(eg, >400 or >1,000) should still be interpreted as indicative of extensive atherosclerosis and prompt aggressive preventive therapies.

When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy. If there is persistent hypertriglyceridemia (fasting triglycerides ≥150 mg/dL), clinicians should refer to the 2021 ACC ECDP on management of hypertriglyceridemia for further evaluation and management.

5.6. Adults With Possible Statin-Associated Side Effects (Figure 7)

A systematic approach to evaluation of SASEs is critically important to encourage adherence to evidence-based statin treatment. The most-encountered SASE in clinical practice is statin-associated muscle symptoms, which may occur in 5% to 20% of patients.[7,92] For patients with SASEs who meet evidence-based guideline criteria for statin therapy, avoiding complete discontinuation of statin treatment is strongly recommended. In the SAMSON (Self-Assessment Method for Statin Side-effects Or Nocebo) trial of patients who discontinued a statin due to SASEs, 90% of the adverse symptom effects experienced with drug therapy can be attributed to what is seen with a blinded placebo. These results suggest that the act of taking a pill may be triggering the anticipated side-effect (the "nocebo" effect). Clinicians should strive to find the highest tolerated statin dose that is as close to the guideline recommendation as possible and work with patients to help understand the nature and severity of symptoms.

Although statin-associated muscle symptoms may occur while on statin therapy, true complete statin intolerance is uncommon.[93,94] A careful history can help to determine whether symptoms are consistent with statin-related effects, which tend to be symmetric myalgias or weakness in large proximal muscle groups. Other causes of muscle symptoms must be ruled out (eg, hypothyroidism, vitamin D deficiency, recent exercise) and drug-drug interactions that can increase systemic statin exposure must be considered. Some patients, such as women, individuals of Asian descent, and the elderly, may be at increased risk for statin-associated muscle symptoms. However, these patients may be able to tolerate a lower statin intensity, an alternative statin, or alternative dosing strategies.

The approach to SASEs should include discontinuation of statin therapy until resolution of symptoms and subsequent rechallenge to verify recurrence of muscle-related symptoms.[93] Although there is no universally accepted definition of statin intolerance, most experts recommend that patients are documented to have unacceptable muscle-related symptoms that resolve with discontinuation of therapy and recur with rechallenge on at least 2 (and preferably 3) statins, preferably ones that are metabolized by different pathways and have different lipophilicity/hydrophilicity, and one of which is prescribed at the lowest approved dose. The predominantly hydrophilic statins are rosuvastatin and pravastatin, whereas the lipophilic statins include simvastatin, fluvastatin, pitavastatin, lovastatin, and atorvastatin. Although not studied in RCTs nor FDA approved, alternative statin regimens may include alternate-day dosing with a long half-life statin (atorvastatin or rosuvastatin), de-escalation dosing (reducing 40-mg daily dosing to alternating between a 40- and a 20-mg statin every other day), or a lower daily dose (from 40 mg daily to 20 mg daily). The majority of patients who experience SASEs are able to tolerate statin rechallenge with an alternative statin or dose reduction with the same statin.

Nonstatin therapies are not considered to be an alternative to evidence-based statin therapy unless SASEs have been systematically and rigorously evaluated and documented. In patients with clinical ASCVD and possible SASEs who have failed at least 2 (and preferably 3) statins, including a trial of 1 attempt at the lowest approved dose or using alternative statin dosing, or who still have not achieved adequate reduction in LDL-C or non-HDL-C on maximally tolerated statin therapy, a trial of ezetimibe or a PCSK9 mAb may be considered as first-line nonstatin therapy (see Figure 7), depending on the patient's clinical scenario. Second-line therapy options that may be considered are bempedoic acid and inclisiran. Inclisiran may be considered in patients with poor adherence to PCSK9 mAbs, patients with adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with or without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. If a patient with ASCVD or baseline LDL-C ≥190 mg/dL has not achieved adequate lowering of LDL-C on maximally tolerated statin therapy with or without ezetimibe, and the patient is considered for prescription of inclisiran, referral should be made to a lipid specialist.

In patients with LDL-C ≥190 mg/dL, with or without clinical ASCVD, who have failed at least 2 (and preferably 3) statins, including a trial of 1 attempt at the lowest approved daily dose or using alternative statin dosing, or who still have not achieved adequate reduction in LDL-C or non-HDL-C on maximally tolerated statin therapy, a trial of either ezetimibe or a PCSK9 mAb may be considered as first-line nonstatin therapy (see Figure 7). Second-