

**Title: Inclisiran for the treatment of hypercholesterolemia in clinical settings.**

Sajid Iqbal<sup>1</sup>, Hani Mohamed Sabbour<sup>1,2</sup>, Tanveer Ashraf<sup>1</sup>, Adam Buckley<sup>1</sup>

<sup>1</sup>Imperial College London Diabetes Centre, Abu Dhabi, UAE

<sup>2</sup>Cleveland Clinic, Abu Dhabi, UAE

**Abstract**

**Background:** Inclisiran is the first clinically available small interfering RNA (siRNA)-based treatment, has been shown to reduce pro-atherogenic lipoproteins in patients with or without familial hypercholesterolemia (FH), diabetes mellitus (DM), or atherosclerotic cardiovascular disease (ASCVD), but has not been evaluated in Middle Eastern populations.

**Methods:** Retrospective review of patients initiating inclisiran treatment for any indication at our centre between 2021 and 2022. All individuals followed-up for at least 90 days or with at least one lipid panel post-initiation were included. Participants subclassified into DLCN-diagnosed FH (n = 36) and non-FH (n = 56) groups.

**Results:** Inclisiran was initiated in 92 individuals, mean  $\pm$  sd age  $54.7 \pm 11.6$  years, 48 (52.2%) males, 70 (76.1%) with secondary prevention (prior history of ASCVD event), 66.7% with DM and 25 (27.2%) with statin intolerance. At 90 days, substantial reductions in serum Low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total cholesterol:HDL-C (TC:HDL-C) were observed in both primary and secondary prevention, and FH and non-FH individuals: FH; median (IQR) reduction in LDL-C was 61.4% (51.2%; 84.8%), TG 25% (7.5%; 45%), TC:HDL-C

42.2% (30.7%; 60.7%), non-FH; LDL-C 33.1% (3.2%; 59.4%), TG 13.5% (-14%; 32.1%), TC:HDL-C 22.9% (0.4%; 40.5%), all p-values < 0.0001. American College of Cardiology / American Heart Association (ACC/AHA) LDL-C targets were consistently achieved in 68 (73.9%) patients during a follow-up of 107 (27-237) days. Non-attainment of LDL-C target was attributed to non-adherence in 13 (54.2%), and discontinuation of treatment in 5 (20.8%) patients. New ASCVD hazard adjusted for age, sex, smoking status, diabetes and FH was 0.66,  $p < 0.05$  in ACC/AHA LDL-C target achievers against non-achievers.

**Conclusions:** Clinically meaningful and sustained reductions in LDL-C, TG, and cholesterol ratios were observed after inclisiran initiation. Inclisiran is safe and effective in the management of hyperlipidemia and ASCVD in a predominantly Arabic population.

**Keywords:** Inclisiran, small interfering RNA (siRNA), Familial hypercholesterolemia, Atherosclerotic cardiovascular disease, Low-density lipoprotein cholesterol, Diabetes Mellitus, PCSK9-Inhibitor.