



## Wouldn't Bet On it: What is the risk of muscle symptoms on statins?

### CLINICAL QUESTION

What are the effects of statins on muscles?

### BOTTOM LINE

**Statins increase the risk of muscle symptoms (includes pain, cramps, and weakness) in their first year of use, from 14% (placebo) to 14.8%, but are similar to placebo after 1 year. When patients report muscle symptoms, only 1 in 15 is due to the statin. Statins may increase muscle symptoms with creatine kinase rise 10x normal for 1 in ~3000 patients over placebo.**

### EVIDENCE

- 7 systematic reviews [11-135 randomized controlled trials (RCTs); 18,192-192,977 patients] from the last 5 years.<sup>1-7</sup> Focusing on the most recent (23 RCTs; 154,664 patients x4.3 years).<sup>1</sup> Results statistically significant unless indicated.
  - Any muscle symptoms, statin versus placebo,
    - Anytime: 27.1% versus 26.6% (placebo).<sup>1</sup>
      - Within 1st year: 14.0% versus 14.8%, number needed to harm=125.
      - After 1st year: 14.8% versus 15.0% (not statistically different).
    - Other systematic reviews<sup>2-7</sup> similar but not statistically different for myalgia,<sup>5</sup> ≥65 age subgroup,<sup>4</sup> or intensity subgroups versus placebo.<sup>2</sup>
    - No difference by statin type,<sup>3</sup> lipophilic/hydrophilic statin,<sup>6</sup> or age groups.<sup>1,5,6</sup>
  - Any muscle symptoms, more versus less-intense statin:

- Any timepoint: 36.1% versus 34.8% (less intense).<sup>1</sup>
    - Other systematic reviews found similar.<sup>2</sup>
  - Creatine kinase >10x upper limit of normal (myopathy): 0.077% versus 0.044% (placebo).<sup>1</sup>
    - 4 other systematic reviews:<sup>2-5</sup> No difference.
    - More versus less-intense statin:<sup>1,2</sup> Results no different for approved statins/doses (excluding simvastatin 80mg).
  - Rhabdomyolysis:
    - 3 systematic reviews:<sup>4,5</sup> No difference.
  - Discontinuation for muscle symptoms<sup>2,4</sup> or any adverse event<sup>4,5,7</sup> not statistically increased.
- Three n-of-1 trials (8-200 patients, previous statin intolerance due to muscle symptoms) randomized to 3-4 cycles of ~3-8 weeks of statin,<sup>8-10</sup> placebo,<sup>8-10</sup> and no-pill<sup>8</sup> each. Muscle symptom scores:
  - Statin versus placebo:<sup>8-10</sup> no difference.
  - Statin versus no-pill:<sup>8</sup> 16 versus 8 (no-pill) (scale=0-100, higher worse).

## CONTEXT

- Mean creatine kinase rise<sup>1</sup> with statin therapy ~2%.
- Events like myopathy and rhabdomyolysis are too infrequent to discern statin effects in meta-analysis of >100,000 RCT participants.
  - Statin-induced rhabdomyolysis estimated at 2-3 excess cases/100,000 patient-years.<sup>11</sup>
- Guidelines recommend:
  - In patients with non-severe muscle-symptoms, offer retreat of same or lower-intensity statin.<sup>12</sup>
  - Monitoring creatinine kinase is generally not encouraged, but check if symptoms or high-risk.<sup>12,13</sup>

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