

**Oltion Mesi, MD**Department of General Internal Medicine,  
Cleveland Clinic, Cleveland, OH**Charlie Lin, MD**Department of General Internal Medicine,  
Cleveland Clinic, Cleveland, OH**Haitham Ahmed, MD, MPH**

AdvantageCare Physicians, New York, NY

**Leslie S. Cho, MD**Section Head, Preventive Cardiology and  
Cardiac Rehabilitation, Heart, Vascular,  
and Thoracic Institute, Cleveland Clinic,  
Cleveland, OH

# Statin intolerance and new lipid-lowering treatments

**C**ORONARY ARTERY DISEASE continues to be the leading cause of death in developed countries, and rates are rapidly rising in the developing world.<sup>1</sup> With the current obesity epidemic and growth of metabolic syndrome, its prevalence is likely to continue to climb. Along with hypertension, diabetes, and smoking, hyperlipidemia has consistently been shown to be one of the most significant and modifiable risk factors of coronary artery disease development and progression.<sup>2</sup>

Lipid-lowering therapy is important for secondary prevention for patients with known cardiovascular disease, as well as for primary prevention for those at increased risk. Although guidelines have historically focused on achieving specific levels of low-density lipoprotein cholesterol (LDL-C), there is increasing recognition that in many cases lower levels are progressively beneficial, making lipid-lowering therapies especially relevant.

## ■ STATINS STILL THE THERAPY OF CHOICE TO LOWER CHOLESTEROL

Several drug classes lower atherosclerotic risk by lowering circulating lipid concentrations and have been thoroughly tested. With a historically proven track record in reducing morbidity and mortality related to atherosclerotic disease, beta-hydroxy beta-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are first-line cholesterol-lowering medications. A large meta-analysis found that sustained moderate- or high-intensity statin therapy over 5 years reduced events related to atherosclerotic cardiovascular disease by 21% for every 1 mmol/L (approximately 40 mg/dL) decrease in LDL-C.<sup>3</sup>

doi:10.3949/ccjm.88a.20165

However, many patients experience musculoskeletal side effects that either prevents them from using statins at all or limits their ability to tolerate a dosage necessary to achieve their cholesterol targets. As suboptimal control keeps them at continued cardiovascular risk, such patients should be thoroughly evaluated for true statin intolerance, and adjunctive or alternative therapies should be considered.

## ■ STATIN INTOLERANCE: MYOPATHY

While the benefits and safety profile of statin therapy are clear, adverse effects such as statin-related myopathy remain elusive, posing diagnostic and therapeutic challenges. Statin intolerance is widely reported in clinical practice, often leading to its discontinuation. Some estimate that up to 20% of patients are unable to tolerate statin therapy owing to muscle symptoms.<sup>4</sup>

Most of our current knowledge regarding statin intolerance originates from observational data, although randomized control trials have also been conducted evaluating drug discontinuation due to intolerance. One meta-analysis of randomized controlled trials found that patients taking a statin and those taking a placebo were not significantly different when discontinuing treatment (odds ratio [OR] 0.99; 95% confidence interval [CI] 0.93–1.06).<sup>5</sup> The Self-Assessment Method for Statin Side-effects or Nocebo (SAMSON) trial<sup>6</sup> found that 90% of side effects experienced on statin therapy were also experienced while taking placebo. Discordant data between randomized controlled trials and observational data may be explained by the healthier and younger populations studied in randomized controlled trials,

**Patients with muscle symptoms should be thoroughly evaluated for true statin intolerance**

as well as lower dosages used during testing in the early statin randomized controlled trials compared with clinical practice.

Rates of myalgia, myositis, and rhabdomyolysis are rare, according to the US Food and Drug Administration (FDA) Adverse Event Reporting system and other large, real-world databases.<sup>7-9</sup> However, not all studies evaluated myalgia or reported creatine kinase levels, and several trials included a run-in period, in which randomization and inclusion occurred only after preliminary trial exposure to statin therapy.

Anti-HMG-CoA reductase antibody-mediated myopathy is an infrequently occurring immunologic necrotizing myopathy, which causes widespread and profound muscle breakdown leading to permanent weakness. Patients report progressive muscle weakness and have persistently elevated creatine kinase levels. Recognizing it promptly is critical so that intravenous immunoglobulin treatment can be started.

### ■ STATIN INTOLERANCE: NONMUSCLE-RELATED SIDE EFFECTS

Nonmuscle-related side effects have also been attributed to statin therapy, several of which have been studied. Reports of peripheral neuropathies are rare. Neurologic cognition changes and memory loss do not appear to be associated with statins.<sup>10,11</sup> No increased risk of hemorrhagic cerebrovascular accidents with the use of statins for primary stroke prevention has been demonstrated, the literature is conflicting regarding their use for secondary prevention, but benefits appear to largely outweigh risks.<sup>12,13</sup>

Liver dysfunction, a rare finding in patients taking high-intensity statins, appears to be a laboratory side effect but is not clinically significant.<sup>14</sup> Liver failure is even more rare.<sup>15</sup> There is a slight increase in diabetes in patients taking statin therapy, but this should be weighed against far greater risk reductions in major cardiovascular events. Cataracts, renal dysfunction, malignancy, and tendonitis have not proven attributable to statin use.

### ■ STATIN-ASSOCIATED MYALGIA

Risk factors for statin-related myalgia have been identified, including older age, female

sex, family history of statin-associated myalgia, alcohol use, and rheumatologic disease. Certain drugs can increase risk: colchicine, verapamil, diltiazem, fibrates, protease inhibitors, azoles, and antimicrobials such as clarithromycin and erythromycin.

Clinical diagnosis is difficult, as no definitive blood markers have been identified. Values for creatine kinase, thyroid function, inflammatory markers, and vitamin D are usually normal. Furthermore, definitions for myopathy, myalgia, myositis, and rhabdomyolysis vary among professional organizations.

Although standardized definitions are lacking, certain diagnostic criteria are consistent across published guidelines.<sup>4,16</sup> Factors favoring a clinical diagnosis of statin-related myopathy include:

- Symmetric, proximal large muscle pain or weakness, worsened by exercise
- Symptoms beginning 2 to 4 weeks after statin initiation
- Resolution of symptoms within 2 weeks of discontinuation
- Symptoms returning within 2 weeks after reintroducing statin
- Symptoms occurring with 2 or more different statins, at least one of which is prescribed at the lowest dosage.

### ■ DETERMINING STATIN INTOLERANCE

A major difficulty in establishing statin intolerance lies in distinguishing statin-associated from nonstatin-associated muscle symptoms. Many patients diagnosed with statin-associated muscle symptoms likely have nonspecific musculoskeletal pain, unrelated to statin therapy.<sup>16</sup> Although the Statin-Associated Muscle Symptom Clinical Index questionnaire was designed to facilitate diagnosis, it requires additional validation.<sup>17</sup>

Whereas previous trials have suggested an almost indistinguishable side-effect profile between low-dose statin therapy and placebo, more recently designed rechallenge crossover studies such as the Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3 (GAUSS-3)<sup>18</sup> and the ODYSSEY ALTERNATIVE<sup>19</sup> trials have been able to establish statin intolerance as a real and verifiable phenomenon.

**Anti-HMG-CoA reductase antibody-mediated myopathy causes widespread and profound muscle breakdown leading to permanent weakness**

TABLE 1

**Nonstatin lipid-lowering medications**

Medication	Mechanism of action	LDL-C reduction	Trials
Ezetimibe	Reduces absorption of cholesterol from small intestine	15%–25%	IMPROVE IT <sup>27</sup>
Bempedoic acid	Inhibition of adenosine triphosphate citrate lyase	15%–20% (alone) 25%–30% (with ezetimibe)	CLEAR Outcomes study (pending)
PCSK9 inhibitors	Inhibition of PCSK9 protein resulting in more LDL receptors available, and increased uptake of LDL-C into cells	45%–60%	FOURIER, 2015 <sup>30</sup> ODYSSEY Outcomes 2015 <sup>19</sup>

LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

The GAUSS-3 trial<sup>18</sup> used a double-cross-over design with atorvastatin and placebo in 491 patients who were self-reported to be intolerant to 2 or more statins. They found a 43% rate of true statin intolerance, determined by symptoms present during atorvastatin therapy but absent during placebo therapy. Although similar rates of myalgia were reported initially in both atorvastatin and placebo groups (hazard ratio [HR] 1.34; 95% CI 1.05–1.71;  $P = .02$ ), after full completion of the washout and double-crossover protocol, significantly more patients experienced muscle-related symptoms when taking atorvastatin than when taking placebo (HR 1.96; 95% CI 1.44–2.66;  $P < .001$ ).

### CONSEQUENCES OF STATIN INTOLERANCE

A diagnosis of statin intolerance comes with significant health and financial costs. Statin-intolerant patients who have their medication down-titrated or discontinued are at increased risk of future cardiovascular events.

A large retrospective cohort study found that patients who were statin-intolerant had a 36% higher rate of recurrent myocardial infarction than those adherent to statin therapy (HR 1.50; 95% CI 1.30–1.73;  $P < .001$ ) and a 43% higher rate of coronary heart disease events (HR 1.51; 95% CI 1.34–1.70;  $P < .001$ ).<sup>20</sup> Another study found significantly higher medical costs in patients with statin intolerance than in controls receiving statin therapy, with a cost ratio of 1.2 (95% CI 1.11–1.28;  $P < .0001$ ).<sup>21</sup>

### MANAGING STATIN INTOLERANCE

#### Confirm statin intolerance

In a patient suspected of having statin intolerance, statin therapy should be discontinued and symptoms monitored over 2 weeks to see if they resolve. Patients should be asked about alcohol intake and nutraceutical medications, as they potentially contribute to and confound muscle symptoms attributed to statins. After 2 weeks, if symptoms have resolved, the same statin can be restarted at a lower dose or an alternative statin prescribed.<sup>22</sup>

Strategies for treating statin intolerance include using an alternative statin, modifying dosage, changing diet, and using other medications.

#### Try another statin

Pharmacologic profiles can differ significantly among statins<sup>23–25</sup>:

- Lipophilic statins diffuse nonselectively into extrahepatic tissues such as muscle; simvastatin, the most lipophilic statin, is most associated with muscle symptoms
- Hydrophilic statins are actively transported into hepatocytes; examples are pravastatin and rosuvastatin, which are less associated with muscle symptoms.

Changing from a lipophilic to a hydrophilic statin is a reasonable first-line alternative drug strategy for patients experiencing myalgia.

#### Adjust dosage

Intermittent rather than daily dosing can also be considered for patients with statin-associated muscle symptoms and for patients who

**Many patients diagnosed with statin-associated muscle symptoms likely have nonspecific musculoskeletal pain, unrelated to statins**

TABLE 2

PCSK9 inhibitor trials

Trial <sup>a</sup>	PCSK9 inhibitor	Definition of statin intolerance	Statin rechallenge	LDL-C reduction with PCSK9 inhibitor	LDL-C reduction with ezetimibe <sup>a</sup>	Patients with muscle events during trial
GAUSS-2, 2014 <sup>32</sup>	Evolocumab	Intolerable muscle-related side effects to ≥ 2 statins; most participants unable to tolerate ≥ 3 statins	No	56.1% (140 mg every 2 weeks)	19.2%	12% (evolocumab)
				55.3% (420 mg per month)		23% (ezetimibe)
GAUSS-3, 2016 <sup>18</sup>	Evolocumab	Intolerance to atorvastatin 10 mg and another statin at any dose; or 3 or more statins, with 1 at the lowest daily dose and 2 others at any dose	Yes	52.8% (420 mg per month)	16.7%	20.7% (evolocumab) 28.8% (ezetimibe) HR 0.68; 95% CI 0.39-1.19
ODYSSEY ALTERNATIVE, 2015 <sup>19</sup>	Alirocumab	Inability to tolerate 2 or more statins because of unexplained skeletal muscle-related symptoms with one of the 2 statins at the lowest-approved daily starting dose.	Yes	45.0% (75 mg every 2 weeks)	14.6%	32.5% (alirocumab) 41.1% (ezetimibe) HR 0.71; 95% CI 0.47 to 1.06

<sup>a</sup>All trials used ezetimibe 10 mg daily as the nonstatin comparator.

CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

have a history of severe myotoxicities and marked creatine kinase elevation.

Studies have found that intermittent dosing can achieve LDL-C reductions of about 20% to 40%, although impacts on cardiovascular outcomes have yet to be established. A large single-center study of statin intolerant patients found a trend toward mortality benefit with intermittent dosing.<sup>26</sup> A statin with a long half-life, such as rosuvastatin, may be a good choice for intermittent dosing.

■ NONSTATIN DRUG THERAPY

For patients with persistent symptoms even after trials of two different statins at their lowest dosages, categorical intolerance is likely, and nonstatin medications should be considered. These include ezetimibe, bempedoic acid, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The actions of these agents are summarized in Table 1.<sup>18,19,27-32</sup>

PCSK9 inhibitor therapy

Monoclonal antibody PCSK9 inhibitors belong to a novel class of lipid-lowering therapy that have been reported to reduce LDL-C concentrations by up to 60%<sup>19,30-33</sup> and reduce the risk of cardiovascular events.<sup>34</sup> PCSK9 inhibitor therapy prevents downregulation and destruction of cell membrane LDL receptors, thereby leading to lower circulating LDL particle concentrations. Several studies have evaluated the efficacy of PCSK9 inhibitors in patients with statin-associated muscle symptoms (Table 2).<sup>18,19,32</sup>

The GAUSS-2 trial<sup>32</sup> randomized more than 300 patients who experienced statin-associated muscle symptoms and discontinued two different statin medications to either evolocumab (a PCSK9 inhibitor), ezetimibe, or placebo. After 12 weeks of therapy, evolocumab was associated with the largest average reduction in LDL-C from baseline val-

ues (56.1%; 95% CI -59.7% to -52.5%;  $P < .001$ ). None of the patients in the evolocumab group discontinued medication due to muscle-related events.

The GAUSS-3 trial<sup>18</sup> randomized confirmed statin-intolerant subjects to evolocumab or ezetimibe for 24 weeks. Evolocumab produced a more significant mean reduction in LDL-C of 52.8% from baseline values (95% CI -55.8% to -49.8%;  $P < .001$ ). Discontinuation of therapy due to muscle-related symptoms occurred in 6.8% of the ezetimibe group vs 0.7% of the evolocumab group.

The ODYSSEY ALTERNATIVE trial<sup>19</sup> compared PCSK9 inhibitor therapy (using alirocumab) with ezetimibe in patients with confirmed statin intolerance. While ezetimibe reduced mean LDL-C by 14.6%, alirocumab reduced mean LDL-C levels by 45.0%. Muscle-related symptoms occurred less frequently with alirocumab (32.5%) than with ezetimibe (41.1%), but the difference was not statistically significant (HR 0.71; 95% CI 0.47–1.06;  $P < .096$ ).

Their findings establish PCSK9 inhibitor therapy as a promising alternative LDL-C lowering strategy in patients with proven statin intolerance. It may ultimately prove superior to statin dosage reduction, dietary modification, and pharmaceutical alternatives.

### Bempedoic acid

In 2020, the FDA approved bempedoic acid for treatment of hypercholesterolemia. It works by inhibiting adenosine triphosphate citrate lyase (ACL), an enzyme critical to the hepatic synthesis of cholesterol.

In the Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Tranquility phase 3 randomized placebo-controlled trial<sup>29</sup> of patients with a history of statin intolerance, bempedoic acid together with ezetimibe led to LDL-C reduction of 28.5% more than ezetimibe alone ( $P < .001$ ), while bempedoic acid led to significant reductions in nonhigh-density lipoprotein cholesterol (23.6%), total cholesterol (18%), apolipoprotein B (19.3%), and C-reactive protein (31%) ( $P < .001$ ).

The ongoing CLEAR Outcomes study is randomizing more than 14,000 patients who are statin-intolerant and at high risk for cardiovascular disease to treatment with bempedoic acid

vs placebo.<sup>35</sup> Results are expected in 2023 to address the effects on cardiovascular outcomes.

### PROMISING NEW AGENTS

While PCSK9 inhibitor therapies and bempedoic acid will likely find their way into routine prescription use in the coming years, ongoing investigations continue to demonstrate promise in other advanced lipid-lowering approaches.

Inclisiran, currently under FDA review, is a small interfering RNA (siRNA) agent that inhibits translation of the PCSK9 protein and therefore its formation. This promotes LDL-C receptor recycling from cell membranes at a stage upstream from the PCSK9 inhibitor therapies. Trials of patients with elevated LDL-C levels despite maximally tolerated statin therapy found that adding inclisiran reduced LDL-C levels by about 50% compared with baseline levels of patients on statin therapy only.<sup>36,37</sup> Inclisiran is administered by subcutaneous injection, followed by a second dose after 90 days, then every 6 months thereafter.

Evinacumab is a monoclonal antibody that blocks angiopoietin-like 3 (ANGPTL3), a protein that inhibits lipoprotein lipase and thereby increases plasma LDL-C levels. Gene mutations resulting in loss of function of this protein are associated with hypolipidemia. A phase 3 clinical trial with 65 patients with homozygous familial hypercholesterolemia found that evinacumab infusion every 4 weeks reduced LDL-C by 49 percentage points vs the placebo group at 24 weeks, with both groups also on maximum lipid-lowering therapy.<sup>38</sup>

Finally, recent evidence from nonhuman primates shows promise in the field of gene editing, a form of next-generation alteration of the biological blueprint that underlies serum lipoprotein concentrations. Gene therapy to mimic natural cardioprotective variants (such as targeted reduction in PCSK9 and ANGPTL3 protein production) have shown reduction in serum cholesterol levels.<sup>39</sup>

### NUTRACEUTICALS

Nutraceuticals are natural food-derived substances that are generally well tolerated and provide health benefits, including the preven-

**A diagnosis of statin intolerance comes with significant health and financial costs**

tion or treatment of medical conditions. Two of the most widely studied in cardiovascular medicine are red yeast rice (which contains monacolin K, the active ingredient of lovastatin) and berberine. Other plant sterols, soluble fibers, probiotics, polyunsaturated fatty acids, and antioxidants have also been evaluated.<sup>40,41</sup> Lipid-lowering effects occur via multiple mechanisms (eg, inhibition of the intestinal absorption of cholesterol, inhibition of cholesterol synthesis, and enhanced excretion of LDL-C).<sup>42</sup>

Nutraceuticals have been found to lower LDL-C when used alone or combined with ezetimibe<sup>43</sup> or a reduced statin dosage<sup>41,42</sup> and can help patients with statin intolerance

achieve their LDL-C goal. Red yeast rice was found to reduce LDL-C by up to 27% compared with placebo after 1 to 3 months.<sup>44</sup>

However, LDL-C reductions are modest compared with pharmacologic therapy, and the long-term effect on cardiovascular outcomes with nutraceutical therapy has not been formally evaluated. Therefore, nutraceuticals should be reserved only for patients who are truly statin-intolerant as an adjunct to non-statin pharmacologic therapy. ■

### DISCLOSURES

Dr. Cho has disclosed doing research for Amgen, Novartis, Esperion, and AstraZeneca, and consulting for Amgen, Esperion, and AstraZeneca. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

### REFERENCES

1. **World Health Organization.** The World Health report 2002—reducing risks, promoting healthy life. <https://www.who.int/whr/2002/en/>. Accessed June 8, 2021.
2. **Stone NJ, Robinson JG, Lichtenstein AH, et al.** 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63(25 Pt B):2889–2934. doi:10.1016/j.jacc.2013.11.002
3. **Baigent C, Keech A, Kearney PM, et al.** Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; 366(9493):1267–1278. doi:10.1016/S0140-6736(05)67394-1
4. **Stroes ES, Thompson PD, Corsini A, et al.** Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015; 36(17):1012–1022. doi:10.1093/eurheartj/ehv043
5. **Riaz H, Khan AR, Khan MS, et al.** Meta-analysis of placebo-controlled randomized controlled trials on the prevalence of statin intolerance. *Am J Cardiol* 2017; 120(5):774–781. doi:10.1016/j.amjcard.2017.05.046
6. **Wood FA, Howard JP, Finegold JA, et al.** N-of-1 trial of a statin, placebo, or no treatment to assess side effects. *N Engl J Med* 2020; 383(22):2182–2184. doi:10.1056/NEJMc2031173
7. **Kashani A, Phillips CO, Foody JM, et al.** Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; 114(25):2788–2797. doi:10.1161/CIRCULATIONAHA.106.624890
8. **Davidson MH, Clark JA, Glass LM, Kanumalla A.** Statin safety: an appraisal from the adverse event reporting system. *Am J Cardiol* 2006; 97(8A):32C–43C. doi:10.1016/j.amjcard.2005.12.008
9. **Nichols GA, Koro CE.** Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. *Clin Ther* 2007; 29(8):1761–1770. doi:10.1016/j.clinthera.2007.08.022
10. **Shepherd J, Blauw GJ, Murphy MB, et al.** Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360(9346):1623–1630. doi:10.1016/S0140-6736(02)11600-x
11. **Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group.** Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004; 363(9411):757–767. doi:10.1016/S0140-6736(04)15690-0
12. **Amarenco P, Bogousslavsky J, Callahan A 3rd, et al.** High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; 355(6):549–559. doi:10.1056/NEJMoa061894
13. **Amarenco P, Labreuche J.** Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol* 2009; 8(5):453–463. doi:10.1016/S1474-4422(09)70058-4
14. **McKenney JM, Davidson MH, Jacobson TA, Guyton JR; National Lipid Association Statin Safety Assessment Task Force.** Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006; 97(8A):89C–94C. doi:10.1016/j.amjcard.2006.02.030
15. **Charles EC, Olson KL, Sandhoff BG, McClure DL, Merenich JA.** Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am J Med* 2005; 118(6):618–624. doi:10.1016/j.amjmed.2005.02.008
16. **Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel.** An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol* 2014; 8(3 Suppl):S58–S71. doi:10.1016/j.jacl.2014.03.004
17. **Rosenson RS, Miller K, Bayliss M, et al.** The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): revision for clinical use, content validation, and inter-rater reliability. *Cardiovasc Drugs Ther* 2017; 31(2):179–186. doi:10.1007/s10557-017-6723-4
18. **Nissen SE, Stroes E, Dent-Acosta RE, et al.** Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA* 2016; 315(15):1580–1590. doi:10.1001/jama.2016.3608
19. **Moriarty PM, Thompson PD, Cannon CP, et al.** Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol* 2015; 9(6):758–769. doi:10.1016/j.jacl.2015.08.006
20. **Serban MC, Colantonio LD, Manthripragada AD, et al.** Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. *J Am Coll Cardiol* 2017; 69(11):1386–1395. doi:10.1016/j.jacc.2016.12.036
21. **Graham JH, Sanchez RJ, Saseen JJ, Mallya UG, Panaccio MP, Evans MA.** Clinical and economic consequences of statin intolerance in the United States: results from an integrated health system. *J Clin Lipidol* 2017; 11(1):70–79.e1. doi:10.1016/j.jacl.2016.10.003
22. **Banach M, Rizzo M, Toth PP, et al.** Statin intolerance—an attempt at a unified definition. Position paper from an international lipid expert panel. *Arch Med Sci* 2015; 11(1):1–23. doi:10.5114/aoms.2015.49807
23. **Schachter M.** Chemical, pharmacokinetic and pharmacodynamic

- properties of statins: an update. *Fundam Clin Pharmacol* 2005; 19(1):117–125. doi:10.1111/j.1472-8206.2004.00299.x
24. **Knauer MJ, Urquhart BL, Meyer zu Schwabedissen HE, et al.** Human skeletal muscle drug transporters determine local exposure and toxicity of statins. *Circ Res* 2010; 106(2):297–306. doi:10.1161/CIRCRESAHA.109.203596
  25. **Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B.** Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005; 19(6):403–414. doi:10.1007/s10557-005-5686-z
  26. **Mampuya WM, Frid D, Rocco M, et al.** Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. *Am Heart J* 2013; 166(3):597–603. doi:10.1016/j.ahj.2013.06.004
  27. **Cannon CP, Blazing MA, Giugliano RP, et al.** Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; 372(25):2387–2397. doi:10.1056/NEJMoa1410489
  28. **Laufs U, Banach M, Mancini GBJ, et al.** Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. *J Am Heart Assoc* 2019; 8(7):e011662. doi:10.1161/JAHA.118.011662
  29. **Ballantyne CM, Banach M, Mancini GBJ, et al.** Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis* 2018; 277:195–203. doi:10.1016/j.atherosclerosis.2018.06.002
  30. **Sabatine MS, Giugliano RP, Wiviott SD, et al.** Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372(16):1500–1509. doi:10.1056/NEJMoa1500858
  31. **Robinson JG, Farnier M, Krempf M, et al.** Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372(16):1489–1499. doi:10.1056/NEJMoa1501031
  32. **Stroes E, Colquhoun D, Sullivan D, et al; GAUSS-2 Investigators.** Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014; 63(23):2541–2548. doi:10.1016/j.jacc.2014.03.019
  33. **Schwartz GG, Steg PG, Szarek M, et al.** Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018; 379(22):2097–2107. doi:10.1056/NEJMoa1801174
  34. **Sabatine MS, Giugliano RP, Keech AC, et al.** Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; 376(18):1713–1722. doi:10.1056/NEJMoa1615664
  35. **US National Institutes of Health.** *ClinicalTrials.gov*. Evaluation of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant treated with bempedoic acid (ETC-1002) or placebo (CLEAR outcomes). <https://clinicaltrials.gov/ct2/show/NCT02993406>. Accessed June 1, 2021.
  36. **Ray KK, Landmesser U, Leiter LA, et al.** Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. *N Engl J Med* 2017; 376(15):1430–1440. doi: 10.1056/NEJMoa1615758
  37. **Ray KK, Wright RS, Kallend D, et al; for the ORION-10 and ORION-11 Investigators.** Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020; 382(16):1507–1519. doi:10.1056/NEJMoa1912387
  38. **Raal FJ, Rosenson RS, Reeskamp LF, et al; for the ELIPSE HoFH Investigators.** Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med* 2020; 383(8):711–720. doi:10.1056/NEJMoa2004215
  39. **Verve Therapeutics presents new data in non-human primates validating gene editing as a treatment approach for coronary heart disease at the ISSCR 2020 virtual annual meeting.** *Businesswire*. June 27, 2020. <https://www.businesswire.com/news/home/20200627005005/en/Verve-Therapeutics-Presents-New-Data-in-Non-Human-Primates-Validating-Gene-Editing-as-a-Treatment-Approach-for-Coronary-Heart-Disease-at-the-ISSCR-2020-Virtual-Annual-Meeting>. Accessed June 8, 2021.
  40. **Gylling H, Miettinen TA.** LDL cholesterol lowering by bile acid malabsorption during inhibited synthesis and absorption of cholesterol in hypercholesterolemic coronary subjects. *Nutr Metab Cardiovasc Dis* 2002; 12(1):19–23. pmid:12125225
  41. **Banach M, Patti AM, Giglio RV, et al; on behalf of the International Lipid Expert Panel (ILEP).** The role of nutraceuticals in statin intolerant patients. *J Am Coll Cardiol* 2018; 72(1):96–118. doi: 10.1016/j.jacc.2018.04.040
  42. **Cicero AFG, Colletti A, Bajraktari G, et al.** Lipid lowering nutraceuticals in clinical practice: position paper from an International lipid expert panel. *Arch Med Sci* 2017; 13(5):965–1005. doi:10.5114/aoms.2017.69326
  43. **Cicero AFG, Morbini M, Bove M, et al.** Additional therapy for cholesterol lowering in ezetimibe-treated, statin-intolerant patients in clinical practice: results from an internal audit of a university lipid clinic. *Curr Med Res Opin* 2016; 32(10):1633–1638. doi:10.1080/03007995.2016.1190326
  44. **Moriarty PM, Roth EM, Karns A, et al.** Effects of Xuezhikang in patients with dyslipidemia: a multicenter, randomized, placebo-controlled study. *J Clin Lipidol* 2014; 8(6):568–575. doi:10.1016/j.jacl.2014.09.002

**Address:** Leslie S. Cho, MD, Department of Cardiovascular Medicine, Heart, Vascular, and Thoracic Institute, J11, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; chol@ccf.org