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# Therapeutic Management of Dyslipidaemia: New Strategies

## Development, safety, and efficacy of novel therapeutics

Cardiovascular (CV) disease is the leading global cause of mortality[1]

Lipid imbalance increases the risk of atherosclerotic vascular disease (ASCVD) and related CV events[2]

Pharmacological interventions can lower the incidence of dyslipidaemia-triggered CV events[3]

## Evolution of lipid-lowering therapeutics[1,3]

| Problem | Solution |
| --- | --- |
| Conventional treatment agents for dyslipidaemia, such as small-molecule therapeutics, can cause off-target events and poor patient compliance | Novel monoclonal antibodies and RNA-based therapeutics can increase compliance while potentially eliminating off-target events |

## Existing and novel therapies[1–3]

### Molecular target

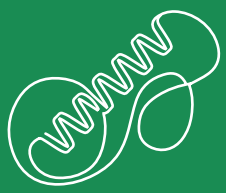
**DNA**

- Gene and base editing (e.g. CRISPR)

**mRNA**

- Anti-sense oligonucleotides (ASOs)
- Small interfering RNA (siRNA)

**Protein**



- Antibodies
- Small molecules

**Conventional statins/oral combinations**

- Ezetimibe
- Icosapent ethyl
- Bempedoic acid

**Monoclonal antibodies**

- Alirocumab
- Evolocumab
- Evinocumab

**ASOs**

- Volanesorsen
- Pelacarsen

**siRNAs**

- Inclisiran
- Olpasiran

Visit https://ascvd-lipidology.knowledgehub.wiley.com/ for additional resources

## Move from conventional to RNA-based targeting[1]

More specific therapy | Clear mechanism of action | Fewer adverse effects

**Example: The ORION trials showed that twice-yearly administration of inclisiran reduces low-density lipoprotein (LDL)-C by 50%, with only mild adverse effects**

## Key points for clinicians[1,2,3]

### What are the key underlying causes of ASCVD?

Elevated concentrations of plasma lipoproteins such as LDL, remnant lipoproteins, or lipoprotein (a) (Lp(a)) significantly contribute to the development of ASCVD

### Why do we need to increasingly consider modern therapeutic agents for ASCVD?

Novel therapeutics need to be increasingly considered because conventional therapies suffer from two major deficiencies: patient non-compliance and serious adverse effects

### Have modern therapies received approval from regulatory agencies?

Yes, the U.S. Food & Drug Administration has already approved some ASOs and siRNAs for the treatment of ASCVD

### What are the usual adverse effects associated with RNA-based therapeutics?

Documented adverse effects resulting from RNA-based therapy include injection site reactions, inflammatory reactions, hepatic steatosis, and thrombocytopenia

## Targets for dyslipidaemia management[1–3]

| Conventional protein targets | Current/promising therapeutics |
|---|---|
| **LDL** | Statins |
| | Ezetimibe |
| | PCSK9 inhibitors |
| | Bempedoic acid |
| **Lp(a)** | Pelacarsen (ASO) |
| | Olpasiran (ASO) |
| | SLN360 |
| | Inotersen |
| **Triglyceride-rich proteins (intermediate-density lipoprotein [IDL] + very low-density lipoproteins [VLDL])** | Vupanorsen (ASO) |
| | Evinacumab (monoclonal antibody) |
| | Eicosapentaenoic acid |

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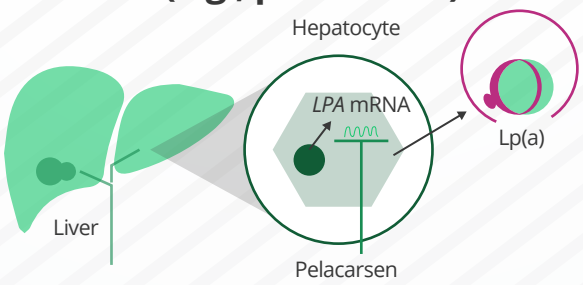
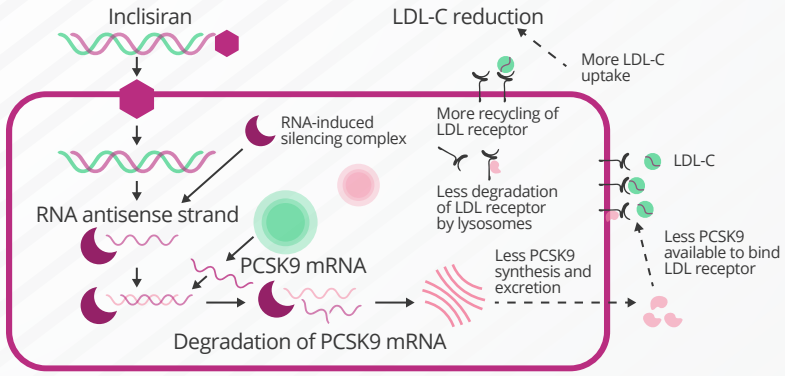
# Mechanisms of action

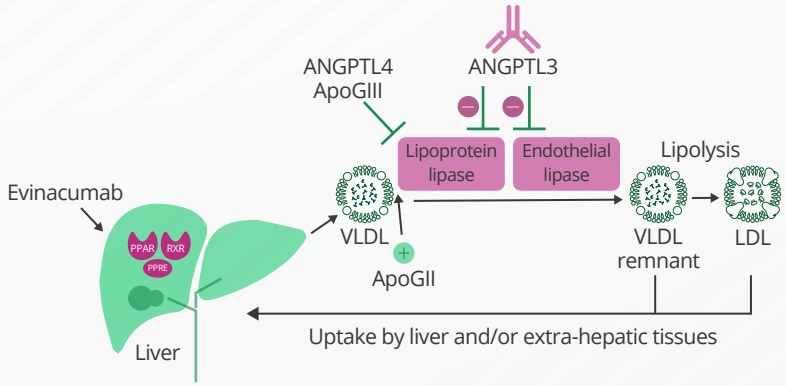
## ASOs (e.g., pelacarsen)




## siRNAs (e.g., inclisiran)




## Antibodies (e.g., evinacumab)




# Current status: Development, safety, and efficacy of novel therapeutics[1–3]

| Target | Therapeutic | Description | Status |
|---|---|---|---|
| LDL | Evolocumab | Monoclonal antibodies targeting PCSK9 | Approved |
| | Alirocumab | | |
| | Inclisiran | siRNA that silences the intracellular translation of PCSK9 mRNA | Approved for some adults with hypercholesterolaemia or mixed dyslipidaemia |
| | Mipomersen | ASO that selectively silences the mRNA responsible for the coding of ApoB100 | Approved, but the FDA issued a black box warning owing to an increased risk of hepatotoxicity |
| | Vupanorsen | Second generation ASO selective for ANGPTL3 mRNA | In development, but found to be safe so far |
| | ARO-ANG3 | Selectively inhibits the hepatic translation of ANGPTL3 mRNA | In development, but no major adverse events reported so far |

| | | | |
|---|---|---|---|
| **Lp(a)** | Pelacarsen | Selectively inhibits the production of apo(a) by targeting *LPA* mRNA | Well-tolerated with no major adverse effects |
| | Olpasiran | siRNA that selectively inhibits *LPA* gene transcription, reducing Lp(a) levels | In development, but no major adverse reactions reported so far |
| | APO(a) Rx | Selectively inhibits the production of apo(a) by targeting *LPA* mRNA | In development, but reported to be safe and well-tolerated so far |
| **Triglyceride-rich lipoprotein** | Evinacumab | Monoclonal antibody that reduces the circulatory levels of ANGPTL3 | Approved |
| | Volanesorsen | Second generation ASO that selectively inhibits apoC3 synthesis | In development, but no significant adverse effects reported so far |
| | ARO-ANG3 | Selective inhibitor of hepatic ANGPTL3 translation | In development, but no major adverse reactions reported so far |

## Take-home messages

- Conventional clinical options for lowering dyslipidaemia include targeting proteins such as LDL, Lp(a), and IDL + VLDL with small-molecule therapeutics
- However, conventional therapies for dyslipidaemia have two major shortcomings: patient non-compliance and physiologically relevant adverse effects
- Novel therapies for dyslipidaemia include siRNAs, ASOs, and monoclonal antibodies
- These novel therapies are well-accepted by patients, thus reducing the worry of patient non-compliance
- Many siRNA, ASO, and monoclonal antibody therapeutics are currently undergoing clinical trials
- Most novel therapeutics for reducing dyslipidaemia appear safe and are associated with fewer adverse effects


**References**

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3. Henney, N. C., Banach, M., & Penson, P. E. (2021). RNA Silencing in the Management of Dyslipidemias. *Current Atherosclerosis Reports, 23,* 69.



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