From Nobel Prize to clinical practice

An update on messenger RNA-based therapies for lipid disorders

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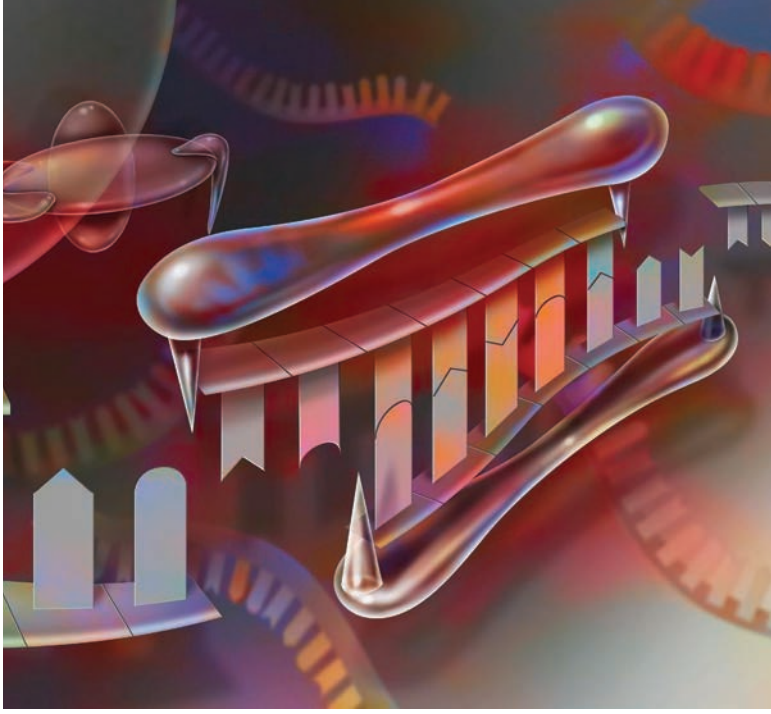

The biological mechanism of gene silencing by messenger RNA (mRNA) inhibition has been harnessed to develop therapies to target specific proteins, such as those involved in lipid metabolism. The first of these, inclisiran, is available in Australia for reducing levels of LDL-cholesterol and is PBS listed for people with familial and nonfamilial hypercholesterolaemia.

On January 6, 2006, the Nobel prize in Physiology or Medicine was awarded to Professor Andrew Fire and Professor Craig Mello for the discovery of RNA interference – using double-stranded RNA to 'silence' genes – following publication of their research in *Nature* on 19 February, 1998.[1] The Nobel Prize press release stated: 'RNA interference is already being widely used in basic science as a method to study the function of genes and it may lead to novel therapies in the future'.[2] This prediction has been fulfilled. Since 2006, research on messenger RNA (mRNA) therapy has resulted in the development of several drugs that inhibit the activity of key mRNA and protein targets. This article outlines the mechanisms of RNA interference and mRNA targets involved in lipid metabolism and discusses the first of these lipid-lowering therapies available in Australia.

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KEY POINTS

- Inhibition of messenger RNA (mRNA) and of target protein synthesis (RNA interference) is now possible using either silencing RNA or antisense oligonucleotide therapy.
- These types of therapies currently require subcutaneous injection.
- Inclisiran is the first siRNA proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor to be listed on the PBS. It has similar efficacy to available monoclonal antibody PCSK9 inhibitors but a longer duration of action allowing six-monthly subcutaneous injections after completion of basal loading doses.
- Inclisiran, in combination with high-dose statins and ezetimibe, can reduce LDL-cholesterol levels by more than 80%, with a further reduction in cardiovascular (CVD) events likely to occur in the longer term.
- Results from a randomised controlled trial on CVD outcomes with inclisiran are expected in 2026.

mRNA interference: targets and mechanisms

The mRNA targets and drugs currently available or in development and their associated mechanisms of action are outlined in Table 1, and are being studied in several clinical trials, including ACCLAIM-Lp(a) (ClinicalTrials.gov ID NCT06292013), OCEAN(a) (ClinicalTrials.gov ID NCT05581303) and LP(a) HORIZON (ClinicalTrials.gov ID NCT04023552) trials. Targets include the following.[3-10]

- Proprotein convertase subtilisin–kexin type 9 (PCSK9), which regulates activity of the LDL-receptor in the liver. Inhibiting PCSK9 results in greater clearance of LDL-cholesterol from the plasma and lower LDL-cholesterol levels.
- Angiopoietin-like 3 (ANGPTL3), an enzyme involved in triglyceride (TG) catabolism, the inhibition of which results in lower plasma levels of TG and LDL-cholesterol.
- Apolipoprotein C3 (ApoC3), a potent inhibitor of

lipoprotein lipase (LPL), the enzyme promoting TG catabolism to free fatty acids. Inhibition of apoC3 results in LPL activation and lower plasma TG levels.

- Apolipoprotein (a) [Apo(a)], a protein attached to LDL to form lipoprotein (a) [Lp(a)], an atherogenic and prothrombotic lipoprotein that is an important risk factor for premature CVD.

The two mechanisms of targeting mRNA involved in lipid metabolism are antisense oligonucleotides (ASOs) and silencing RNA (siRNA), summarised in Figure 1. These techniques promise a significant benefit in reducing cardiovascular (CVD) events through improved control of lipid-related CVD risk factors.[3-10]

ASOs are small single-stranded nucleic acid sequences that bind with complementary target mRNA within the nucleus, resulting in degradation and inactivity of the mRNA (Figure 1).[3]

siRNA uses a 20 to 25 nucleotide sequence of double-stranded RNA, of which one strand (the guide strand) is complementary with and binds to the mRNA sequence to be silenced, while the other strand (the passenger strand) is eventually degraded in the cytoplasm (Figure 1).[3] The enzyme Dicer separates each strand of the double-stranded RNA. The guide RNA then complexes with the RNA-induced silencing complex (RISC), resulting in degradation of the target mRNA sequence, thereby preventing synthesis of the target protein.[3] Recycling of RISC and its attached guide strand account for the prolonged (three to six months) duration of activity of a single dose of siRNA.

Therapy with apoC3 siRNA restores LPL activity, resulting in a significant reduction of plasma TG levels. Silencing PCSK9 mRNA with inclisiran uses similar mechanisms, involving the actions of Dicer and RISC, resulting in upregulation of hepatic LDL-receptors, increased uptake of LDL-cholesterol into the liver, and about a 50% further reduction in lower plasma LDL-cholesterol levels than that achieved with high-dose statins and ezetimibe (Figure 2).[9,10]

TABLE 1. MECHANISMS OF ACTION OF, AND TARGETS FOR, mRNA-BASED LIPID-LOWERING THERAPY[3-10]

mRNA target	Mechanisms of action	
	Silencing RNA	Antisense oligonucleotide
PCSK9	Inclisiran	AZD0780 (in development)
ANGPTL3	Zodasiran	In development
ApoC3	Plozasiran	Olezarsen
Lp(a)	Olpasiran, lepodisiran	Pelacarsen

Abbreviations: ANGPTL3 = angiopoietin-like 3; ApoC3 = apolipoprotein C3; Lp(a) = lipoprotein (a); PCSK9 = proprotein convertase subtilisin–kexin type 9.

The potency and long duration of action of siRNA therapies and their potential for reducing CVD events is shown by the close to 100% inhibition of plasma Lp(a) levels over a 12-month period with a single injection of the siRNA lepodisiran.[6] Zilebesiran, an siRNA drug for inhibiting angiotensinogen, has also been shown to reduce levels of its target protein by almost 100% over 12 weeks after a single injection.[6,11]

Inclisiran

Inclisiran has undergone seven phase 3 clinical trials (the ORION clinical development program) to determine its LDL-cholesterol-lowering efficacy and potential side effects.[12-14] This innovative lipid-lowering mRNA therapy inhibits PCSK9 and is indicated for the treatment of patients with symptomatic CVD and elevated LDL-cholesterol levels while taking maximally tolerated oral lipid-lowering therapy or for patients who are statin intolerant. It is available as an injectable therapy and PBS-listed (since 1 April, 2024)

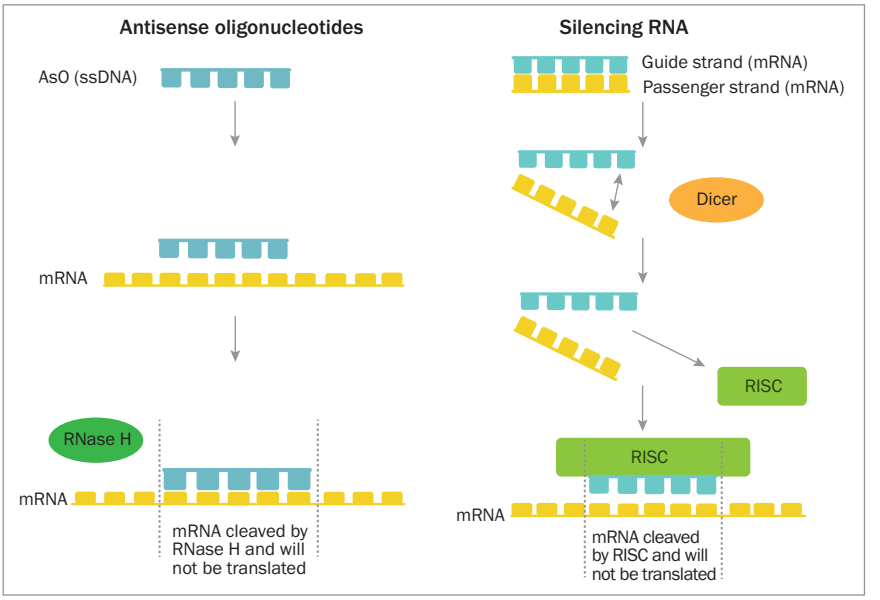


Figure 1. Mechanisms of action of antisense oligonucleotides (ASOs) and silencing RNA (siRNA). (left). ASOs are single stranded DNA (ssDNA) nucleotides that bind to target mRNA in the nucleus and recruit the enzyme RNase H, resulting in degradation of the target mRNA. (right). siRNA introduces a double-stranded short RNA complex, which dissociates in the cytoplasm into passenger and guide strands. The enzyme Dicer separates the RNA strands. The guide strand binds to the RNA-induced silencing complex (RISC), resulting in cleavage of the target mRNA. Recycling of RISC accounts for a long duration of mRNA inhibition.

Adapted from: Chebli J, et al. Curr Opin Endocrinol Diabetes Obes 2024.[3]

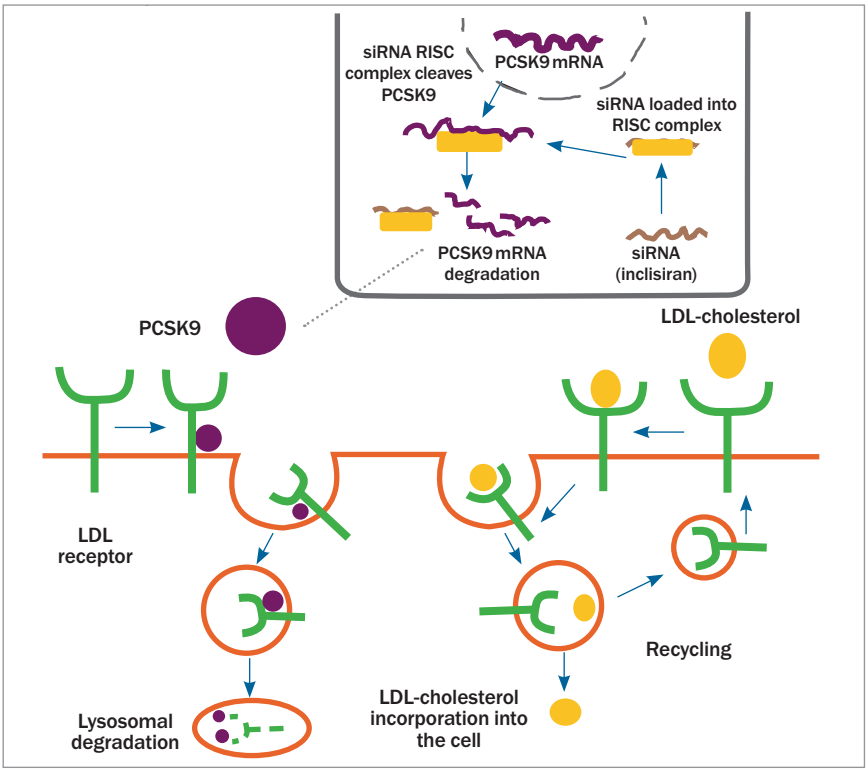


Figure 2. Mechanism of siRNA inhibition of PCSK9 synthesis by inclisiran. PCSK9 binds to hepatic LDL-receptors and directs them to undergo lysosomal degradation (lower left). Recycling of LDL-receptors is thereby prevented, reducing hepatic uptake of plasma LDL and resulting in higher LDL-cholesterol levels. In the absence of PCSK9, LDL-receptors are recycled and promote uptake of LDL, resulting in lower plasma LDL-cholesterol levels (lower right). The guide strand of the siRNA binds to RISC, resulting in degradation of PCSK9 mRNA (top).

Abbreviations: PCSK9 = proprotein convertase subtilisin–kexin type 9; RISC = RNA-inducing silencing complex ; siRNA = silencing RNA.
Reproduced under a Creative Commons Attribution 4.0 International licence from: Kosmas CE, et al. Diseases 2018.[9]

for patients with familial heterozygous hypercholesterolaemia and nonfamilial hypercholesterolaemia (Table 2).

Inclisiran has a prolonged duration of action, which differentiates if from the injectable monoclonal antibody inhibitors of PCSK9. About 50% LDL-cholesterol reduction can be achieved with an initial dose of inclisiran, a second dose after three months and subsequent six-monthly dosing intervals over 18 months, compared with placebo (Figure 3).[12]

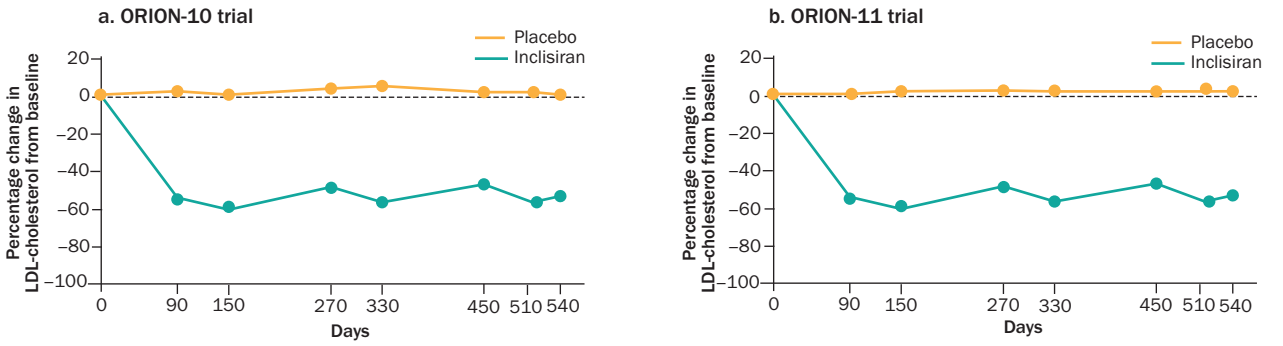
The efficacy of 180 days of inclisiran therapy compared with placebo in individual patients is shown in Figure 4.[12] Patients taking inclisiran had a consistent reduction in LDL-cholesterol levels (mean, 52.6%; maximum, 80.9%) compared with those on placebo, who had little change in mean LDL-cholesterol levels and considerable variation between individuals. In a pooled analysis of seven ORION trials, inclisiran therapy achieved target LDL-cholesterol levels below 1.8 mmol/L and below 1.3 mmol/L in 87% and 75% of patients, respectively.[15]

The current paradigm for lipid-lowering therapy is to achieve the lowest possible LDL-cholesterol levels for the longest possible duration, starting at

TABLE 2. PBS INDICATIONS FOR INCLISIRAN*

Heterozygous familial hypercholesterolaemia (FH)	Nonfamilial hypercholesterolaemia
• Condition confirmed by genetic testing or a Dutch Lipid Clinic Network score of at least 6 • LDL-cholesterol level >1.8 mmol/L (results no more than 8 weeks old) if symptomatic atherosclerotic CVD (prior MI, stroke, PAD or revascularisation) • LDL-cholesterol level >5 mmol/L (results no more than 8 weeks old) in the absence of symptomatic CVD • There is no indication for treating children or patients with homozygous FH	• Symptomatic atherosclerotic CVD (prior MI, stroke, PAD, or revascularisation) • LDL-cholesterol level >1.8 mmol/L (results no more than 8 weeks old) • Must have one or more additional risk factor: – diabetes (either age ≥60 years, have microalbuminuria or be an Aboriginal or Torres Strait Islander) – severe multivessel CHD (50% stenoses in at least two large vessels) – at least 2 CVD events within 5 years – CVD in ≥2 vascular territories (coronary/peripheral/cerebrovascular) – secondary prevention TIMI risk score ≥4
• Optimised lipid therapy for at least 12 weeks with atorvastatin 80 mg or rosuvastatin 40 mg or at the maximum tolerated dose (unless intolerant or contraindicated†) plus ezetimibe (if tolerated) • Treatment by a specialist physician or a physician who has consulted a specialist physician • No concomitant PCSK9-inhibitor monoclonal antibody therapy • Treatment must be in conjunction with dietary therapy and exercise	

Abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; PAD = peripheral artery disease; TIMI = thrombolysis in myocardial infarction.
* Full PBS criteria are available and should be consulted online at: https://www.pbs.gov.au.
† Clinically important product-related adverse events necessitating withdrawal as defined in the TGA-approved Product Information.



	Day							
Group	**0**	**90**	**150**	**270**	**330**	**450**	**510**	**540**
Placebo (n)	780	762	745	724	715	698	666	670
Inclisiran (n)	781	758	757	737	731	721	691	705

	Day							
Group	**0**	**90**	**150**	**270**	**330**	**450**	**510**	**540**
Placebo (n)	807	797	785	774	773	764	739	749
Inclisiran (n)	810	790	796	778	773	768	724	742

Figure 3. Efficacy of inclisiran in reducing LDL-cholesterol levels in the ORION-10 (a, left) and ORION-11 (b, right) clinical trials.
Abbreviation: n = number of patients.
Adapted from: Ray KK, et al; ORION-10 and ORION-11 Investigators. N Engl J Med 2020.[12]

the lowest suitable age. 'Earlier, lower and longer' is the current paradigm for LDL-cholesterol reduction regardless of therapy choice, including statins, PCSK9 inhibitors, ezetimibe, bile acid-binding resins, fibrates or bempedoic acid (not yet available in Australia). Lipid-lowering monotherapy or specific combinations of lipid-lowering drugs can be used to achieve specific LDL-cholesterol targets (Table 3 and Table 4, respectively).[16] Current targets for LDL-cholesterol depend on underlying CVD risk. Australian guidelines suggest targets of less than 2 mmol/L for primary prevention and less than 1.8 mmol/L for secondary prevention, consistent with PBS criteria for PCSK9 inhibitors (Table 2).[9] Other guidelines, such as the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines have targets of less than 1.4 mmol/L for those with very high CVD risk (Figure 5).[17] Randomised controlled CVD outcome trials using monoclonal antibody PCSK9 inhibitors have achieved mean LDL-cholesterol levels of 0.8 to 0.9 mmol/L, with a significant proportion of patients with levels below 0.5 mmol/L and approaching physiological LDL-cholesterol levels between 0.6 and 1.3 mmol/L.[18-20]

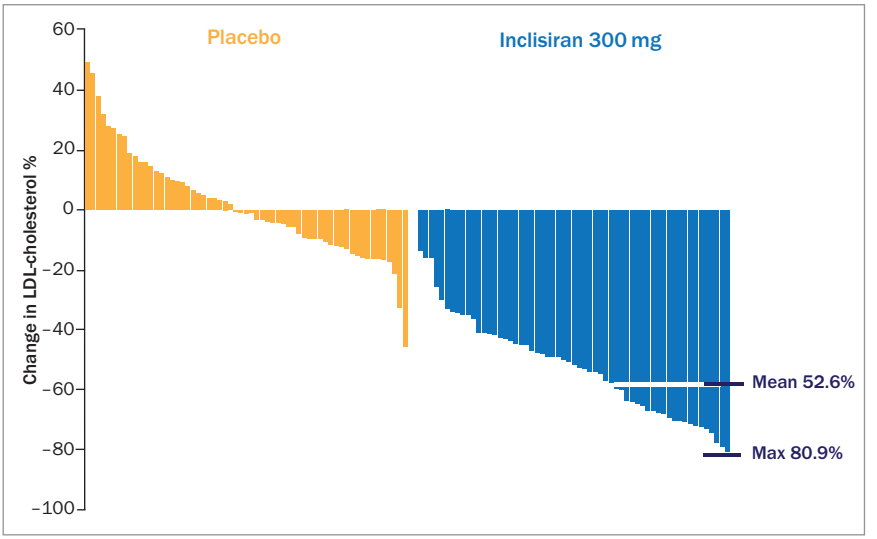


Figure 4. Individual percent reduction in LDL-cholesterol in people taking placebo versus inclisiran at 180 days.[13]
Adapted from: Ray KK, et al; ORION Phase III investigators. Eur Heart J 2023.[13]

Advantages

Inclisiran is conjugated with N-acetylgalactosamine (GalNAc), a ligand that specifically binds to hepatic carbohydrate receptors. It is therefore specifically absorbed by the liver and its actions are liver-specific and do not directly affect other tissues.

Patient adherence is a key issue for all drugs. The prolonged activity of inclisiran requires a low frequency of administration compared with other PCSK9 inhibitor therapies and is likely to improve adherence. Inclisiran is given as an injection at six-monthly intervals, compared with monthly or fortnightly injections of monoclonal antibody PCSK9 inhibitors and oral medications. Additionally, it does not affect hepatic cytochromes and has a low potential for drug interactions.

The efficacy of inclisiran in lowering LDL-cholesterol levels is comparable with

TABLE 3. LDL-CHOLESTEROL LOWERING EFFICACY OF LIPID-LOWERING MONOTHERAPY[16]

LDL-cholesterol reduction		
Low (<30%)	**Moderate (30 to 49%)**	**High (≥50%)**
• Simvastatin 5 to 10 mg • Fluvastatin 20 to 40 mg • Pravastatin 5 to 20 mg • Ezetimibe 10 mg • Plant sterols 1 g twice daily • Bile acid resins • EPA ethyl esters • Fenofibrate 145 mg	• Simvastatin 20 to 40 mg • Rosuvastatin 5 to 10 mg • Atorvastatin 10 to 20 mg • Bempedoic acid 180 mg*	• Rosuvastatin 20 to 40 mg • Atorvastatin 40 to 80 mg • PCSK9 inhibitors (inclisiran and monoclonal antibodies)

Abbreviations: EPA = eicosapentanoic acid; PCSK9 = proprotein convertase subtilin/kexin-9.
* Bempedoic acid is available in Europe and the USA but not currently available in Australia.

monoclonal antibody PCSK9 inhibitors. A recent meta-analysis, however, showed slightly lower LDL-cholesterol levels after 24 weeks with the addition of monoclonal antibodies to maximally tolerated statins (mean percentage reduction with evolocumab 61.8% *vs* 50.1% with inclisiran).[21] ApoB reduction was also greater with evolocumab (58.4% *vs* 45.1%).[21] Like monoclonal antibodies, inclisiran also reduces levels of non-HDL cholesterol by 40 to 50% and Lp(a) by 20 to 30% thereby contributing significantly to CVD risk reduction in the longer term.[12,13,22] There are no clinically significant changes in HDL-cholesterol and triglyceride levels with inclisiran treatment.

Adverse events and contraindications

Adverse events in inclisiran-treated and placebo groups in the ORION-10 trial are summarised in Table 5.[12] Adverse events were similar for both groups, with the exception of local skin reactions, which occurred more frequently with inclisiran, but were usually mild and reversible.[12]

Elevated alanine and aspartate transaminase levels (one to three times the upper limit of normal) seen in randomised controlled trials with inclisiran use were similar to those seen in the placebo group.[12,13,22] According to a recent review of drug-induced liver injury, regular monitoring of routine liver tests is not recommended with inclisiran as elevated serum alanine transaminase levels were invariably transient, mild to moderate in severity, and without accompanying symptoms or jaundice.[23] A study of patients with mild to moderate hepatic impairment showed clinically significant increases in liver enzymes both before and after inclisiran therapy, which is likely to be attributed to underlying liver disease.[24] No enzyme elevation occurred in those with normal liver function.[24]

Inclisiran therapy is not recommended for patients with severe liver disease and end-stage renal disease (creatine clearance rate <15 mL/min) and should be used with caution in patient with severe renal impairment.[25] It is approved for use with no dose adjustment in patients with mild or moderate liver disease, those with mild, moderate or severe renal failure or in older people.[25]

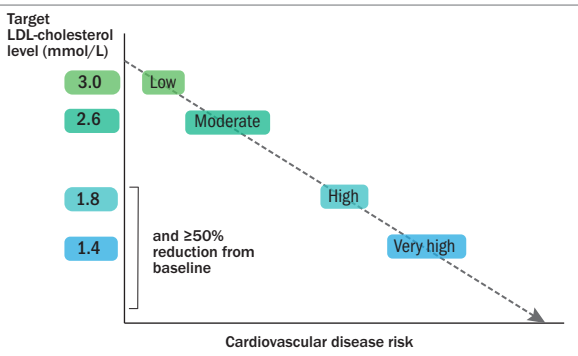
Long-term outcomes

Cost-efficacy data from long-term CVD outcomes studies are not yet available, as the first outcome data are expected in

TABLE 4. LDL-CHOLESTEROL LOWERING EFFICACY OF COMBINATION LIPID-LOWERING THERAPY[16]

LDL-cholesterol reduction			
Moderate (30 to 49%)	**High (50 to 59%)**	**Very high (60 to 79%)**	**Extremely high (80 to 84%)**
Oral drugs			
Ezetimibe + • simvastatin 10 mg or • fluvastatin 40 mg or • pravastatin 20 mg	Ezetimibe + • simvastatin 20 mg or • atorvastatin 10 to 20 mg or • rosuvastatin 5 to 10 mg	Ezetimibe + • atorvastatin 40 to 80 mg or • rosuvastatin 20 to 40 mg	–
Oral + subcutaneous drugs			
–	–	PCSK9 inhibitor (SC) (inclisiran and monoclonal antibodies) + • atorvastatin 10 to 20 mg or • rosuvastatin 5 to 10 mg or • simvastatin 40 mg	PCSK9 inhibitor (SC) (inclisiran and monoclonal antibodies) + ezetimibe + • atorvastatin 40 to 80 mg or • rosuvastatin 20 to 40 mg

Abbreviations: PCSK9 = proprotein convertase subtilin/kexin-9 (includes monoclonal antibodies and inclisiran); SC = subcutaneous.



Low – target 3.0 mmol/L
- SCORE <1%

Moderate – target 2.6 mmol/L
- SCORE ≥1% and <5%
- Young patients (type 1 diabetes <35 years; type 2 diabetes <50 years) with diabetes duration <10 years without other risk factors

High – target 1.8 mmol/L
- SCORE ≥5% and <10%
- Markedly elevated single risk factors, in particular total cholesterol >8 mmol/L or LDL cholesterol >4.9 mmol/L or BP ≥180/110 mmHg
- Familial hypercholesterolaemia without other major risk factors
- Moderate chronic kidney disease (eGFR 30 to 59 mL/min/1.73m^2)
- Diabetes mellitus without target organ damage, with diabetes duration ≥10 years or other additional risk factor

Very high – target 1.4 mmol/L
- Atherosclerotic CVD (clinical or imaging)
- SCORE ≥10%
- Familial hypercholesterolaemia with atherosclerotic CVD or with another major risk factor
- Severe chronic kidney disease (eGFR <30 mL/min/1.73m^2)
- Diabetes mellitus and target organ damage: ≥3 major risk factors; or early onset of type 1 diabetes of long duration (>20 years)

Abbreviations: BP = blood pressure; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

Figure 5. European LDL-cholesterol targets for lipid-lowering therapy.
Adapted from Mach F, et al; ESC Scientific Document Group. Eur Heart J 2020; 42: 111-188.[17]

2026 with the results of the ORION-4 randomised control trial in over 16,000 patients with prior CVD, treated over a period of 5 years.[26] Other inclisiran trials in patients with and without prior CVD (VICTORION-2 PREVENT and VICTORION-1 PREVENT) are expected to report in 2027-29.[27,28]

An exploratory analysis of 3655 participants from the ORION-9, -10 and -11 trials, using nonadjudicated pooled patient-level data, showed a significant 26% reduction in prespecified CVD events, including cardiac death, cardiac arrest, nonfatal myocardial infarction and stroke (fatal and nonfatal), along with a 50.6% (1.37 mmol/L) reduction in LDL-cholesterol.[13] Reductions in non-prespecified CVD events (20% reduction in total myocardial infarction and 14% reduction in total strokes) were not statistically significant. The ORION-9 to -11 meta-analyses were not powered for CVD outcomes, but these exploratory data are encouraging.

Conclusion

The post-statin era of genetic manipulation by targeting mRNA is now established, with effective therapies for certain lipid disorders and new therapies likely to become available for clinical practice in the near future. Control of LDL-cholesterol levels, however, remains the major focus of current lipid therapy. mRNA-based PCSK9 inhibition with inclisiran expands the selection of available drugs for LDL-cholesterol control and, when added to statins and ezetimibe, can achieve target LDL-cholesterol levels with a high degree of efficacy and safety in most patients. MT

TABLE 5. INCLISIRAN ADVERSE EVENTS (ORION-10)[12,13,23]

Adverse events	Prevalence (%)	
	Placebo (n= 1822)	Inclisiran (n = 1833)
Injection site reaction*	1.8	8.2
Arthralgia	4.0	5.0
Back pain	4.2	4.5
Pain in extremity	2.6	3.3
Diarrhoea	3.5	3.9
Bronchitis	2.7	4.3
Nasopharyngitis	7.4	7.6
Urinary tract infection	3.6	4.4
Cough	3.0	3.3
Dyspnoea	2.6	3.2
Diabetes mellitus	11.4	11.6
Dizziness	3.0	3.2
Headache	3.1	3.2
Angina pectoris	3.1	3.2
Alanine aminotransferase level >3×ULN	0.3	0.3
Aspartate aminotransferase level >3×ULN	0.6	0.5
Alkaline phosphatase level >3×ULN	0.4	0.6
Bilirubin level >2×ULN	0.4	0.5
Creatinine level >2 mg/dL	3.9	3.8
Creatine kinase level >5×ULN	1.0	1.3

Abbreviation: ULN = upper limit of normal.
*Statistically significant.

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Professor Hamilton-Craig is honorary Chairman of the SA Lipid Group, sponsored by Amgen (Australia).

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An update on messenger RNA-based therapies for lipid disorders

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