

Review

An Evidence-Based Guide to Cholesterol-Lowering Guidelines

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Since 2014, guidelines for the management of lipid disorders to reduce cardiovascular (CV) events have been updated in the United States, the United Kingdom, Europe, and Canada. Some of these guidelines are almost entirely evidence-based whereas others are a mix of evidence and expert opinion. Guidelines differ on such simple questions as to whether blood samples should be fasting or non-fasting, and whether low-density lipoprotein cholesterol (LDL-C) or another lipid parameter should be the primary focus of treatment. Different risk assessment tools are recommended by different guidelines. Lifetime risk is highlighted in some guidelines, with the suggestion that earlier treatment will reduce lifetime risk in younger people even when short-term risk is low. Some guidelines have numerical treatment targets that differ according to level of risk, while others eschew targets but recommend statins at high or moderate intensity to reduce LDL-C by $\geq 50\%$ or 30%–50%, respectively. Statins are the backbone of therapy in all guidelines. Ezetimibe produced a 6.4% relative risk reduction in the only large clinical outcomes trial in which it was tested, and is recommended for high-risk patients with an

RÉSUMÉ

Depuis 2014, les États-Unis, le Royaume-Uni, l'Europe et le Canada ont procédé à l'actualisation des lignes directrices sur la prise en charge des anomalies lipidiques pour réduire les événements cardiovasculaires (CV). Certaines de ces lignes directrices sont presque entièrement fondées sur les données probantes, tandis que les autres constituent une combinaison de données probantes et d'opinions d'experts. Les lignes directrices diffèrent sur de simples questions quant à savoir si les échantillons de sang devraient être prélevés à jeun ou non à jeun, et si l'objectif principal du traitement devrait porter sur le cholestérol à lipoprotéines de faible densité (cholestérol LDL) ou sur un autre paramètre du bilan lipidique. Les diverses lignes directrices recommandent différents outils d'évaluation des risques. Certaines lignes directrices mettent en relief les risques à vie, et suggèrent qu'un traitement plus précoce les réduira chez les personnes plus jeunes même lorsque les risques à court terme sont faibles. Certaines lignes directrices ont des cibles numériques de traitement qui diffèrent selon le niveau de risque, tandis que d'autres évitent les cibles, mais recommandent un traitement par statines d'intensité élevée ou modérée pour réduire

It is the beginning of wisdom when you recognize that the best you can do is choose which rules you want to live by, and it's persistent and aggravated imbecility to pretend you can live without any.

—Wallace Stegner, *All the Little Live Things*

Guidelines: Quantity and Quality

A dictionary definition of guideline is a rule or instruction that shows or tells how something should be done. Synonyms include recommendation, instruction, direction, regulation,

rule, principle, standard, and criterion. Medical guidelines have proliferated over the past 2 decades; as an example, the National Guideline Clearinghouse of the Agency for Healthcare Research lists 417 different guidelines just for hypertension.¹

Medical guidelines have increasingly become evidence-based, and less dependent on expert opinion. Level of evidence is graded as A when on the basis of multiple randomized clinical trials or meta-analyses, B when on the basis of a single randomized trial or nonrandomized studies, and C when on the basis of a consensus of opinion of experts, small studies, retrospective studies, and/or registries.

In a survey of American College of Cardiology (ACC)/American Heart Association (AHA) guidelines from 1984 to 2008, it was noted that levels of evidence only began to be introduced in 1998.² From 1998 to 2008, of 16 guidelines that reported levels of evidence, comprising a total of 2711 recommendations, only 314 recommendations (11%) were supported

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inadequate response to statins, despite the high number needed to treat to prevent 1 CV event. Proprotein convertase subtilisin/kexin 9 inhibitors lack outcome data to support their use, but are approved for patients with familial hypercholesterolemia or clinical atherosclerotic CV disease who require additional LDL-C lowering beyond statins. All these new guidelines are aimed at improving the problem of undertreatment of high-risk groups, leading to better outcomes for these patients.

by level of evidence A. For acute coronary syndrome, heart failure, and secondary prevention, more than 20% of recommendations were supported by level of evidence A, compared with < 1% of recommendations for valvular heart disease.

In the United States, the Medicare Improvements for Patients and Providers Act of 2008 directed the Institute of Medicine to develop standards for clinical practice guidelines.³ The report, released in 2011, listed the following standards:

“Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.

To be trustworthy, guidelines should

- be based on a systematic review of the existing evidence;
- be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups;
- consider important patient subgroups and patient preferences, as appropriate;
- be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest;
- provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of the recommendations; and
- be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.”

The report emphasized the importance of transparency in the guideline development process, the need for standards or rules for conflict of interest, and the appropriate level of patient and public input into the guideline development process. The National Guideline Clearinghouse adopted stricter rules as a result of the Institute of Medicine report, and the number of clinical practice guidelines that were accepted in 2014-2015 decreased to 126 from an annual average of 616 over the previous 5 years.⁴

With the foregoing general comments as background, let us turn to examine several issues specific to cholesterol-lowering guidelines.

respectivement le cholestérol LDL de $\geq 50\%$ ou de 30% à 50% . Les statines sont le pilier de traitement de toutes les lignes directrices. L'ézétimibe entraînait une réduction du risque relatif de 6,4 % dans la seule grande étude sur les résultats cliniques au cours de laquelle il était testé, et est recommandé chez les patients exposés à un risque élevé qui ont une réponse inadéquate aux statines, en dépit du nombre élevé de sujets à traiter pour empêcher 1 événement CV. Les inhibiteurs de la proprotéine convertase subtilisine/kexine de type 9 manquent de données sur les résultats cliniques pour soutenir leur utilisation, mais sont approuvés chez les patients atteints d'une hypercholestérolémie familiale ou d'une maladie CV athérosclérotique clinique qui nécessitent un hypocholestérolémiant pour abaisser le cholestérol LDL en plus des statines. Toutes ces nouvelles lignes directrices visent l'amélioration du problème de l'insuffisance de traitement des groupes exposés à un risque élevé afin d'entraîner de meilleurs résultats cliniques chez ces patients.

Same Evidence, Different Conclusion

Because evidence-based guidelines are on the basis of the same body of evidence, why do they differ? In fact, should not all guidelines be almost identical because they are derived from the same evidence base? The following 2 examples show how different guideline committees can interpret the same evidence and arrive at opposite recommendations.

It is generally agreed that fasting and nonfasting blood samples yield similar measurements for high-density lipoprotein (HDL) cholesterol, and that nonfasting samples are slightly higher for total and LDL-C, and up to 25 mg/dL higher for triglycerides.⁵ The 2011 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommended that blood sampling should be performed after a 12-hour fast.⁶ The British National Clinical Guideline Center (National Institute for Health and Care and Excellence [NICE]) guidelines state that a fasting sample is not needed,⁷ and the ACC/AHA guidelines state that a fasting sample is preferred but not mandatory,⁸ whereas the new Canadian guidelines recommended a nonfasting lipid determination “as a suitable alternative” to fasting levels.⁹ The 2016 ESC/EAS guidelines agree that a nonfasting sample is acceptable for risk assessment, but recommend a fasting sample for follow-up of patients with severe hyperlipidemia or hypertriglyceridemia.¹⁰

LDL-C has traditionally been the primary measurement upon which treatment decisions are based, and is a strong, independent predictor of future cardiovascular (CV) events. However, it is now widely accepted that non-HDL cholesterol and apolipoprotein (apo) B are somewhat superior predictors of events.¹¹ Non-HDL cholesterol does not require an additional measurement as does apo B, and does not require a fasting sample. Have guideline writers recognized the superiority of non-HDL cholesterol? The NICE guidelines do recommend that non-HDL cholesterol be used during follow-up to assess treatment,⁷ but the ESC/EAS guidelines still recommend LDL-C and total cholesterol as the primary target of therapy,^{6,10} whereas the ACC/AHA guidelines recommend either LDL-C or non-HDL cholesterol,⁸ and the Canadian guidelines recommend LDL-C as the primary target, with non-HDL cholesterol and apo B as alternate targets.⁹

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