Lowering LDL-C & Controlling Elevated BP & Lp(a) Can Lower Cardiovascular Risk 80%

What To Do If Patients Can't Tolerate Statins?

Ezetimide, (Zetia), A PCSK9 Inhibitor, Inclisiran, Bempedoic Acid (Nexletol)

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No disclosures

We need to take risk modification seriously

Triple Medical Therapy to Prevent MI, Stroke and Amputation

1. **Anti-thrombotic therapy**
2. **LDL-lowering therapy**
3. **Blood pressure lowering therapy**

80% Reduction in CV Risk Achievable?

	Relative Risk Reduction
Anti-thrombotic Therapy (dual pathway)	30%
2mmol/L reduction in LDL-C	40%
10 mm/Hg reduction in SBP	20%
'Total'	**90%**

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PAD = 30% 5-year risk of MACE

	RRR	Absolute Risk
Patient with PAD		*30%*
Anti-thrombotic Therapy (dual pathway)	30%	21%
2mmol/L reduction in LDL-C	40%	13%
10 mm/Hg reduction in SBP	20%	10%

Combined Relative Risk reduction of 66%

CHOLESTEROL

Lower is Better

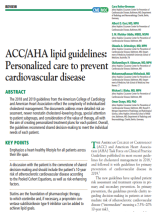
ACC/AHA/ESC Lipid Guidelines 2019-20

Statins = foundation of Rx

Target = LDL-C <70 mg/dL

Very High Risk<55 mg/dL

Rx 80mg atorvastatin


ACC/AHA lipid guidelines: Personalized care to prevent cardiovascular disease

ABSTRACT

KEY POINTS

Use other LDL-lowering drugs when patients unable to tolerate high-dose (or any) statins

Lp(a)

Independent cause of vascular disease

Genetically determined

Not amenable to lifestyle modification

Prevalence of elevated Lp(a) ~10-30%

Higher in African-American and Asian populations

Lp(a) Lowering Interventions…

Lepodisiran (Eli Lilly)	ACCLAIM-Lp(a): n=12,500
Zerlasiran (Silence Tx)	ALPACA (Phase II): 80%↓
Olpisiran (Amgen)	OCEAN(a): n=7,000
Pelacarsen (Novartis)	**Lp(a)HORIZON: n=8,325 RESULTS DUE 2025**

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Watch this space

Ezetimibe

↓ cholesterol absorption in small bowel (ileum)

Dose = 10mg

Lowers LDL-C by ~20% when used alone

Typically used in combination with statins

Evidence: IMPROVE-IT

(18 000 ACS patients simva + Eze v simva alone →7% RRR

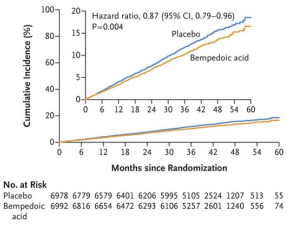
CLEAR Outcomes Trial

Bempedoic Acid effective

MACE reduced by 13%
819/[11.7%] *BA* vs. 927/ [13.3%] *placebo*;
HR=0.87 (0.79 to 0.96); P=0.004)

Slight excess of gout and gall stone disease (AR~1%)

4-point MACE



SE Nissen et al. N Engl J Med 2023;388:1353-1364.

Therapies targeting PCSK9
(proprotein convertase subtilisin/kexin type 9)

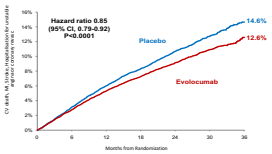
Two approaches to reducing PCSK9 activity

Monoclonal antibodies → **PCSK9 'blockers' (act in circulation)**
Evolocumab, Alirocumab

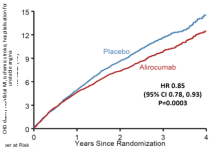
Small interfering RNA → **PCSK9 synthesis inhibitor (acts in liver)**
Inclisiran

Trials of PCSK9 monoclonal antibodies

fourier
- Evolocumab vs placebo
- **27,500 participants** (stable CVD)
- Median follow-up 2.2 years
- LDL-C ↓ **1.4 mmol/L**



ODYSSEY OUTCOMES
- Alirocumab vs placebo
- **18,924 participants** (post ACS)
- Median follow-up 2.8 years
- LDL-C ↓ **1.4 mmol/L**



15% Relative Risk Reduction in MACE at 2-3 years

Summary: PCSK9 monoclonal antibodies

Lessons learned	Disadvantages
• PCSK9 inhibition reduces LDL-C substantially • Effect on CVD as predicted • Very low LDL-c achieved –On/Off statin therapy • Safe –Cognition –New-onset DM –Cancer	• Inconvenience –Injection 2-4 weeks (self administered) –Storage conditions –Immunogenicity • Cost –Injection

Inclisiran: an inhibitor of PCSK9 synthesis

Small interfering RNA (siRNA)

Protein synthesis

DNA —transcribed→ mRNA —translated→ protein

Specifically reduces hepatic PCSK9 synthesis

Mono-therapy or co-prescribed with statins

6 monthly injections - sustained 40% reduction in LDL-C

Evidence of clinical efficacy due mid-2020s

ORION-4 & VICTORION 2PREVENT (30 000 patients)

How I approach LDL-C lowering in clinic

- **Rx high dose generic statin (80mg atorva)**
- **If side effects, check CK, but remember the 3Rs**
  - **Reassure, Reduce, Re-challenge**
- **If LDL-C target (70 mg or 55 mg/dL if VHR) not met**
  - **Check compliance**
  - **Consider adjunctive therapies**

Ezetemibe / PCSK9i / Bempedoic Acid / (Inclisiran)