

The risk of arteriosclerosis and its complications are increased by:
1) LDL-Clevels; 2) Elevated Lp(a); 3) Inflammation

What are the best medical strategies to decrease these parameters?

Statins, adjunctive LDL-C lowering drugs inclisiran, bempedoic acid, ezetimibe, PCSK-9 inhibitors, lepodisiran, colchicine, olezarsen, etc and anti-inflammatories...

How should they be administered?

Prof Richard Bulbulia
Vascular Surgeon
CTSU, University of Oxford, UK

VEITH 2024

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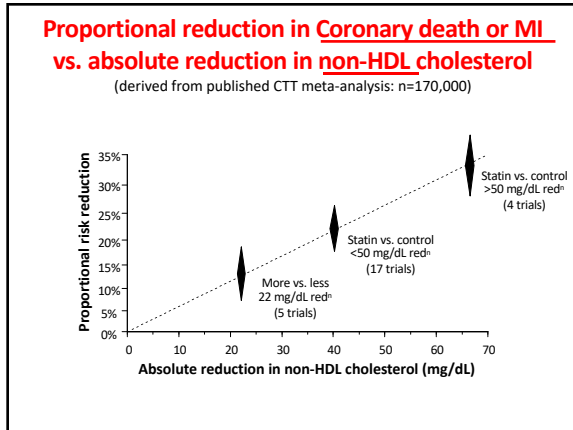
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No disclosures

LDL-C

'There is no longer an 'LDL-C hypothesis', but established facts that increased LDL-C values are causally related to ASCVD, and that lowering LDL particles... as much as possible reduces CV events.'

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk
European Heart Journal (2020) 41, 111-188



Lower is Better

High risk patients need high dose statins

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)

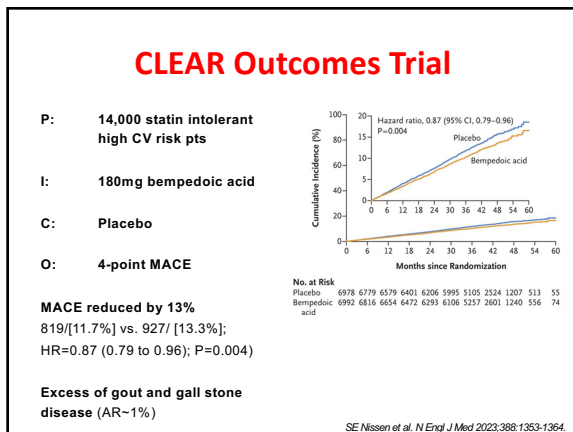
Bempedoic Acid

Inhibits ATP-citrate lyase (upstream from HMG-CoA R)

Dose = 180mg

Lowers LDL-C by ~20% when used alone

Combination therapy (+ Ezetimibe / + Statins)



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)

Lp(a)

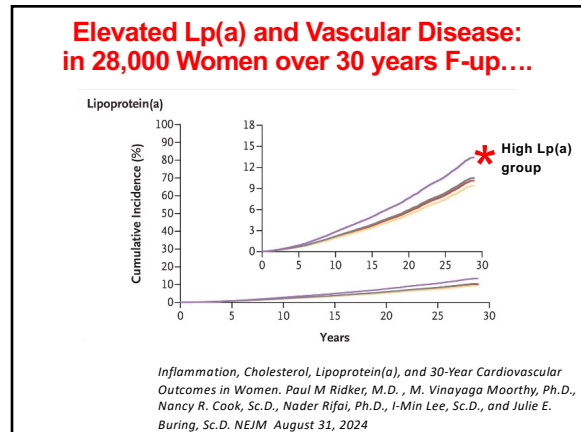
Independent cause of vascular disease

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

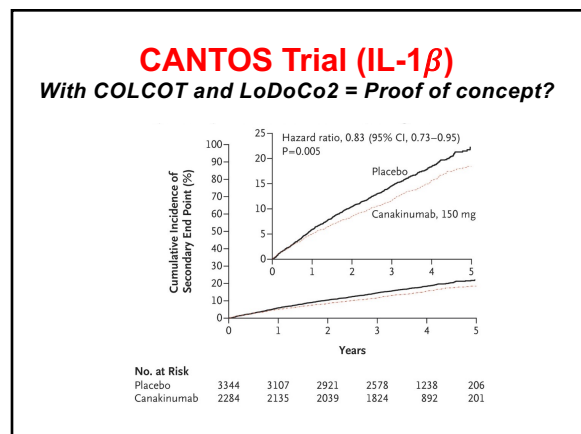
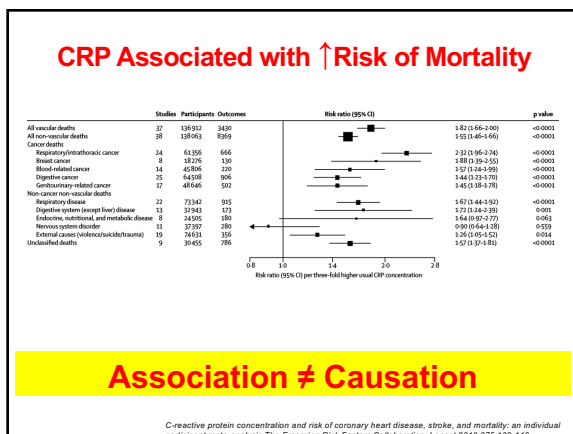
Zertasiran (Silence Tx) ALPACA (Phase II): 80% ↓

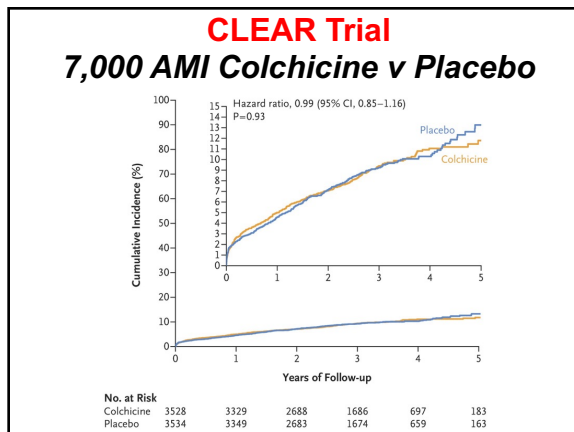
Olipisiran (Amgen) OCEAN(a): n=7,000

Pelacarsen (Novartis) Lp(a)HORIZON: n=8,325
RESULTS DUE 2025

The Inflammatory Hypothesis

- Atherosclerosis = An inflammatory process
- Are elevated markers of inflammation (hsCRP) causal, or innocent bystanders?





Summary

LDL-C = Prime time, 'fire and forget'
 Lp(a) = One to watch, but limited appeal
 Inflammation = The holy grail...

Strategy - Use Generic Tx Well

Triple Medical Therapy

- Intensive LDL-C lowering drugs
- Good BP control
- Anti-thrombotic therapy

How I approach LDL-C lowering in clinic

- Rx high dose generic statin (80mg atorva)
- If side effects, 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 / Inclisiran/ Bempedoic Acid*