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Special Article

Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016)

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ABSTRACT

The Canadian Consensus Working Group has updated its evaluation of the literature pertaining to statin intolerance and adverse effects. This overview introduces a pragmatic definition of statin intolerance (goal-inhibiting statin intolerance) that emphasizes the effects of symptoms on achieving nationally vetted goals in patients fulfilling indications for lipid-lowering therapy and cardiovascular risk reduction. The Canadian Consensus Working Group provides a structured framework for avoiding, evaluating and managing goal-inhibiting statin intolerance. Particularly difficult practice situations are reviewed, including management in young and elderly individuals, and in athletes and labourers. Finally, targeted at specialty practitioners, more detailed analyses of specific but more unusual adverse effects ascribed to statins are updated including evidence regarding new-onset diabetes, cognitive dysfunction, cataracts, and the rare but important immune-mediated necrotizing myopathy.

RÉSUMÉ

Le Canadian Consensus Working Group a mis à jour son évaluation de la littérature concernant l'intolérance et les effets indésirables des statines. Cet aperçu présente une définition pragmatique de l'intolérance aux statines (intolérance aux statines GISI) qui souligne les effets des symptômes sur l'atteinte des objectifs approuvés à l'échelon national chez les patients qui remplissent les indications de traitement hypolipidémiant et de réduction du risque cardiovasculaire. Le Canadian Consensus Working Group offre un cadre structuré pour éviter, évaluer et prendre en charge l'intolérance aux statines GISI. Nous passons en revue des situations particulièrement difficiles dans la pratique, dont la prise en charge des individus jeunes et âgés, des athlètes et des ouvriers. Finalement, destinées aux praticiens spécialistes, des analyses plus détaillées sur les effets secondaires particuliers, mais plus inhabituels attribués aux statines sont mises à jour, y compris les données probantes concernant le diabète de novo, le dysfonctionnement cognitif, les cataractes, et la rare, mais importante, myopathie nécrosante immunomédiée.

There continues to be much interest in the academic literature and in social media about side effects potentially associated with statin use. The Canadian Consensus Working Group (CCWG) for the diagnosis, prevention, and management of statin adverse effects and intolerance has published reviews in 2011 and 2013.[1,2] Key elements included an attempt to provide a working definition of statin intolerance, an overview of the literature about the most common management problems (mainly myalgia) (Table 1), implications for statin use when liver disease is present or suspected, and review of new-onset diabetes (NOD) during statin use. Finally, principles of management were put forward with a strong emphasis on systematic cessation and reinitiation of statins as not just an essential component of verifying intolerance but also a frequently successful way to identify a statin-based regimen that would ensure

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See page S56 for disclosure information.

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Table 1. Canadian Consensus Working Group terminology for myopathic syndromes and hyperCKemia

Term	Characteristics	
	Laboratory	Clinical
Myopathy	NA	General term referring to any disease of muscle
Symptomatic myopathy		
Myalgia	CK ≤ ULN	Muscle ache/weakness
Myositis	CK > ULN	Muscle ache/weakness (true myositis generally requires biopsy confirmation)
Rhabdomyolysis	CK > 10 times ULN (CK > 10,000 U/L)	Muscle ache/weakness; renal dysfunction might result from myoglobulinuria; need for hydration therapy
HyperCKemia		
Mild, grade 1	CK > ULN, ≤ 5 times ULN	Might/might not have myositis
Mild, grade 2	CK > 5 times ULN, ≤ 10 times ULN	Might/might not have myositis
Moderate	CK > 10 times ULN; ≤ 50 times ULN	Might/might not have rhabdomyolysis with/without renal dysfunction
Severe	CK > 50 times ULN	Might/might not have rhabdomyolysis with/without renal dysfunction

In patients with benign or idiopathic and chronic elevations of CK, symptom and severity descriptors should be referenced to the patient-specific baseline level of CK. Also, see Table 2 regarding normal CK levels according to sex and ethnicity.

CK, creatine kinase; NA, not applicable; ULN, upper limit of normal.
Modified from Mancini et al.[2] with permission from Elsevier.

long-term lipid management and cardiovascular (CV) risk reduction. Many other excellent overviews are available that are generally concordant with the conclusions and recommendations of the CCWG, and thus an international consensus is emerging with respect to this difficult issue that impairs chronic adherence to effective and safe therapy.[4-28] Importantly, the therapeutic context has changed in 3 fundamental ways. First, nonstatin agents have emerged that are efficacious in safely lowering levels of low-density lipoprotein (LDL) cholesterol (LDL-C) and reducing CV risk in conjunction with statins. Second, data continue to show that achievement of a sustained physiological state characterized by even lower LDL-C than currently recommended in many national guidelines might be associated with a further reduction of LDL-C-related residual risk of CV events without incurring any substantive augmentation of adverse side effects. Finally, expensive biologics are now available. Unlike currently available adjuncts to statins that generally do not achieve profound LDL-C-lowering, these agents provide lowering competitive in magnitude with the most effective statins and they have been tested specifically in patients who cannot be practically treated with statins or with sufficient doses of statins to achieve treatment goals. These 3 forces require careful reassessment of how to rationally identify and treat patients warranting lipid- and CV risk-lowering and to do so in a fashion that is fiscally responsible and pragmatic. Use of nonstatin adjuncts might achieve therapeutic goals, lower LDL-C-related CV risk, improve adherence, and improve quality of life. Thus, these forces are particularly germane in the statin-intolerant patient whose ostensible side effects reduce quality of life, deter adherence, and limit therapeutic benefit.

Accordingly, the purpose of this consensus statement is to update an approach that integrates the overlapping issues of establishing a diagnosis of statin intolerance with the therapeutic imperative to achieve optimal LDL-C and CV risk reduction and to accomplish both from a pragmatic perspective. We also review common challenging scenarios and, finally, provide an overview of particular relevance to the specialist charged with determining whether more unusual adverse effects are truly related to statins.

Principles of Management and Introduction of the Pragmatic Concept of "Goal-Inhibiting Statin Intolerance"

This section is based upon introduction of a pragmatic definition of statin intolerance (Table 3) and 6 key principles of management (Table 4). The goal-inhibiting statin intolerance (GISI) definition is broadly applicable to the diverse nature of complaints facing clinicians and is rigourous but nonjudgemental with respect to the exact origin, etiology, or mechanism that might explain the patient's problem. The rationale for this definition is developed further in this article and within the context of the principles of management of GISI, which requires answers to the key questions summarized in Table 4.

Table 2. Assessment of increased levels of CK in relation to ethnicity and sex

Ethnicity	Sex	Ethnicity- and sex-specific 97.5 percentile of CK	Relative reference value (97.5 percentile for white ethnicity and sex)	Relative ULN compared with white ethnicity	Mild, grade 1b "hyperCKemia" threshold relative to CK limits for white ethnicity
White	F	201	201	1.0 times	> 5.0 times ULN
	M	322	322	1.0 times	> 5.0 times ULN
South East Asian	F	313	201	1.6 times	> 8.0 times ULN
	M	641	322	2.0 times	> 10.0 times ULN
Black	F	414	201	2.0 times	> 10.0 times ULN
	M	801	322	2.5 times	> 12.5 times ULN

CK, creatine kinase; F, female; M, male; ULN, upper limit of normal.
Data from Brewster et al.[3]