL-C and apolipoprotein B** (P<0.001)
	Percentage change in PCSK9 at Month 17: −83.3% relative to placebo (95% CI: −89.3 to −77.3; P<0.001)	**Time-adjusted absolute change in LDL-C between Months 3 and 18:** −1.38 mmol/L relative to placebo (95% CI: −1.44 to −1.31; P<0.001)

ORION-11:[1]

As compared with baseline:	**Absolute change in LDL-C at Month 17:** −1.34 mmol/L relative to placebo (95% CI: −1.42 to −1.26; P<0.001)	Improvement relative to placebo in other key secondary endpoints at Month 17 including **lower levels of total cholesterol, non-HDL-C and apolipoprotein B** (P<0.001)
	Percentage change in PCSK9 at Month 17: −79.3% relative to placebo (95% CI: −82.0 to −76.6; P<0.001)	**Time-adjusted absolute change in LDL-C between Months 3 and 18:** −1.26 mmol/L relative to placebo (95% CI: −1.33 to −1.20; P<0.001)

CI – confidence interval; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; PCSK9 – proprotein convertase subtilisin/kexin type 9

Reference: [1] Ray KK et al. N Engl J Med 2020;382(16):1507-1519.

Safety and efficacy

The safety and efficacy of inclisiran were investigated in three Phase III trials, including over 3,500 patients worldwide[1,2]

	ORION-10	ORION-11	ORION-9
PHASE	3		
STUDY DESIGN	Multicenter, double-blind, randomized, placebo-controlled 18-month trial. Patients were randomized to receive inclisiran or placebo. Patients were taking a maximally tolerated dose of statin with/without other lipid modifying therapy.		
STUDY SIZE	N=1561	N=1414	N=482
PATIENT POPULATION	Established ASCVD*	Patients had either established ASCVD or ASCVD-risk equivalents	Heterozygous familial hypercholesterolaemia
CO-PRIMARY ENDPOINT 1	% change in LDL-C from baseline to Day 510/month 17 relative to placebo		
CO-PRIMARY ENDPOINT 2	Time adjusted % change in LDL-C from baseline after Day 90 (3 months) and up to Day 540 Month 18)		
SECONDARY ENDPOINT 1	Several, including % of patients who achieved LDL-C target < 70 mg/dL at month 17		
SECONDARY ENDPOINT 2	Several, including % of patients who achieved LDL-C target < 50 mg/dL at month 17		

*ASCVD was defined as coronary heart disease, cerebrovascular disease or peripheral arterial disease

References: [1] Ray KK et al. N Engl J Med 2020;382(16):1507-1519. [2] Raal FJ et al. N Engl J Med 2020;382(16):1520-1530.

Side effects

No contraindications apart from allergy to ingredients

- No known clinically significant interactions
- Limited data on the use in pregnancy and breastfeeding

Common side effects

- Injection site reactions – all reported mild-moderate
- ▼ black triangle drug – report any side effects via the Yellow Card Scheme – responsibility of all healthcare professionals
- The black triangle is used for all relatively new drugs for a period of time, it does not mean the treatment is dangerous

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Inclisiran guidelines: NICE and GMMMG

Inclisiran indication: NICE approval and guidelines

On 1 September 2021, NICE issued draft final guidance (NICE TA733) recommending inclisiran 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 (secondary prevention):
  - 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 or if statin intolerant, or a statin is contraindicated

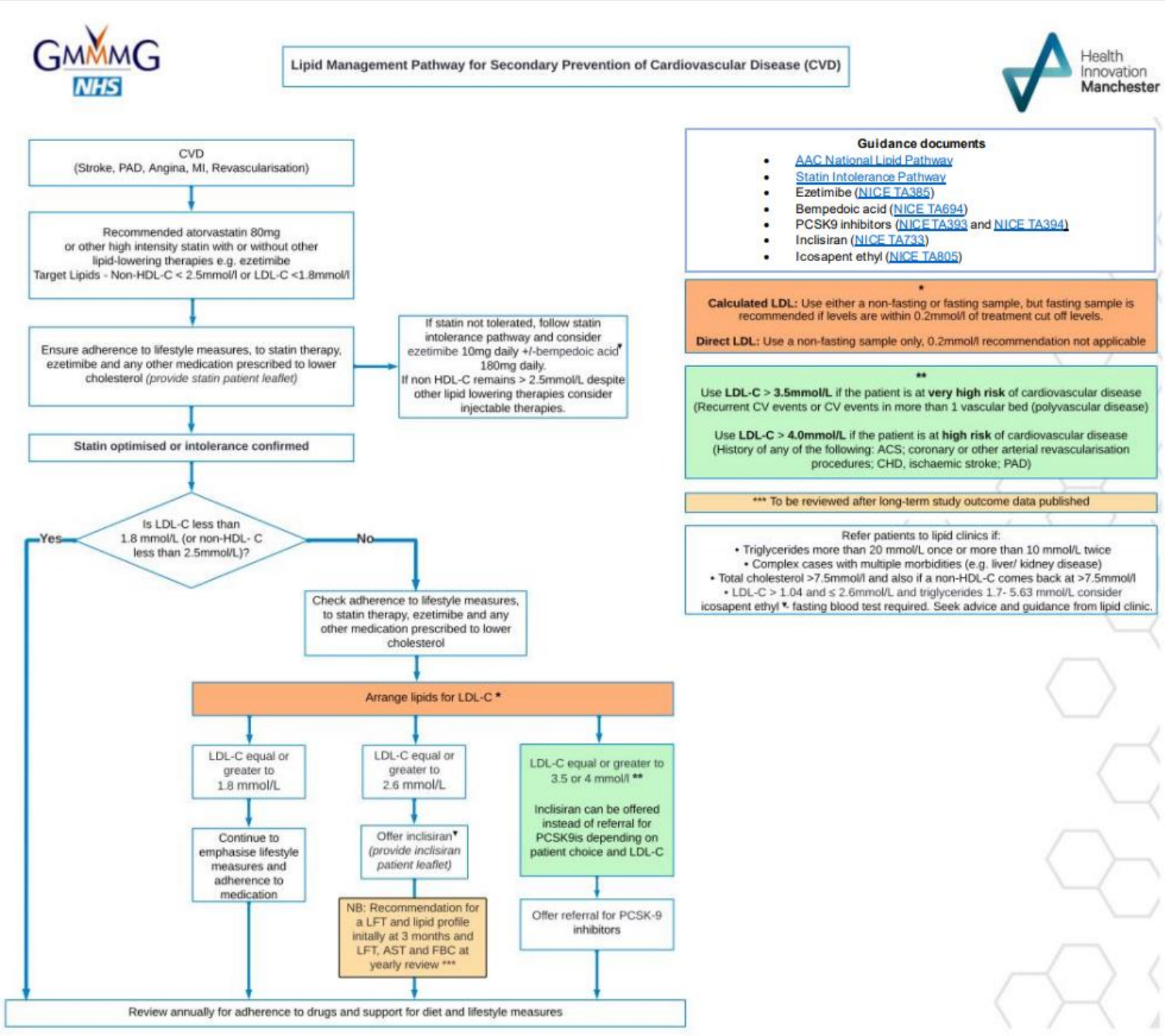
Inclisiran indication: GMMMG guidelines

- **Inclisiran has now been listed as GREEN by GMMMG for Greater Manchester Formularies**

GMMMG have published two resources:

- The Greater Manchester lipid management pathway for secondary prevention of CVD
- Inclisiran prescribing and ordering information
- The pathway was created in collaboration with clinicians from across Greater Manchester and was adapted from the NICE-endorsed lipid pathway published 15th Dec 2021

Available on GMMMGs website [here]



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Practical prescribing: administration, ordering

Practical prescribing

All information is in the GMMMG inclisiran implementation toolkit.

Recommended dose is 284 mg inclisiran administered as a subcutaneous injection using a single use, *pre-filled syringe*

Inclisiran is given by subcutaneous injection into the abdomen; alternative injection sites include the upper arm or thigh

Dose and administration

Administered by a healthcare professional (HCP).
HCP can be a HCA, pharmacist, physicians associate, nurse or GP- just qualified to give a sub cut injection

Ensure adherence to lifestyle measures, to statin therapy, ezetimibe and any other medication prescribed to lower cholesterol

Practical prescribing

- After an initial dose, inclisiran is administered again at 3 months, followed by every 6 months

- No dose adjustments are required for patients with mild or moderate hepatic impairment, mild, moderate or severe renal impairment or end-stage renal disease, or elderly patients
- Recommendation for a LFT and lipid profile 3 months, 9 months and LFT, AST and FBC at yearly review- as shown in lipid management secondary prevention pathway

If patient misses a dose

- If doses missed – see the SPC for clear guidance (3 months rule)
- If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule.
- If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months.

Storage

- Inclisiran has a 3-year shelf life
- It does not require any special storage conditions, and should not be frozen
- The solution should be clear, colourless to pale yellow and essentially free of particulates
- If the solution contains visible particulate matter, the solution should not be used

Ordering inclisiran

You can order inclisiran (Leqvio) using AAH Point or your PMR system using the following codes:

Product Name	EAN Code	PIP Code
Inclisiran (Leqvio)	7613421044237	4174751

- Inclisiran is available from the wholesaler (AAH) at £45 (Nominal Charge), which is payable 30 days from the end of that month. Inclisiran is listed in the Drug Tariff as a 'zero discount' item (no claw-back applicable)
- No minimum order is required
- If you need any further support regarding inclisiran (Leqvio®), please contact AAH Customer Care. You can Live Chat with via AAH Point from 9am-5pm Monday to Friday or call them on 0344 5618899
- See 'Summary information on the funding and supply of inclisiran' for more information

Patient leaflet

- Available on HInM website & inclisiran template on clinical system

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Case finding

Case finding for lipid management for secondary prevention of CVD

- EMIS, SystmOne and Vision guidance documents
- Searches available for the identification of high-risk people requiring lipid optimisation for secondary prevention of cardiovascular disease (CVD)

Report name
BLOODS - PATIENT LIST - BRING IN FOR BLOODS (LAST LIPIDS OVER 12m AGO) Based on results of search CVDPL4a
COHORT 1 - PATIENT LIST - Not on a Statin Based on results of search COHORT 1
COHORT 2 - PATIENT LIST - On Suboptimal Statin Based on results of search COHORT 2
COHORT 3 - PATIENT LIST - On Suboptimal Statin Dose Based on results of search COHORT 3

Report name
COHORT 4a - PATIENT LIST - Statins Maximised - Eligible for Injectables Based on results of search COHORT 4
COHORT 4b - PATIENT LIST - Statins Maximised - Not Eligible for Injectables Based on results of search COHORT 4
COHORT 5 - PATIENT LIST - Remaining patients Based on results of search COHORT 5