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Immunomodulatory effect of different statin regimens on regulatory T-cells among patients with acute coronary syndrome: a systematic review and network meta-analysis of randomized clinical trials

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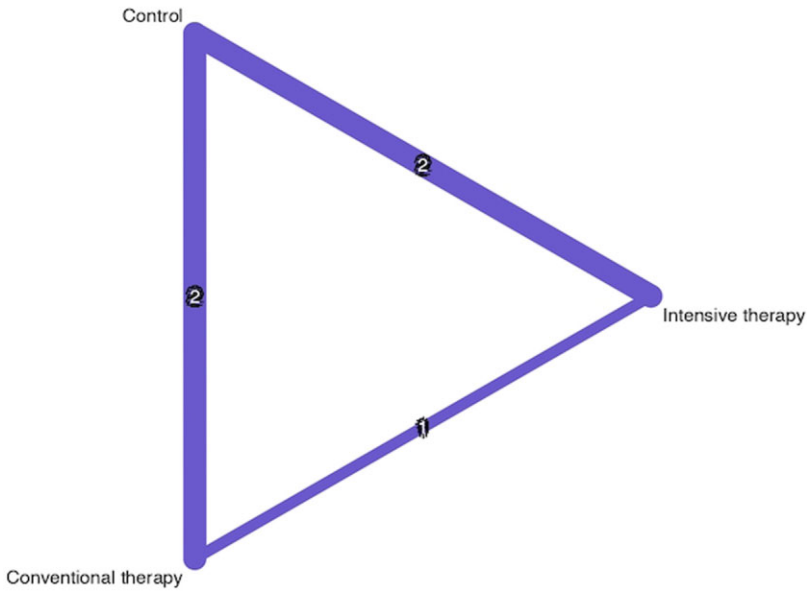
Introduction: In patients with acute coronary syndrome (ACS), studies suggest that statin therapy, besides its role in reducing the progression of atherosclerosis through its pharmacological effect, plays a pivotal role in controlling the pathogenesis of ACS through the anti-inflammatory effects of suppressor regulatory T cells (Tregs).

Purpose: We conducted a network meta-analysis (NMA) to determine the effects of low-dose conventional statin therapy (CST) (20 mg/day or less) and high-dose intensive statin therapy (IST) (40 mg/day or more) on the frequency of Tregs and their associated cytokines (IFN-γ, IL-10, TGF-β), compared to placebo.

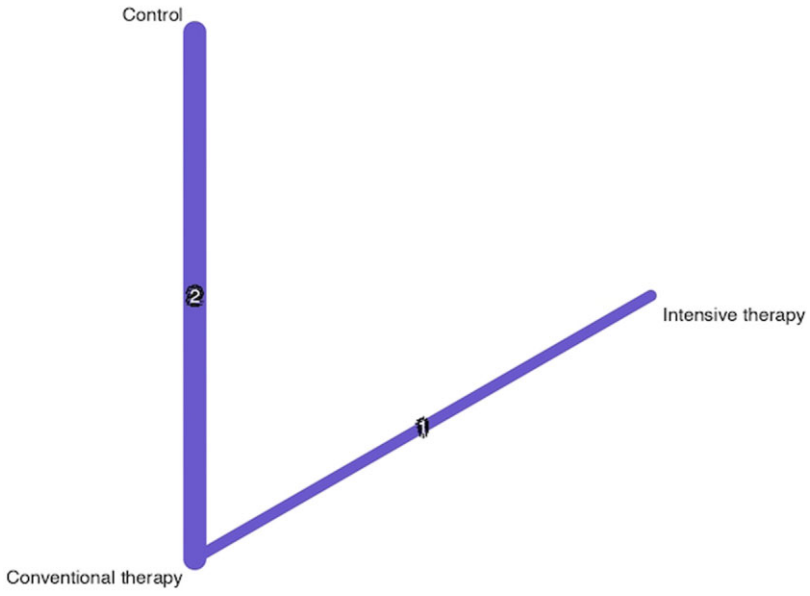
Methods: The PubMed, Cochrane Library, and EMBASE databases were searched for randomized clinical trials (RCTs) to identify relevant articles published until June 2021. We pooled data extracted from the included studies using the standardized mean difference (SMD). A random-effects model was used to conduct this NMA. Heterogeneity was evaluated using Cochran's Q- and the I2-test. GRADE(Grading of Recommendations, Assessment, Development and Evaluations) was used to assess the study's quality. Data analysis was conducted using R software.

Results: A total of 505 patients were enrolled in the 5 RCTs. The NMA indicated a significant increase in Treg frequency in the CST group compared with the control group (SMD 1.77; 95% CI: 0.77 – 2.76; P-value = 0.0005) and a larger increase in the Treg frequency associated with the IST group compared with the control group (SMD 2.12; 95% CI: 1.15 – 3.10; P-value < 0.0001). However, there was significant heterogeneity and inconsistency among the included studies ($\tau 2 = 0.6096$; $\tau = 0.7808$; I2 = 91.2% [80.5%; 96.0%]). When compared to the placebo, both CST and IST increased levels of secreted IL-10 (SMD 2.69; 95% CI: 2.07 – 3.31; P-value < 0.0001 and (SMD 2.14; 95% CI: 1.76 – 2.52; P-value < 0.0001), respectively. In comparison to the control group, CST was associated with increased levels of TGF-β (SMD 3.83; 95% CI: 0.63 – 7.0; P-value = 0.0189). This association was not seen in the IST group. IFN-γ levels decreased significantly in both the IST and CST groups (SMD -1.52; 95% CI: -1.94 – -1.10; P-value < 0.0001) and (SMD -2.34; 95% CI: -2.73 – -1.95; P-value < 0.0001) respectively.

Conclusions: Our study suggests that both high and low dose statin groups showed increased Treg frequency compared to the placebo group. IST showed larger benefits. Statin therapy also increased IL-10 and TGF-β cytokine levels and decreased IFN-γ levels. Therefore, statins have the potential to be the main treatment to reduce the incidence of cardiovascular events and improve cardiac function in patients with ACS through immunomodulatory effect on Treg.



Network plots of Treg



Network plot of IL 10