A Multicenter, Randomized, Placebo-Controlled Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis

Background: Individuals with rheumatoid arthritis are at high risk for cardiovascular events. Almost half of all deaths in RA are attributed to cardiovascular disease. Some experts believe this population may benefit from universal statin prescribing. There have been no major studies evaluating the efficacy of statin therapy specifically in the population of rheumatoid arthritis.

Objective: Determine if atorvastatin is more effective than placebo in the primary prevention of cardiovascular events in patients with rheumatoid arthritis.

Methods:

- *Design:* Multicenter, randomized, double-blind, placebo-controlled trial
- *Duration:* The study was unexpectedly discontinued early; the planned duration was 5 years, but with the early discontinuation, the median duration was 2.5 years (IQR 1.9 – 3.49 years)
- *Inclusion:* Fulfilled the American College of Rheumatology 1987 criteria for RA; >50 years old OR had RA for >10 years; gave informed consent; taken stable doses of RA medications for 3 months
- *Exclusion*: Currently taking a statin; contraindication to statin therapy; Known cardiovascular risk requiring statin already; diabetes mellitus…etc.
- There were 3,002 patients enrolled in the study. 1504 patients were analyzed in the treatment group and 1498 patients were analyzed in the placebo group. Patients either received atorvastatin 40mg once daily or matching placebo.
- *Outcome measures*:
    - Primary: Major vascular events (nonfatal MI, nonfatal presumed ischemic stroke, TIA, any coronary or non-coronary revascularization, or cardiovascular death)
    - Secondary: Separate components of primary endpoints
    - Tertiary: Safety-related outcomes, hospitalizations, total and cause-specific mortality
- *Power*: For 3,002 patients and a 32% relative risk reduction, power was less than 20%.
- Data handling method followed the intent-to-treat model. All patients randomized were analyzed in the study at the time of dropout or at study discontinuation.

Results:

- Because there was an extremely low number of primary endpoints (cardiovascular events) that occurred between both the treatment and placebo groups, the trial was discontinued earlier than expected. Those primary endpoints that did occur were not found to be statistically significant ($P = 0.127$).
- There were 298 adverse events in the atorvastatin group and 292 in the placebo group ($p = 0.854$) which was not statistically significant.
- The low number of primary endpoints led to a low relative risk reduction (34%) which did not meet power based on the population size of 3,002.
- The effect size for true reduction in CVEs could range from a 61% reduction to an 11% increase, rendering it not statistically significant.

Strengths:

- The rationale behind the trial was defensible
- Statistical analyses were appropriate and reported for each outcome measure

Limitations:

- Only one treatment dose was included, and it was compared against placebo for the reduction of cardiovascular events in a high-risk patient population
- Patients included in this trial may not have been those at highest risk for CVEs within the RA population (excluded those at high risk)
- All participants in the study could receive non-study statin therapy without being removed from the study
- No baseline assessment of lipids (could have been within the last 12 months) or blood pressure
- Participants could stop treatment for 4 weeks and remain in the study
- No assessment of blinding
- Adherence measured using "most, some, or none" which is subjective to the patient
- Adherence rates were very low
- May have missed some primary endpoints
- Rheumatoid arthritis management could have different medications, doses, etc.
- Patients included were primarily women and the mean age was 61 (lower risk of CVE)
- Adverse events were reported by patients; no evaluation
- Study makes several biased statements (drug is safe, adverse effects not due to study drug)
- Study received "unrestricted grants" from drug manufacturer
- Conclusion does not address the study objective of atorvastatin being superior to placebo

Conclusions: In conclusion, the article found that there was no difference between placebo and atorvastatin, but there were very limited cardiovascular events, which led to an insufficient power and low effect size. Because there were very limited primary endpoints, most of the data reported was found to be statistically insignificant. While it appears that atorvastatin is safe, there were concerning adverse effects that were reported as not due to study drug. There was no rationale behind these statements, exposing potential bias. The clinical implications for statin use in patients with rheumatoid arthritis is still unknown. The study has many limitations that should be taken into consideration for future research. Studies performed in the future should analyze statin use in male and female patients with rheumatoid arthritis who may or may not be well controlled, with high risk or low risk, to better represent the population. Future studies should follow patients over a longer period of time and exclude patients who received other statins during the study.

Reference: Kitas GD, Nightingale P, Armitage J, Sattar N, Belch JJF, Symmons DPM. TRACE RA Consortium. A Multicenter, Randomized, Placebo-Controlled Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis. Arthritis & Rheumatology. 2019 Sep; 71(9):1437-1449.

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