PAGNY RESEARCH DAY

Physician Affiliate Group of New York, P.C.

Presentation Title:

The Safety Profile of Inclisiran in Patients with Dyslipidemia: A Systematic Review and Meta-Analysis

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Financial Disclosure

- None

Introduction

- ASCVD is the leading cause of death globally, affecting over 500 million people, with 19 million annual deaths worldwide.
- In the US, ASCVD affects 26 million people, leading to 2 million hospitalizations and 400,000 deaths annually.
- Elevated LDL cholesterol is a major contributor to ASCVD.
- High-intensity statins are the first-line treatment for preventing and treating ASCVD in high-risk individuals.
- Ezetimibe lowers LDL-C by up to 24% and is used as an adjunct to statins for patients not responding to maximum doses.
- Many high-risk patients fail to reach LDL targets due to non-adherence and prescribing patterns.
- Monoclonal antibodies targeting PCSK9 reduce LDL levels by 65% and decrease major adverse cardiac events.
- Meta-analysis shows no significant difference in treatment-emergent adverse events between PCSK9 inhibitors and placebo.

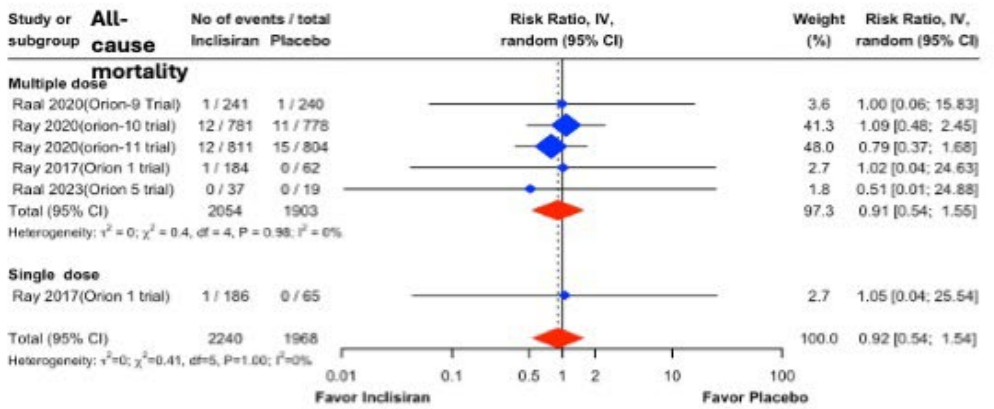
Inclisiran

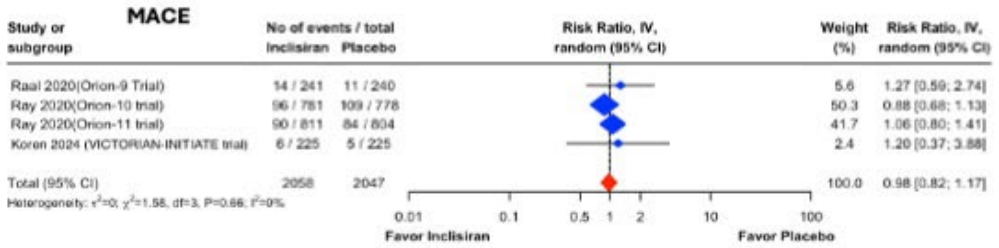
- Inclisiran is a new siRNA-based therapy that lowers LDL by binding to mRNA coding for PCSK9, preventing its production.
- Inclisiran, administered every 3 to 6 months, significantly reduces LDL in patients with dyslipidemia and high ASCVD risk.
- The review aims to assess the safety of inclisiran in dyslipidemia patients with ASCVD or equivalent risk, providing insights into its utility in cardiovascular care.

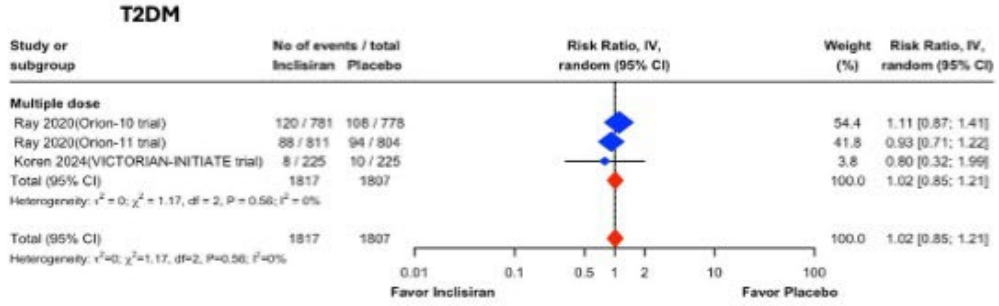
Methods

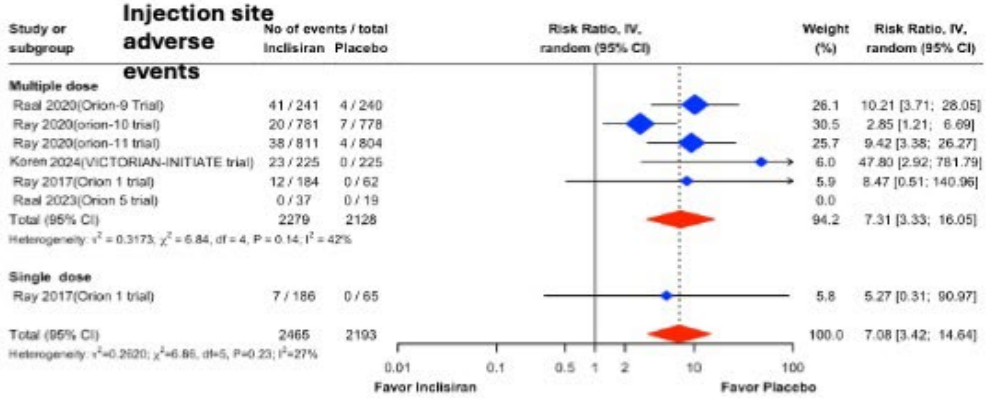
- Databases reviewed: PubMed/MEDLINE, Embase, Web of Science, and ClinicalTrials.gov from inception until June 2024.
- Eligibility criteria: Included RCTs with adults (≥18 years) on inclisiran for dyslipidemia, and ASCVD or risk equivalent. The term ASCVD risk equivalent refers to individuals without a known history of ASCVD, but who either have type 2 diabetes mellitus, heterozygous familial hypercholesterolemia or a 10-year cardiovascular risk greater than 20% based on the Framingham Risk Score or an equivalent assessment .Excluded studies without control groups, retrospective studies, cross-sectional studies, review articles, case reports, , extensions of previous trials and crossover portion of RCTs and non-human studies.
- Outcomes of interest: 1.All-cause mortality,2. major adverse cardiovascular events (MACE)[a composite of of cardiac arrest, nonfatal myocardial infarction (MI) and nonfatal stroke],3. injection site adverse events[which include injection-site erythema, pain, hypersensitivity, pruritus, rash and thrombophlebitis], 4.new onset or worsening of type 2 diabetes, and 5.nasopharyngitis.

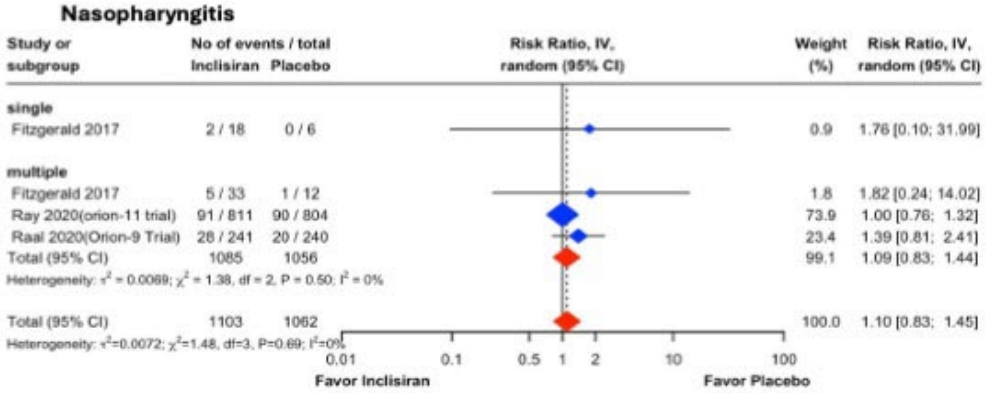
Figures


All-cause mortality
Study or subgroup
No of events / total Inclisiran Placebo
Risk Ratio, IV, random (95% CI)
Weight (%)
Risk Ratio, IV, random (95% CI)
Multiple dose
Raal 2020(Orion-9 Trial) 1 / 241 1 / 240 3.6 1.00 [0.06; 15.83]
Ray 2020(orion-10 trial) 12 / 781 11 / 778 41.3 1.09 [0.48; 2.45]
Ray 2020(orion-11 trial) 12 / 811 15 / 804 48.0 0.79 [0.37; 1.68]
Ray 2017(Orion 1 trial) 1 / 184 0 / 62 2.7 1.02 [0.04; 24.63]
Raal 2023(Orion 5 trial) 0 / 37 0 / 19 1.8 0.51 [0.01; 24.88]
Total (95% CI) 2054 1903 97.3 0.91 [0.54; 1.55]
Heterogeneity: τ² = 0; χ² = 0.4, df = 4, P = 0.98; I² = 0%
Single dose
Ray 2017(Orion 1 trial) 1 / 186 0 / 65 2.7 1.05 [0.04; 25.54]
Total (95% CI) 2240 1968 100.0 0.92 [0.54; 1.54]
Heterogeneity: τ²=0; χ²=0.41, df=5, P=1.00; I²=0%
0.01 0.1 0.5 1 2 10 100
Favor Inclisiran
Favor Placebo

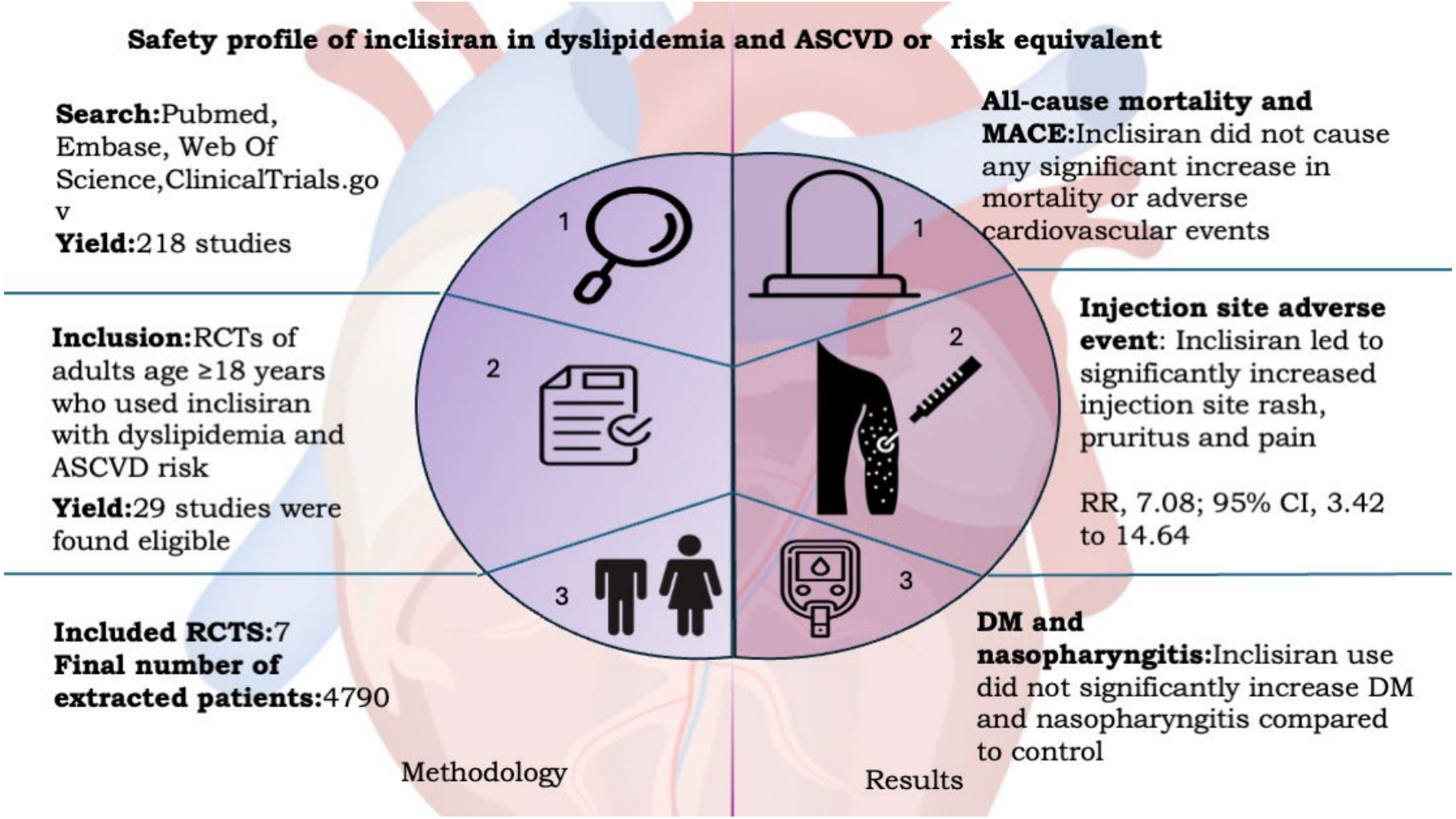

MACE
Study or subgroup
No of events / total Inclisiran Placebo
Risk Ratio, IV, random (95% CI)
Weight (%)
Risk Ratio, IV, random (95% CI)
Raal 2020(Orion-9 Trial) 14 / 241 11 / 240 5.6 1.27 [0.59; 2.74]
Ray 2020(Orion-10 trial) 96 / 781 109 / 778 50.3 0.88 [0.68; 1.13]
Ray 2020(Orion-11 trial) 90 / 811 84 / 804 41.7 1.06 [0.80; 1.41]
Koren 2024 (VICTORIAN-INITIATE trial) 6 / 225 5 / 225 2.4 1.20 [0.37; 3.88]
Total (95% CI) 2058 2047 100.0 0.98 [0.82; 1.17]
Heterogeneity: τ²=0; χ²=1.58, df=3, P=0.66; I²=0%
0.01 0.1 0.5 1 2 10 100
Favor Inclisiran
Favor Placebo


T2DM
Study or subgroup
No of events / total Inclisiran Placebo
Risk Ratio, IV, random (95% CI)
Weight (%)
Risk Ratio, IV, random (95% CI)
Multiple dose
Ray 2020(Orion-10 trial) 120 / 781 108 / 778 54.4 1.11 [0.87; 1.41]
Ray 2020(Orion-11 trial) 88 / 811 94 / 804 41.8 0.93 [0.71; 1.22]
Koren 2024(VICTORIAN-INITIATE trial) 8 / 225 10 / 225 3.8 0.80 [0.32; 1.99]
Total (95% CI) 1817 1807 100.0 1.02 [0.85; 1.21]
Heterogeneity: τ² = 0; χ² = 1.17, df = 2, P = 0.56; I² = 0%
Total (95% CI) 1817 1807 100.0 1.02 [0.85; 1.21]
Heterogeneity: τ²=0; χ²=1.17, df=2, P=0.56; I²=0%
0.01 0.1 0.5 1 2 10 100
Favor Inclisiran
Favor Placebo


Injection site adverse events
Study or subgroup
No of events / total Inclisiran Placebo
Risk Ratio, IV, random (95% CI)
Weight (%)
Risk Ratio, IV, random (95% CI)
Multiple dose
Raal 2020(Orion-9 Trial) 41 / 241 4 / 240 26.1 10.21 [3.71; 28.05]
Ray 2020(orion-10 trial) 20 / 781 7 / 778 30.5 2.85 [1.21; 6.69]
Ray 2020(orion-11 trial) 38 / 811 4 / 804 25.7 9.42 [3.38; 26.27]
Koren 2024(VICTORIAN-INITIATE trial) 23 / 225 0 / 225 6.0 47.80 [2.92; 781.79]
Ray 2017(Orion 1 trial) 12 / 184 0 / 62 5.9 8.47 [0.51; 140.96]
Raal 2023(Orion 5 trial) 0 / 37 0 / 19 0.0
Total (95% CI) 2279 2128 94.2 7.31 [3.33; 16.05]
Heterogeneity: τ² = 0.3173; χ² = 6.84, df = 4, P = 0.14; I² = 42%
Single dose
Ray 2017(Orion 1 trial) 7 / 186 0 / 65 5.8 5.27 [0.31; 90.97]
Total (95% CI) 2465 2193 100.0 7.08 [3.42; 14.64]
Heterogeneity: τ²=0.2620; χ²=6.86, df=5, P=0.23; I²=27%
0.01 0.1 0.5 1 2 10 100
Favor Inclisiran
Favor Placebo


Nasopharyngitis
Study or subgroup
No of events / total Inclisiran Placebo
Risk Ratio, IV, random (95% CI)
Weight (%)
Risk Ratio, IV, random (95% CI)
single
Fitzgerald 2017 2 / 18 0 / 6 0.9 1.76 [0.10; 31.99]
multiple
Fitzgerald 2017 5 / 33 1 / 12 1.8 1.82 [0.24; 14.02]
Ray 2020(orion-11 trial) 91 / 811 90 / 804 73.9 1.00 [0.76; 1.32]
Raal 2020(Orion-9 Trial) 28 / 241 20 / 240 23.4 1.39 [0.81; 2.41]
Total (95% CI) 1085 1056 99.1 1.09 [0.83; 1.44]
Heterogeneity: τ² = 0.0089; χ² = 1.38, df = 2, P = 0.50; I² = 0%
Total (95% CI) 1103 1062 100.0 1.10 [0.83; 1.45]
Heterogeneity: τ²=0.0072; χ²=1.48, df=3, P=0.69; I²=0%
0.01 0.1 0.5 1 2 10 100
Favor Inclisiran
Favor Placebo

Graphical abstract



Discussion

- Across seven RCTs involving 4,790 patients, inclisiran was generally well tolerated and safe.
- No significant difference was found in all-cause mortality (RR 0.92) or MACE (RR 0.98) between inclisiran and placebo groups.
- The findings differ from previous studies by Asbeutah et al. and Cicero et al., which reported a reduction in MACE, possibly due to shorter-term data in those studies.
- Inclisiran did not increase the risk of new-onset or worsening T2DM (RR 1.02), unlike statins, which are linked to insulin resistance.
- No significant increase in nasopharyngitis (RR 1.10) was observed, countering previous reports of increased respiratory complications like bronchitis.
- Injection-site reactions were more common with inclisiran (RR 7.08), typically mild to moderate, including erythema, swelling, pain, and pruritus.
- Injection-site reactions were linked to higher doses and longer treatment duration, as seen in trials like ORION-9, which used higher doses and reported a higher incidence.
- These reactions are typical for injectable biologics and future studies should investigate formulation or administration changes to improve patient comfort and adherence.

Conclusions

- Limitations: Included phase 2/3 trials with varying drug regimens and lacked long-term follow-up or patient-level data.
- Overall, inclisiran shows an acceptable safety profile with increased injection-site reactions. Long-term studies like ORION-4 and VICTORIAN-2P/1P will offer further insights into inclisiran's safety and efficacy, especially regarding MACE and injection-site reactions.

Questions?