Novel Lipid Therapies

Dr Tatiana Christmas

ST4 Metabolic Medicine/Chemical Pathology

Imperial College Healthcare NHS Trust

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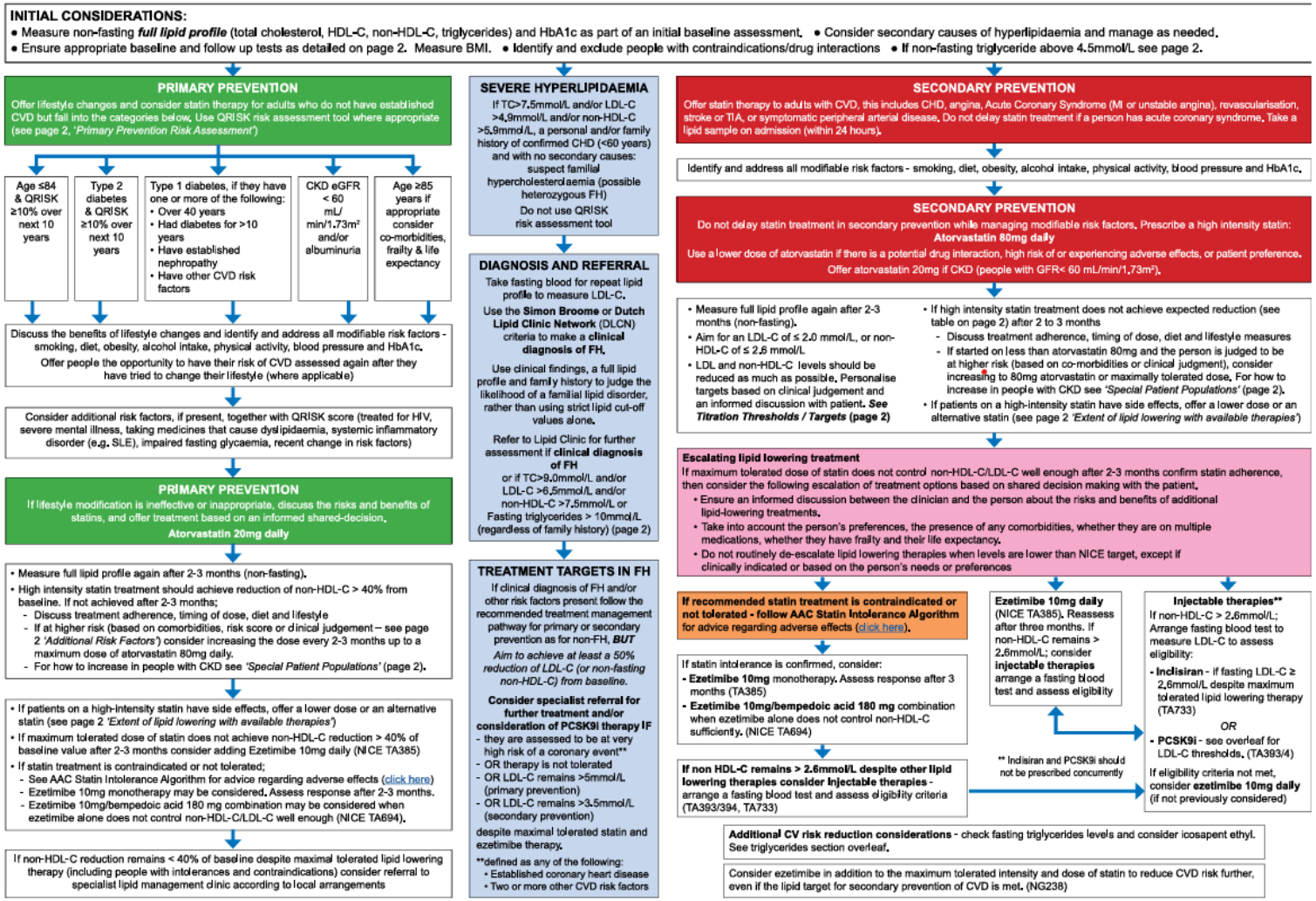
- Brief overview of management of dyslipidaemia for secondary prevention
- Newer therapies
  - Inclisiran
  - PCSK9I

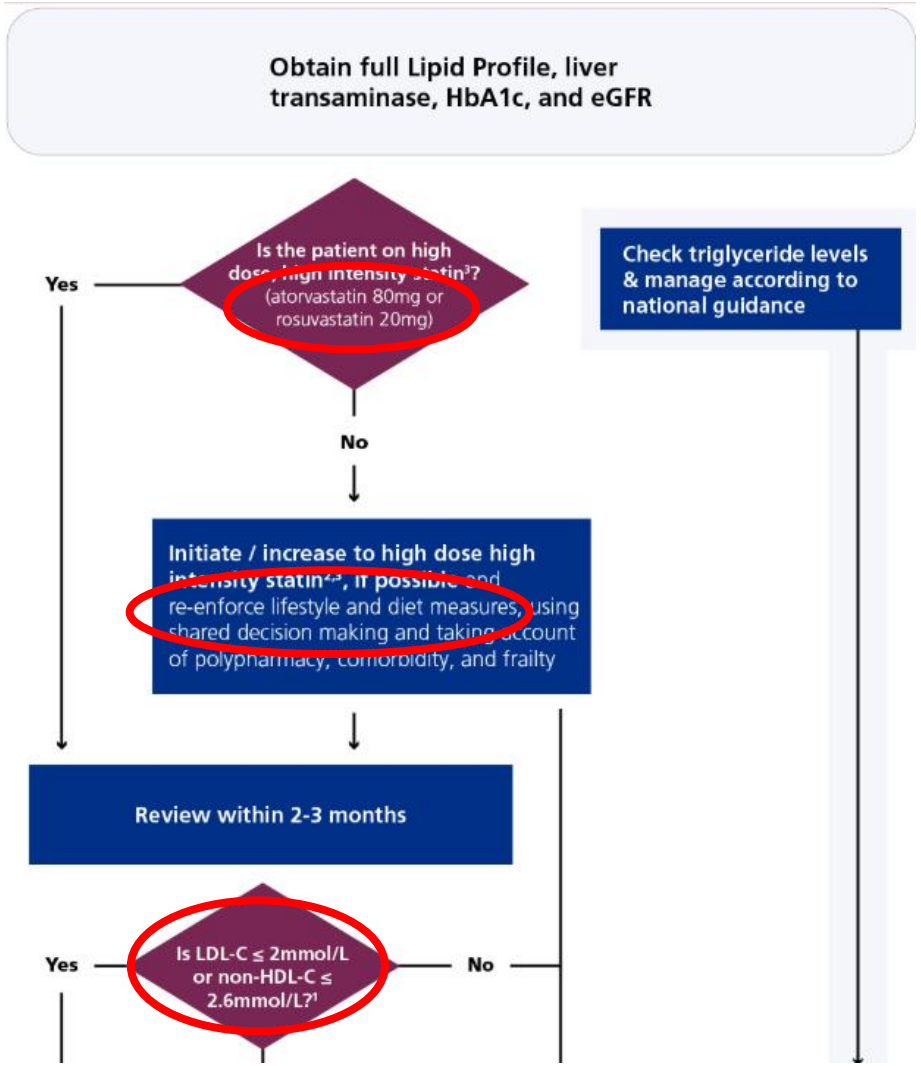
Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD



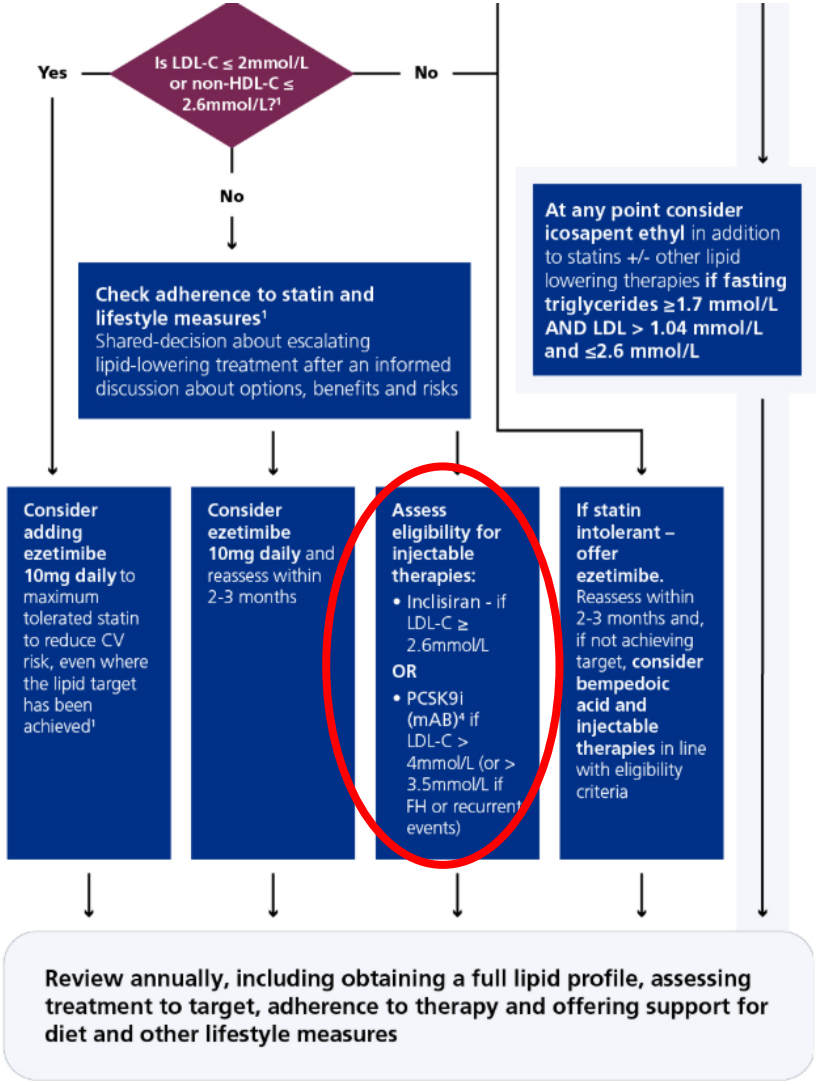
ACCELERATED ACCESS COLLABORATIVE

NHS

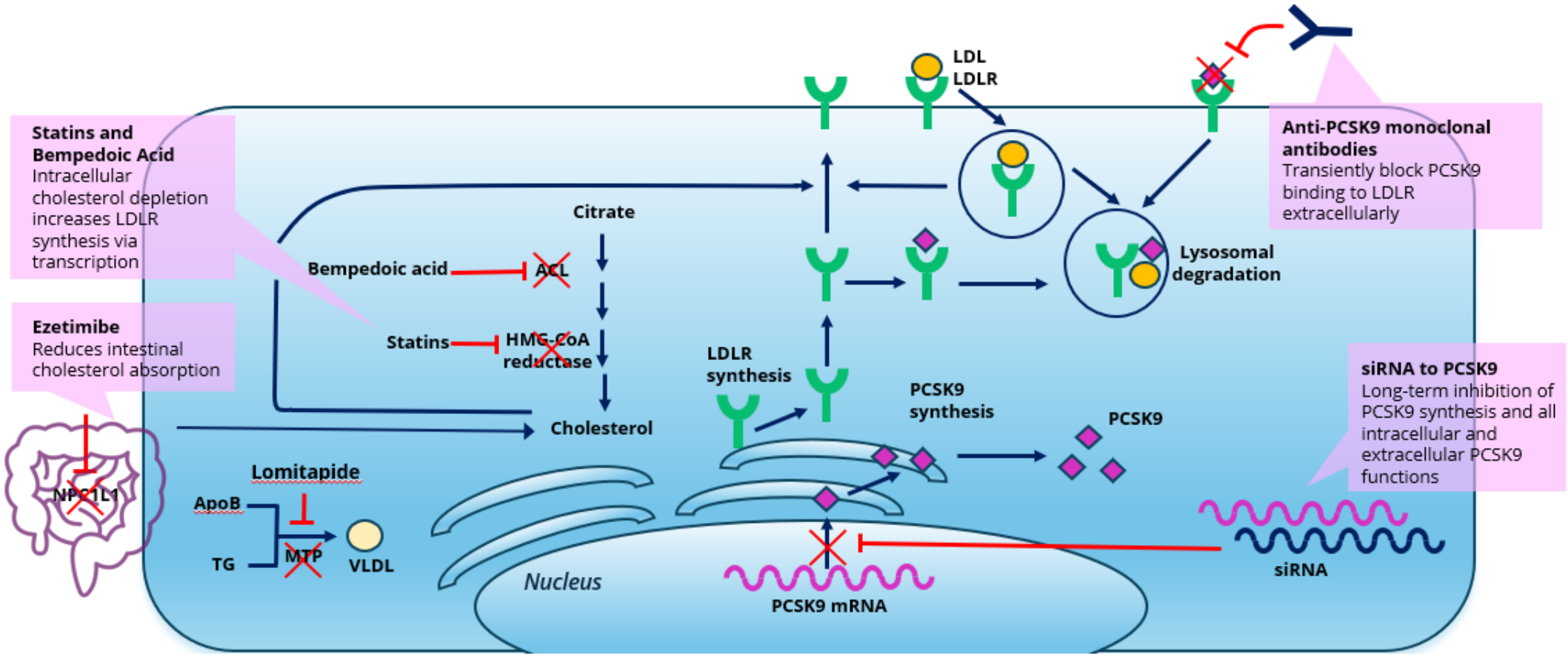
Lipid optimisation pathway for secondary prevention in primary care and the community



Lipid optimisation pathway for secondary prevention in primary care and the community



Current targets for LDL lowering



Cegla, Heart 2022

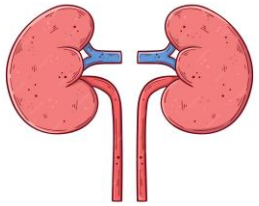
Inclisiran

Mechanism of action:

- **Inclisiran** is a **small interfering RNA**
- Limits production of **PCSK9**, increasing uptake of LDL-cholesterol
- Thereby lowering levels in blood

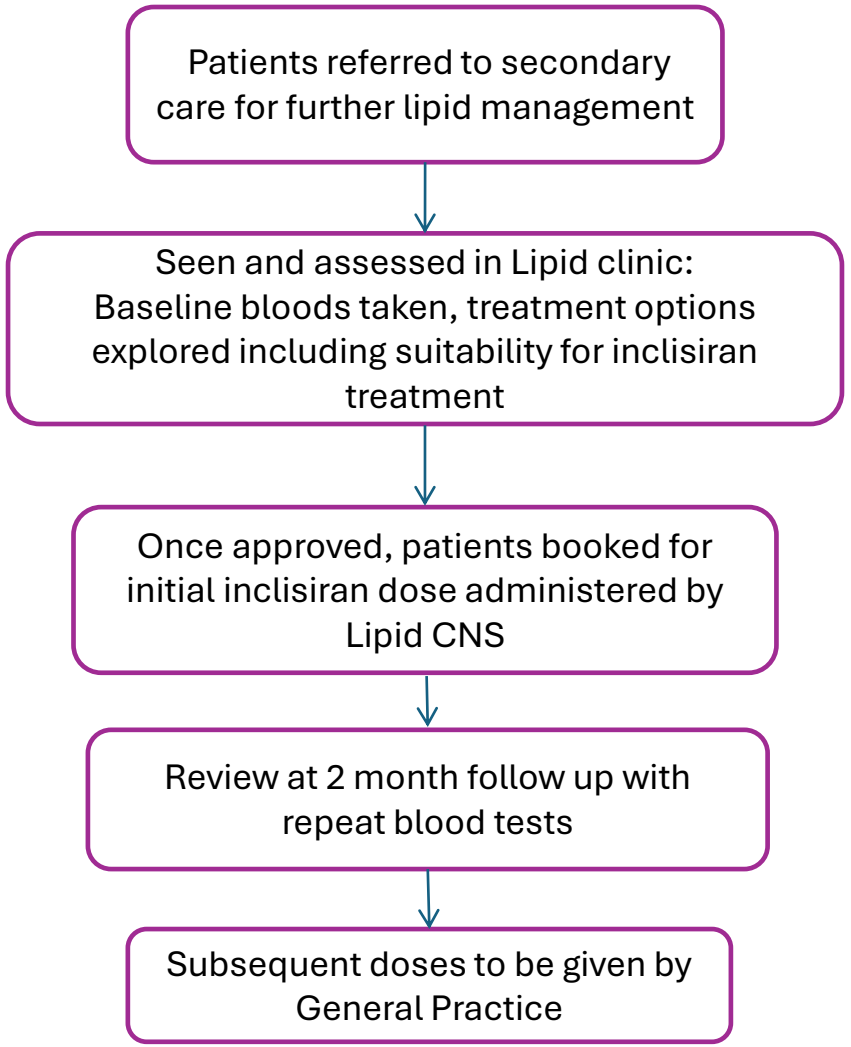
Eligibility:

- Secondary prevention
- **LDL-c ≥2.6 mmol/L**



Inclisiran – experience at ICHT

- ~300 patients



Subcutaneous injection

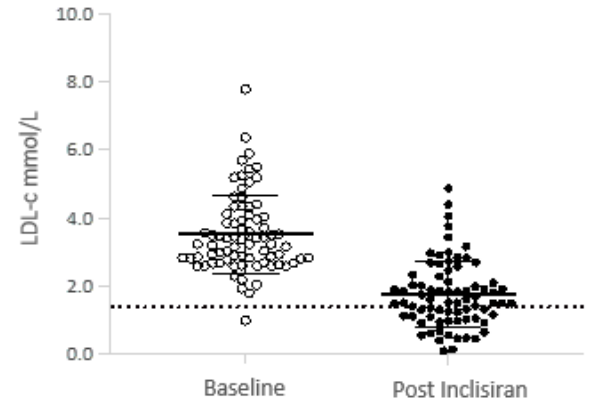
First two doses given three months apart, then every six months

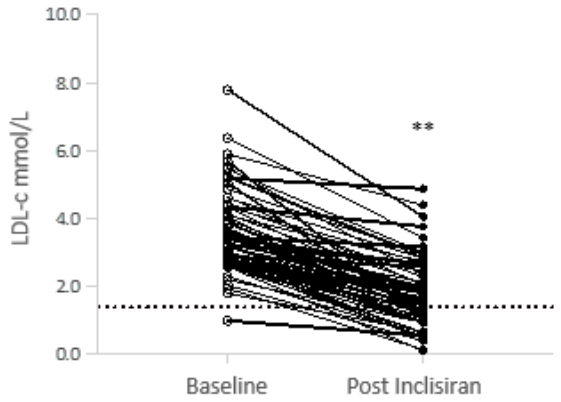
Inclisiran – experience at ICHT

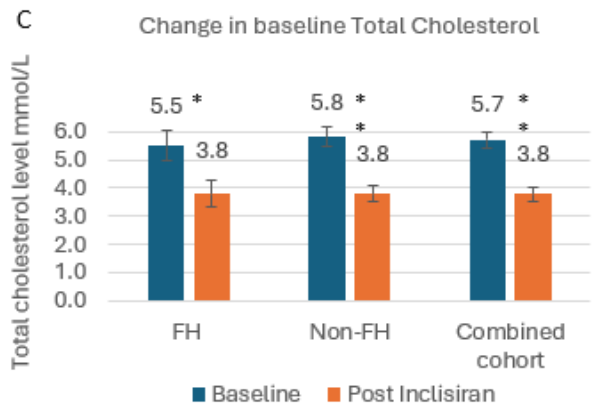
	FH n = 30	Non-FH n = 50	Total n = 80
Sex n (%)			
Male	18 (60)	34 (68)	52 (65)
Female	12 (40)	16 (32)	28 (35)
Age, mean (SD, range)	61.7 (± 12.6, 34-83)	65.3 (± 8.5, 51-83)	64 (± 10.3, 34-83)
Ethnicity n (%)			
Asian	8 (26.7)	10 (20)	18 (22.5)
Black	2 (6.7)	-	2 (2.5)
Mixed	1 (3.3)	2 (4)	3 (3.8)
Other	3 (10)	9 (18)	12 (15)
White	16 (53.3)	29 (58)	45 (56.3)
Atherosclerotic disease n (%)			
Coronary artery disease	23 (76.7)	44 (88)	67 (83.8)
CABG	2 (6.7)	7 (34)	9 (11.3)
MI	8 (26.7)	12 (24)	20 (25)
PCI	2 (6.7)	13 (26)	15 (18.8)
Subclinical cor. disease	11 (36.7)	17 (34)	28 (35)
Cerebrovascular disease	4 (13.3)	10 (20)	14 (17.5)
Stroke	1 (3.3)	1 (2)	2 (2.5)
TIA	1 (3.3)	3 (6)	4 (5)
Subclinical carotid disease	2 (6.7)	6 (12)	8 (10)
Peripheral arterial disease	1 (3.3)	3 (6)	4 (5)
Cardiovascular risk factors n (%)			
Hypertension	7 (23.3)	25 (50)	32 (40)
Diabetes mellitus	3 (10)	16 (32)	19 (23.8)
Smoking history	3 (10)	9 (18)	12 (15)
Lipid profile, mmol/L, mean (SD)			
Total cholesterol	5.5 (± 1.3)	5.9 (± 1.4)	5.8 (± 1.4)
LDL-c	3.5 (± 1.2)	3.6 (±1.1)	3.5 (± 1.2)
Triglycerides [a]	1.4 (1.0 - 1.4)	1.7 (1.3 - 2.9)	1.6 (1.2 - 2.3)
HDL-c	1.4 (± 0.3)	1.3 (± 0.4)	1.3 (± 0.4)
Lipid Lowering treatment [b] n (%)			
Atorvastatin alone	5 (16.7)	4 (8)	9 (11.3)
Rosuvastatin alone	1 (3.3)	1 (2)	2 (2.5)
Ezetimibe alone	3 (10)	10 (20)	13 (16.3)
Statin and Ezetimibe	14 (46.7)	6 (12)	20 (25)
Colesevelam alone	1 (3.3)	1 (2)	2 (2.5)
Bempedoic acid	-	1 (2)	1 (1.3)
Bempedoic acid and Ezetimibe	-	1 (2)	1 (1.3)
Triple combinative therapy [c]	6 (20)	7 (14)	13 (16.3)
No Lipid lowering treatment	-	19 (38)	19 (23.8)

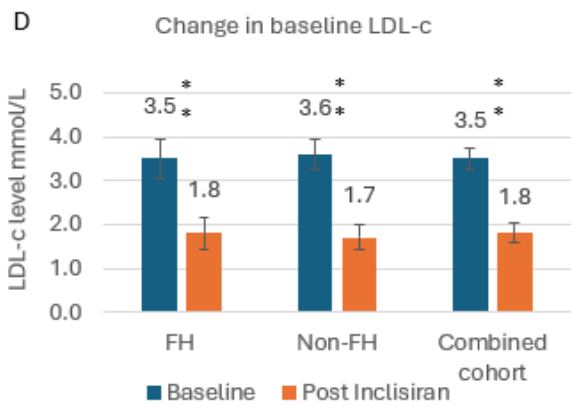
Padam et al, Open Heart 2022

Inclisiran - experience at ICHT



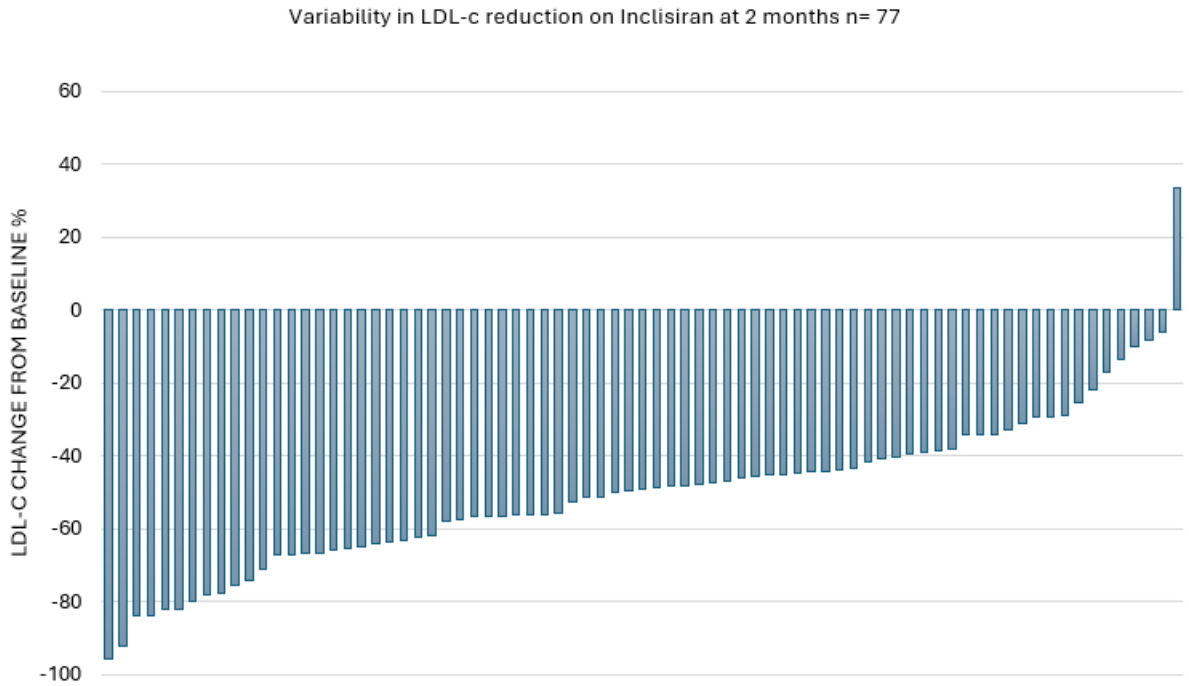






Padam et al, Open Heart 2022

Inclisiran



Padam et al, Open Heart 2022

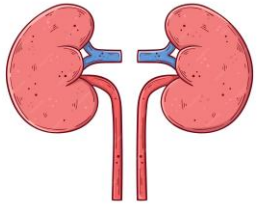
PCSK9I

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

- Chaperones LDL-R to destruction circulating ↑, LDL-C

Evolocumab/Alirocumab

- Fully human anti-PCSK9 mAb
- ~60% ↓LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Subcut injection every 2 wks



PCSK9 mAbs and NICE

	Without CVD	With CVD	
		High risk of CVD [1]	Very high risk of CVD [2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

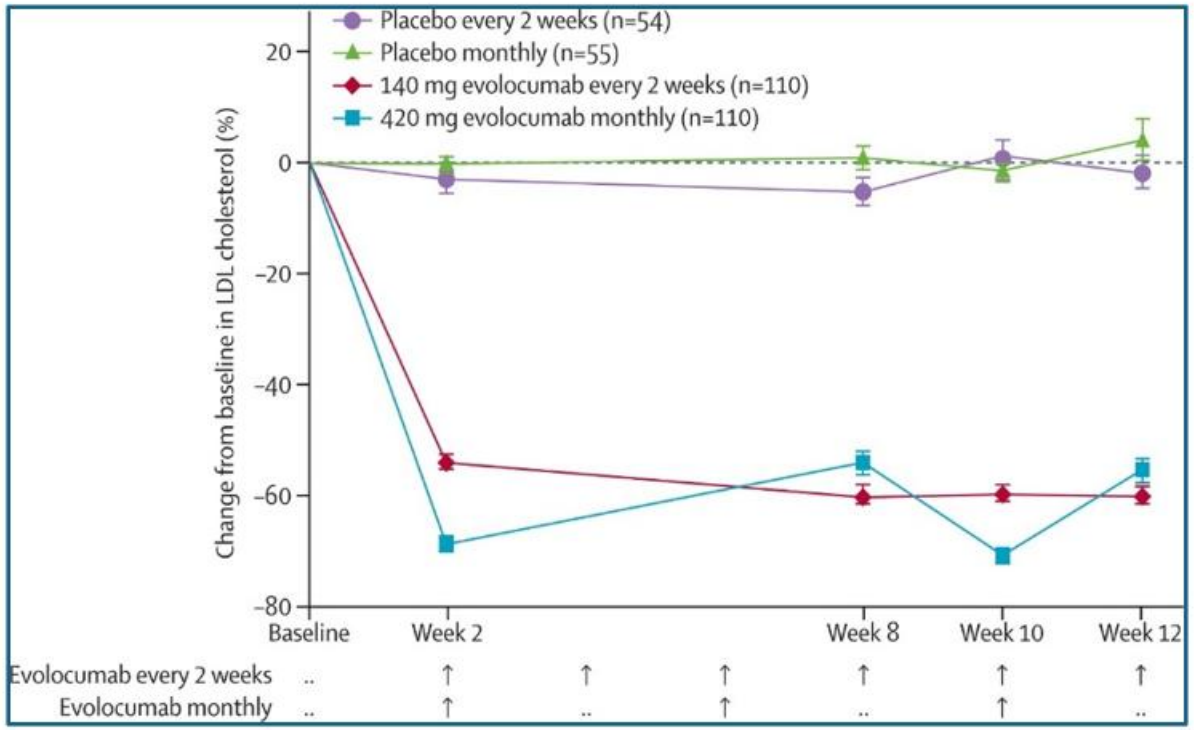
[1] High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

[2] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

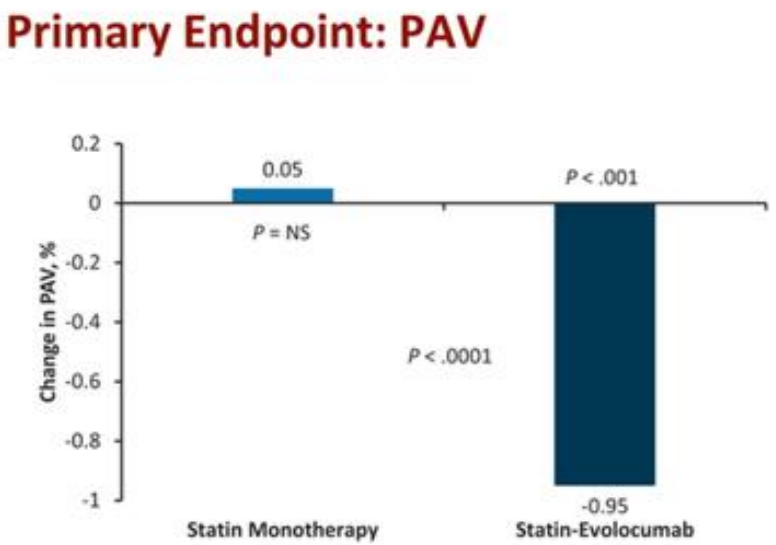
NICE TA394

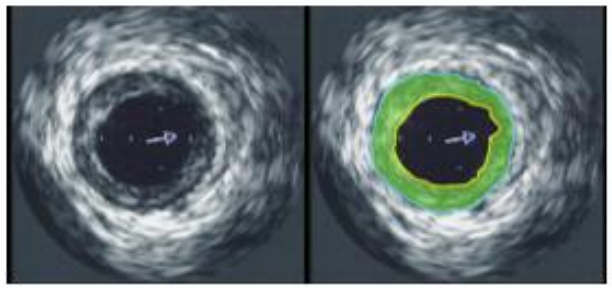
PCSK9 mAbs and LDL-c lowering



Raal et al, Lancet. 2015

PCSK9 mAbs and effect on the coronaries





Yellow = lumen
Blue = external elastic membrane
Green = atheroma

Nicholls et al, JAMA, 2016

Summary

- Inclisiran:
  - Good real-world experience
  - Good evidence of safety in renal impairment (CKD 3 and 4), but data limited in CKD stage 5

- PCSK9I:
  - Effective reduction of LDL-c of up to 60%
  - Good evidence of safety in renal impairment (CKD 3 and 4), but data limited in CKD stage 5

Acknowledgement:

Dr Jai Cegla, Consultant in Metabolic Medicine
Lead of Lipid Service at ICHT
Dr Julia Kenkre, Consultant in Metabolic Medicine

Recommended resources

1. Summary of national guidance for lipid management, NHS England. lipid-management-pathway-v7.pdf

2. Lipid optimisation pathway: secondary prevention in primary care and the community, NHS England. NHS England » Lipid optimisation pathway: secondary prevention in primary care and the community

3. Heart UK. HEART UK - The Cholesterol Charity

Thank you for listening.

Any questions?

ESC Guidelines