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C10 LIPID MODIFYING AGENTS

ADJUSTED INDIRECT COMPARISON BETWEEN PLOZASIRAN AND ZODASIRAN IN MIXED HYPERLIPIDEMIA

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BACKGROUND AND IMPORTANCE

- **Plozasiran** and **zodasiran** → RNA interference agents developed for the treatment of mixed hyperlipidemia.
- No direct comparisons between these drugs have been performed.

AIM AND OBJECTIVES

To conduct **adjusted indirect comparisons (AICs)** on **efficacy** between plozasiran and zodasiran in mixed hyperlipidemia.

MATERIAL AND METHODS

- A search was developed in **Pubmed®** database to select pivotal randomised clinical trials (RCTs) including plozasiran and zodasiran in mixed hyperlipidemia.
- These RCTs had to presented comparable populations, follow-up periods, endpoints and comparator arms.
- **AICs** of regimens with best benefit-risk balance were developed using **Bucher's method** on the following **endpoints**: percentage change in plasma levels from baseline to week 24 of fasting triglyceride, non-HDL cholesterol, ApoB, LDL cholesterol, HDL cholesterol, remnant cholesterol and lipoprotein(a).
- The **absolute risk reduction (ARR)** was calculated for AICs.

RESULTS

- Two **phase II RCTs** were selected, one of each drug.
- A total of 557 patients were included.
- Doses of **plozasiran 25 mg quarterly** (PLOZ-25q) and **zodasiran 200 mg** (ZOD-200) were selected based on their superior risk-benefit balance.
- **Placebo** was common comparator.
- **AICs limitations:** short patient follow-up and minor differences in population characteristics (percentage of high-intensity statins and fibrates received).

PLOZ-25q showed significant benefit on HDL cholesterol.

ZOD-200 presented significant favorable differences in non-HDL cholesterol, LDL cholesterol and remnant cholesterol.

ENDPOINTS (percentage change in plasma levels from baseline to week-24)	ARR (IC95%) PLOZ-25q vs. placebo	ARR (IC95%) ZOD-200 vs. placebo	AICs: ARR (IC95%) PLOZ-25q vs. ZOD-200
Triglyceride	-56.0% (-65.1%, -46.8%)	-63.1% (-73.6%, -52.7%)	7% (-7.16%, 21.16%)
Non-HDL cholesterol	-17.5% (-25.1%, -9.8%)	-36.4% (-45.5%, -27.2%)	19% (6.96%, 31.04%)
ApoB	-13.0% (-20.6%, -5.4%)	-21.9% (-29.7%, -14.1%)	8% (-2.61%, 18.61%)
LDL cholesterol	-2.7% (-12.4%, 7.0%)	-19.9% (-31.0%, -8.8%)	17% (2.08%, 31.92%)
HDL cholesterol	42.0% (32.1%, 52.0%)	-24.5% (-32.6%, -16.5%)	66% (53.19%, 78.81%)
Remnant cholesterol	-48.9% (-62.7%, -35.2%)	-82.0% (-103.4%, -60.6%)	34% (8.61%, 59.39%)
Lipoprotein(a)	-23.8% (-134.1%, 86.4%)	-17.1% (-31.9%, -2.3%)	-6% (-116.95%, 104.95%)

CONCLUSION AND RELEVANCE

Significant favourable differences on differing surrogate endpoints were found for PLOZ-25q (HDL cholesterol) and ZOD-200 (non-HDL cholesterol, LDL cholesterol, remnant cholesterol) in mixed hyperlipidaemia. RCTs with harder endpoints and longer follow-up are needed to establish better therapeutic positioning.