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EAS Consensus Panel Focuses on Muscle Symptoms Associated with Statin

Therapy: How to Manage

- **Recommendations for management in patients at high risk of heart attack and stroke who report muscle symptoms on statin**
- **State of the art insights into possible mechanism(s) contributing to statin-associated muscle symptoms**

While statins are effective in reducing heart attack and stroke, many patients do not take statins as recommended or stop treatment because of side effects, in particular muscle symptoms such as muscle pain, weakness or aching. This has important repercussions for the effectiveness of statins in reducing the patient's risk of heart attack and stroke. The European Atherosclerosis Society (EAS) focused on this important unmet clinical issue in this latest EAS Consensus Panel Position Statement.

According to lead author, Professor Erik S. Stroes, Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands *'While we have made tremendous progress in cardiovascular disease prevention using statin therapy, we have failed to pay attention to the persistently high risk in patients who do not take their statin therapy because of muscle symptoms. This EAS Consensus Panel statement provides important clinical guidance for diagnosis and management, which will help clinicians to optimise cardiovascular risk in those patients with statin-associated muscle symptoms.'*

Statin-associated muscle symptoms: a common unmet clinical need

Lack of adherence with statin treatment can markedly alter the patient's cardiovascular risk. For example, in one study in older patients with heart disease, the risk of an event was 15% higher, and risk of death nearly 50% higher, in patients with poor compared with good adherence.¹

Among the range of side effects reported to statins, muscle symptoms are most common.

While controlled trials report similar rates of muscle symptoms (often reported as myalgia) with statin or placebo, in the real-life clinical setting, reporting of muscle symptoms is invariably higher, ranging from 7-29% of patients.²⁻⁷ Information on the true rate of statin-

associated muscle symptoms from the Effects of Statins on Muscle Performance (STOMP) study, which specifically investigated this issue, showed that 9.4% of statin-treated versus 4.6% of control subjects developed myalgia.⁸ Even though this represents a small increase in reporting, given that statins are so widely prescribed, a large number of patients will undoubtedly be affected.

Who is at risk?

Typically, patients reporting statin-associated muscle symptoms are older (>75 years), female, with a low body mass index, and more often of Asian descent. A history of increased creatine kinase (CK), the enzyme (protein) released from muscle cells, or unexplained muscle/joint/tendon pain, inflammatory or inherited metabolic, neuromuscular/muscle defects, or muscle symptoms on other lipid-lowering therapy, are among other contributing factors. Patients who are more physically active may be also at risk.

Treatment with high dose statin therapy, or with multiple drug treatments, especially those which interact with the metabolism and clearance of statins from the body, may also predispose to risk. Metabolism of some of the statins in patients may also be affected by consumption of grapefruit or cranberry juice.

What is new about this EAS Consensus Panel statement?

This EAS Consensus Panel Statement brings important new information to the definition, assessment and management of statin-associated muscle symptoms.

- **The Panel provides a clinical definition of statin-associated muscle symptoms.** The likelihood of muscle symptoms being due to a statin are based on the nature of the muscle symptoms and increase in CK, and their timing in relation to starting, stopping or re-starting statin treatment. The Panel makes the point that in most cases, statin-associated muscle symptoms are not accompanied by marked increases in CK.
- **The Panel recommends how best to diagnose statin-associated muscle symptoms.** Typical symptoms such as muscle pain, weakness and aches are usually symmetrical and affect muscles in the thighs, buttocks, calves and back muscles. While these tend to occur early after starting a statin, they can occur after many years of treatment, or when the statin dose is increased, other treatments are prescribed, or in physically active individuals.

The Panel recommends evaluating patients for risk factors which can predispose to statin-associated muscle symptoms, excluding secondary causes (e.g. conditions such as hypothyroidism, polymyalgia rheumatica, or increased physical activity), and considering other medication taken by the patient which may interact with statins.

In patients at high cardiovascular risk, withdrawal of statin therapy followed by one or more re-challenges (after a washout) with a statin may help in determining causality.

- **The Panel recommends how best to manage patients with statin-associated muscle symptoms.** In patients considered to be at low cardiovascular risk, therapeutic life style changes may be sufficient.

In high cardiovascular risk patients in whom a statin is indicated, a lower dose of a statin (either the same or an alternative), or dosing with a high intensity statin with a long-half-life (i.e. a statin that reduces low-density lipoprotein cholesterol levels by more than 50 percent, such as atorvastatin, rosuvastatin and pitavastatin) every other day or twice-weekly, is recommended. Non-statin lipid lowering medications are also recommended to improve cholesterol lowering, with ezetimibe the first choice, based on its safety profile and evidence of cardiovascular benefit in IMPROVE-IT.⁹

In terms of dietary approaches, the Panel recommends a low saturated fat diet and avoidance of trans fats. Viscous fibre (mainly psyllium, 10 g daily) and foods with added plant sterols or stanols, either alone or with pharmacotherapy, may be considered depending on the patient's cardiovascular risk.

The Panel emphasises that in patients with persistent CK elevation, clinicians may consider referral to a neuromuscular specialist for investigation of any underlying muscle problem. Importantly, in the rare event that the patient has severe muscular pain, general weakness and signs of myoglobin, a skeletal muscle protein, in the urine (causing 'tea-coloured' urine with a positive urine dipstick for blood), rhabdomyolysis should be suspected, and the statin should not be restarted. .

Do nutraceuticals have a role in managing patients with statin-associated muscle symptoms?

On the basis of current evidence, the Panel does not recommend the use of nutraceuticals such as red yeast rice, coenzyme Q10 (ubiquinone) and vitamin D supplementation for management of patients with statin-associated muscle symptoms.

What causes muscle-associated muscle symptoms?

Understanding of the mechanisms contributing to these symptoms is still far from conclusive. In their appraisal of the current evidence, the Panel suggests that it is likely that statins decrease the function of mitochondria (the major energy generator within cells), attenuate energy production, and alter muscle protein degradation, each of which may contribute to the onset of muscle symptoms. Statins may also trigger inflammatory myositis

or immune-mediated necrotising myopathy by mechanisms that as yet have not been described.

Is genetic testing for susceptibility to statin-associated muscle symptoms a viable option in the future?

While the Panel highlights evidence that some variants of genes coding for drug transporters in the liver and skeletal muscle that increase plasma statin levels are linked to muscle side effects, further investigation is needed. Current data do not support recommendations for genetic testing as part of the diagnostic work-up of patients with statin-associated muscle symptoms.

Dr Robert Cramb, Trustee of Heart UK, The Cholesterol Charity, comments:

'These are much needed objective guidance to help clinicians with the common problems of muscle symptoms in patients given statin therapy. While the data from clinical trials emphasise that maximum doses lead to greatest benefit, the pragmatic approach in this statement is to use doses of drug lower than those in the trials and in some cases intermittently means that patients can still benefit from statin therapy. Sensible dietary approaches including the use of plant stanols/sterols are considered and recommended in conjunction with appropriate pharmacotherapy.'

More information

The EAS Consensus Panel Position Statement on statin-associated muscle symptoms is available to download for free from: <http://www.ncbi.nlm.nih.gov/pubmed/25694464>

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Key sessions at EAS Glasgow:

- Symposium: Statin intolerance: an impactful and yet unresolved clinical challenge. Monday March 23: 13:00-14:30
- Symposium: Latest developments in difficult-to-treat patients with hypercholesterolaemia. Tuesday 24 March: 13:00-14:30
- EAS Updates: EAS Initiatives – from Science to Education. Tuesday 24 March, 15:00-16:30
- Advanced Clinical Seminar: Therapeutic challenges in statin intolerance & secondary dyslipidemia. Wednesday 25 March, 11:00-11:45.

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