Therapeutic Management of Dyslipidaemia: New Strategies

Development, safety, and efficacy of novel therapeutics

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

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

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

Evolution of lipid-lowering therapeutics

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solution</th>
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<tbody>
<tr>
<td>Conventional treatment agents for dyslipidaemia, such as small-molecule therapeutics, can cause off-target events and poor patient compliance</td>
<td>Novel monoclonal antibodies and RNA-based therapeutics can increase compliance while potentially eliminating off-target events</td>
</tr>
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Existing and novel therapies

<table>
<thead>
<tr>
<th>DNA</th>
<th>mRNA</th>
<th>Protein</th>
</tr>
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<tbody>
<tr>
<td><strong>Gene and base editing (e.g. CRISPR)</strong></td>
<td><strong>Anti-sense oligonucleotides (ASOs)</strong></td>
<td><strong>Antibodies</strong></td>
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<td></td>
<td><strong>Small interfering RNA (siRNA)</strong></td>
<td><strong>Small molecules</strong></td>
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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

- 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

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

<table>
<thead>
<tr>
<th>Conventional protein targets</th>
<th>Current/promising therapeutics</th>
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<tbody>
<tr>
<td>LDL</td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>Ezetimibe</td>
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<tr>
<td></td>
<td>PCSK9 inhibitors</td>
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<tr>
<td></td>
<td>Bempedoic acid</td>
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<tr>
<td>Lp(a)</td>
<td>Pelacarsen (ASO)</td>
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<tr>
<td></td>
<td>Olpasiran (ASO)</td>
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<td></td>
<td>SLN360</td>
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<td></td>
<td>Inotersen</td>
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<tr>
<td>Triglyceride-rich proteins</td>
<td>Vupanorsen (ASO)</td>
</tr>
<tr>
<td>(intermediate-density lipoprotein [IDL] + very low-density lipoproteins [VLDL])</td>
<td>Evinacumab (monoclonal antibody)</td>
</tr>
<tr>
<td></td>
<td>Eicosapentaenoic acid</td>
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### Current status: Development, safety, and efficacy of novel therapeutics

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

**Mechanisms of action**

- **ASOs (e.g., pelacarsen)**
  - Liver
  - Pelacarsen
  - LPA mRNA
  - Lp(a)

- **siRNAs (e.g., inclisiran)**
  - RNA antisense strand
  - RNA-induced silencing complex
  - Degradation of PCSK9 mRNA
  - More LDL-C uptake
  - Less degradation of LDL receptor by lysosomes
  - Less PCSK9 available to bind LDL receptor
  - Less PCSK9 synthesis and excretion

- **Antibodies (e.g., evinacumab)**
  - Evinacumab
  - ANGPTL4 ApoGIII
  - ANGPTL3
  - Lipoprotein lipase
  - Endothelial lipase
  - Lipolysis
  - VLDL remnant
  - LDL
  - Uptake by liver and/or extra-hepatic tissues

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### 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