



# INCLISIRAN PROVIDES ADDITIONAL LDL CHOLESTEROL-LOWERING BENEFIT FOR SELECTED PATIENTS

Consultant Cardiologist Dr Yew Kuan Leong elaborates on the efficacy and safety of inclisiran, a new LDL cholesterol-lowering injectable medication now available in Malaysia, and the target group of patients benefiting from the additional LDL cholesterol-lowering therapy.



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as low-, intermediate- (moderate-), high- or very high-risk for cardiovascular disease, and treated accordingly (**Table 1**).<sup>1</sup> The American College of Cardiology/American Heart Association Clinical Practice Guidelines stratified patients according to their age and CV risk: 20–39 years old to be treated if their LDL-C  $\geq 4.1$  mmol/L and they have a family history of premature ASCVD; 40–75 years old with LDL-C 1.8–4.8 mmol/L to be treated if their 10-year ASCVD risk  $\geq 5\%$ ; any age group to be treated if their LDL-C  $\geq 4.9$  mmol/L.<sup>2</sup> Apart from high LDL-C levels, patients may also have other CV risk factors including high triglyceride levels and diabetes mellitus. These lead to accelerated atherosclerosis process in the entire CV system resulting in CV events such as stroke, renal vascular disease, and coronary artery disease.<sup>1</sup>

## The target LDL cholesterol levels

According to the Malaysian and international guidelines, target low-density lipoprotein cholesterol (LDL-C) levels depend on the patient's cardiovascular (CV) risk factors. Patients are classified

**Table 1. Definition of CV risk and dyslipidaemia, and target LDL-C levels<sup>1,3</sup>**

Global CV risk	LDL-C levels to start drug therapy (mmol/L)	Target LDL-C levels (mmol/L)
Low risk <ul style="list-style-type: none"> <li>Framingham risk score (FRS) that confers 10-year CV risk of <math>&lt;10\%</math></li> </ul>	Clinical judgment*	$<3.0^{1,2}$
Intermediate/ Moderate risk <ul style="list-style-type: none"> <li>FRS that confers 10-year CV risk of 10–20%</li> </ul>	$>3.4^*$	$<3.0^1$ $<2.6^2$
High risk <ul style="list-style-type: none"> <li>FRS that confers 10-year CV risk <math>&gt;20\%</math></li> <li>Diabetes without target organ damage</li> <li>CKD with GFR 30–60 mL/min/1.73m<sup>2</sup> (stage 3)</li> <li>BP <math>&gt;180/110</math> mmHg</li> </ul>	$>2.6$	$\leq 2.6$ or reduction of $>50\%$ from baseline <sup>1**</sup> $<1.8$ and reduction of $\geq 50\%$ from baseline <sup>2</sup>
Very high risk <ul style="list-style-type: none"> <li>Established CVD</li> <li>Diabetes with proteinuria or a major risk factor such as smoking, hypertension, or dyslipidaemia</li> <li>CKD with GFR <math>&lt;30</math> mL/min/1.73m<sup>2</sup> but not dependent on dialysis (<math>\geq</math> stage 4)<sup>***</sup></li> </ul>	$>1.8$	$<1.8$ or reduction of $>50\%$ from baseline <sup>1**</sup> $<1.4$ and reduction of $\geq 50\%$ from baseline (requires high-intensity LDL-C lowering therapy) <sup>2</sup>

\*After 8–12 weeks of therapeutic lifestyle changes and following discussion of the risk-benefit ratio of drug treatment with the patient.

\*\*whichever results in low LDL-C levels.

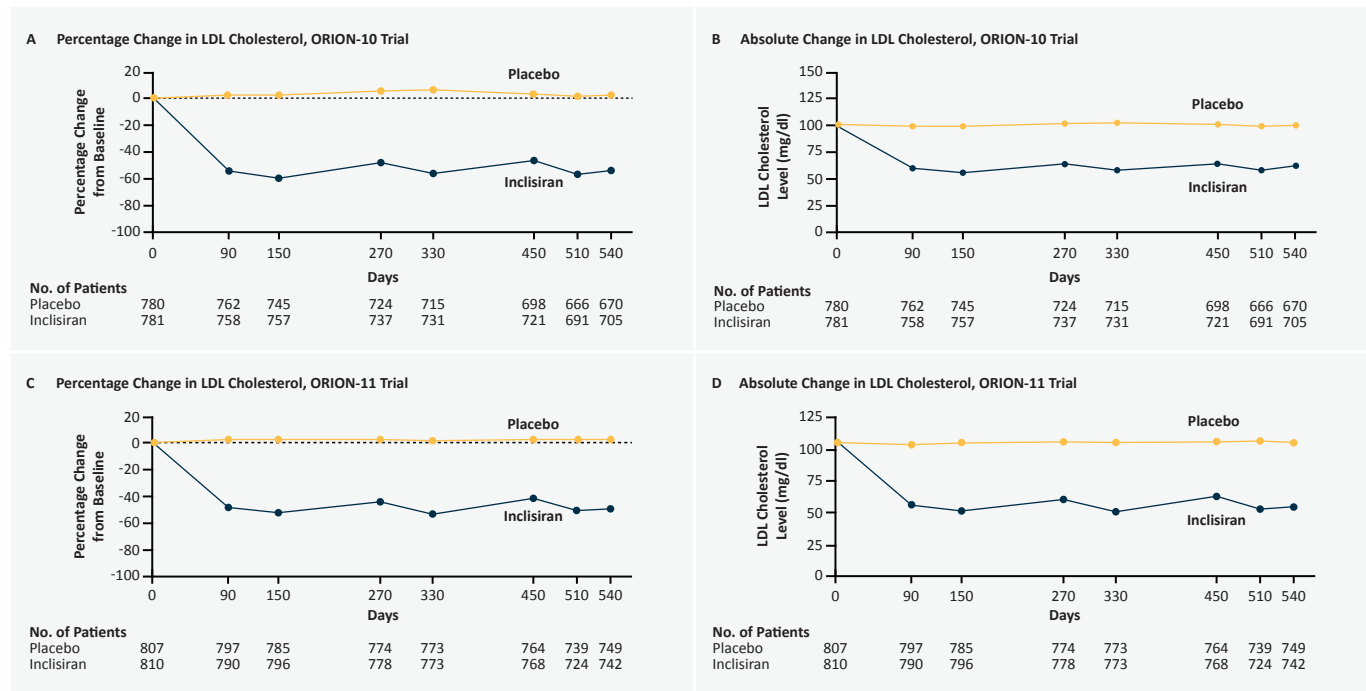
\*\*\*In patients on dialysis, drug treatment is not indicated for primary prevention of CVD.

## The efficacy and safety of inclisiran

The new LDL-C lowering therapy, inclisiran is in the form of a pre-filled syringe, which is convenient to store, does not need refrigeration, and easily administered as a single dose of inclisiran 284 mg in 1.5 mL solution via subcutaneous injection in the

abdomen, upper arm, or thigh.<sup>4</sup> The injection is well tolerated though some patients may have adverse reactions at the injection site.<sup>4</sup>

Inclisiran is potent with a rapid LDL-C lowering effect that lasts for at least 6 months when given in combination with oral LDL-C lowering therapy as shown in the ORION-10 and ORION-11 trials (**Figure 1**).<sup>5</sup>

Figure 1. Inclisiran's LDL-C lowering effect<sup>5</sup>

Therefore, inclisiran is a convenient solution for patients by reducing the frequency of doctor's follow up to every 6 months.

The target groups that would benefit from inclisiran include high-risk patients with multiple recurrent CV events despite being on maximum tolerated oral dose of statin with or without ezetimibe; those intolerant of the maximum or any dose of statin; those with heterozygous familial hypercholesterolaemia (FH); and those who forget to take the oral statin regularly.<sup>4</sup>

## Case study<sup>6</sup>

In 2018, a 68-year-old woman presented with minor heart disease, which was detected via CT coronary angiogram. Despite this, she ceased medication. Fast forward to 2022, she presented with chest pain which was attributed to exertional angina due to artery narrowing. By then, her LDL-C levels had surged to 4.28 mmol/L. Optical coherence tomography (OCT) images taken during angiography delineated the atherosclerotic plaque in her coronary artery. The OCT clearly showed how untreated high cholesterol hastened the atherosclerotic process in just 4 years. Urgent intervention ensued: a stent was inserted to restore the blocked artery and the patient was subsequently treated with atorvastatin 80 mg and then inclisiran to reduce LDL-C levels.\* After 1 month, her LDL-C levels dropped to 0.860 mmol/L and dropped further to 0.20

### References

1. Ministry of Health Malaysia. 5th Edition of Clinical Practice Guidelines. Management of Dyslipidaemia 2017. Available at: <https://www.moh.gov.my/moh/resources/Penerbitan/CPG/CARDIOVASCULAR/4.pdf>. Accessed 18 April 2023. 2. Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140(11):e563–e595. 3. Mach F, et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. *Eur Heart J* 2020;41(1):111–188. 4. Novartis Malaysia. Inclisiran Full Prescribing Information. Updated 3 Dec 2020. 5. Ray KK, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med* 2020;382(16):1507–1519. 6. Direct communication by Dr Yew Kuan Leong.

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mmol/L after another 4 weeks. The atorvastatin dose was tapered to 40 mg and after 4 months, her LDL-C levels stabilised at 0.61 mmol/L. This case study demonstrates the potency of combined high-dose statin and inclisiran to achieve target LDL-C levels, which may not be possible if a single agent is used alone. When inclisiran was given together with atorvastatin, the atorvastatin dose could be reduced from 80 mg to 40 mg to overcome muscle ache.

### Key takeaways

1. Target low-density lipoprotein cholesterol (LDL-C) levels depend on the patient's CV risk factors.<sup>1,2</sup>
2. The new LDL-C lowering therapy, inclisiran is in the form of a pre-filled syringe, which is convenient to store, does not need refrigeration, and easily administered as a single dose of inclisiran 284 mg in 1.5 mL solution via subcutaneous injection in the abdomen, upper arm, or thigh.<sup>4</sup>
3. Inclisiran is potent, with a rapid LDL-C lowering effect that lasts for at least 6 months when given in combination with oral LDL-C lowering therapy.<sup>5</sup>

ASCVD, atherosclerotic cardiovascular disease; CPG, clinical practice guidelines; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; FRS, Framingham risk score; LDL-C, low-density lipoprotein cholesterol.



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\*When administered by an HCP.<sup>1</sup>  
LDL-C, low-density lipoprotein cholesterol.

Reference: 1. Novartis Malaysia. SYBRAVA™ (inclisiran) Full Prescribing Information. Updated 3 Dec 2020.

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