Evolution of lipid management guidelines

Evidence might set you free

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Abstract

Objective To understand how the new guidelines for management of cardiovascular risk by the American Heart Association and the American College of Cardiology (AHA-ACC) can be interpreted and used in a Canadian setting.

Sources of information The AHA-ACC guidelines were reviewed, along with all references. Independent PubMed searches were done to include the addition of other lipid-lowering therapy to statins and the use of medical calculators to enhance patient understanding.

Main message The new AHA-ACC guidelines are based on the best current evidence related to lipid management. This includes use of 10-year cardiovascular disease (CVD) risk as the treatment threshold in place of low-density lipoprotein cholesterol levels, as well as abandonment of low-density lipoprotein treatment targets. There is increased emphasis on dietary and exercise interventions, with the beginning of an effort to quantify the effect of these interventions. Statins are the main drug intervention, and the addition of other drugs to augment lipid lowering is no longer recommended. For application in Canada, Framingham risk tables are more appropriate for risk assessment than the pooled cohort equations used in the United States. Risk calculators for CVD risk should contain information on cardiovascular age and have the ability to represent risk and alternative interventions graphically in order to improve patient understanding and promote informed decision making.

Conclusion Focus on the best evidence in CVD risk can simplify lipid management for both the physician and the patient.

"I don't see much sense in that," said Rabbit.
"No," said Pooh humbly, "there isn't. But there was going to be when I began it. It's just that something happened to it along the way."

A.A. Milne, *Winnie-the-Pooh*

Until the release in November of 2013 of the long-awaited lipid guidelines by the American Heart Association and the American College of Cardiology (AHA-ACC),[1] lipid management was directed mainly at low-density lipoprotein (LDL) cholesterol levels. The Canadian Cardiovascular Society (CCS) guidelines,[2] last revised in 2012, had been among the most evidence-based of these protocols.[3] However, these and the previous directives had several features that lacked a sound evidence base, including use of LDL thresholds and targets for therapy,[4,5] use of multiple drugs to achieve these targets,[1,6] and use of high-sensitivity C-reactive protein (hsCRP) levels as a risk modifier.[7] The new AHA-ACC lipid guidelines[1] have acknowledged and addressed these problems.

EDITOR'S KEY POINTS

- The new lipid management guidelines by the American Heart Association and the American College of Cardiology abandon low-density lipoprotein levels as a target or threshold for treatment when considering statin therapy. A 10-year cardiovascular disease risk is used as an alternative treatment threshold.
- There is increased emphasis on diet and exercise interventions as the primary intervention in lipid management.
- Statins are the primary drug intervention for lipid reduction. No other drugs added to statins have been shown to improve clinical outcomes.
- Risk reduction alternatives are best presented to the patient in terms of cardiovascular age and graphic representation of the effects of proposed interventions on cardiovascular risk. The patient must be increasingly involved in the intervention decision.

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- Low-density lipoprotein targets for treatment have been removed.
- The 10-year cardiovascular disease (CVD) risk is used as a reference treatment threshold of LDL levels between 2.0 and 5.0 mmol/L. Low-density lipoprotein levels are referenced only as extremes of the primary prevention spectrum and are no longer used as thresholds for intervention.
- If drug treatment is indicated, the decision becomes whether to use a moderate- or high-dose statin. Lipid levels are part of global CVD risk assessment, but are otherwise not relevant to treatment type or intensity.
- Risk reduction using drugs involves statin therapy. No other drugs added to statins are believed to improve hard CVD end points.
- High-sensitivity C-reactive protein levels are not part of the treatment decision.

A summary comparing the AHA-ACC lipid management with the previous CCS approach appears in **Table 1**.[1,2,8,9]

Table 2[1] identifies the 4 treatment groups that are likely to benefit from statin therapy. The subset most likely to generate controversy is the group of patients without diabetes, who are between 40 and 75 years of age, and who have LDL levels between 2.0 and 5.0 mmol/L. Those with a 10-year CVD risk that is greater than or equal to 7.5% are advised to consider moderate- to high-intensity statin therapy depending on level of risk.

Table 3[8,10-15] provides suggestions on the practical application of the evolving guidelines.

Problems with the AHA-ACC approach

Using the new guidelines and applying CCS algorithms to populations without CVD or diabetes will result in a treatment recommendation for all women aged 71 to 75 years and all men aged 55 to 75 years on the basis of age alone and in the absence of any risk factors. According to the guideline authors,[16] 31.9% of adults aged 40 to 79 would be eligible for statin treatment using the old Adult Treatment Panel III algorithms, while 32.9% would receive a recommendation using the 10-year risk cutoff of 7.5% used in the new guidelines. While the evidence supports treatment down to very low levels of risk,[17] the absolute benefit of intervention can become very small indeed. Treatment of a population based on 10-year CVD risk leads to the following concerns.

Available calculators are dissimilar and produce variable results.[18] Some calculators consider only coronary artery disease, while most now include all cardiovascular events. Some calculators retain inputs for hsCRP and family history. Some of them treat diabetes by different algorithms. In Canada it might be best to use a Framingham-based tool evaluating all cardiovascular risk.[10] This is the algorithm used in the CCS guidelines and it has been validated in Canada.[8] The AHA-ACC guidelines use new pooled cohort equations designed to more appropriately evaluate risk for African Americans, and these equations are not likely to be validated in Canada. Calculator inputs for both formats are identical apart from racial origin.

Drug therapy in healthy people whose risk is perceived to be small can lead to clinical inertia—a failure to begin or augment therapy despite evidence for benefit.[19] This is not always a bad thing,[20] and it might even act as a safeguard against treatment that is recommended simply because a statistically significant, but small, reduction in end points exists.[21] While this reduction in risk might be of little importance to the individual patient and physician, it might have a strong effect on the population,[22] in that almost half of events actually occur in those evaluated as low risk.[23,24]

Treatment of a lower-risk population can be disruptive to the lives of otherwise healthy people who might qualify for treatment based on age alone. Most of those in this population will not benefit from treatment and their absolute CVD risk is low. Even more disruption exists for those with chronic illness and multiple comorbidities[25] who are already taking multiple medications and who already spend a large proportion of their time on illness-related tasks. In these people the benefits of treatment are clear, but patient priorities and additional risks of medication error and drug interaction must be considered.

Benefits of a risk-based approach

Intervention benefits are put into perspective. The AHA-ACC lipid and lifestyle guidelines attempt to give equal weight to lifestyle and drug interventions in CVD. Unfortunately the document referencing lifestyle considers only surrogate outcomes rather than hard CVD end points and does not include research after 2011. This is said to be related to insufficient resources,[15] but omission of current lifestyle data on hard end points blunts the effect of these important recommendations.

The guidelines do not address weight loss, as diet and exercise are the interventions that influence risk,[15] and weight loss is not always necessary to achieve CVD risk reduction.[26-29] It is actually possible, using recent information, to quantify the potential benefits of diet and exercise, and to present these interventions as alternatives to, or in addition to, statins for mitigation of CVD risk. **Table 4**[1,17,23,30-33] presents evidence on the effects of interventions on CVD or mortality.

The best evidence for dietary intervention in reduction of CVD events comes from a recent large randomized trial of the Mediterranean diet.[30] Adherence to this diet, along with extra supplements of nuts or

Table 1. The AHA-ACC statin guidelines compared with the CCS guidelines

RISK CATEGORY	AHA-ACC[1]	CCS[2]	RATIONALE	IMPLEMENTATION
LDL level used as threshold or target for treatment	• No treatment if LDL < 2.0 mmol/L • Look for FH or secondary cause if LDL > 5.0 mmol/L • LDL level not otherwise a target or threshold	• Treatment threshold of LDL > 3.5 mmol/L if intermediate risk • Treatment if LDL > 5.0 mmol/L • Treatment target LDL ≤ 2.0 mmol/L or reduced to ≤ 50%	Statin trials have been randomized to dose or potency, but never to thresholds or targets	• LDL is rarely a trigger for treatment and does not need to be followed as an end point for treatment • No LDL goals for therapy
Basis of 10-y global risk assessment	Pooled cohort equations	• FRS • Validated in Canada[8]	Appropriate weighting of risk for the black population	Pooled cohort equations used in place of FRS to calculate 10-y risk
10-y global CVD risk used as threshold for treatment	For those aged 40 to 75 y with no cardiovascular or metabolic disease, treatment threshold derived from pooled cohort equation is ≥ 7.5%	• FRS used to determine risk as low (< 10%), intermediate (≥ 10% to < 20%), or high (≥ 20%) • FRS ≥ 20% always treated	Pooled cohort equations are well validated in the United States, and intervention is effective down to risk levels as low as 5%	• Risk ≥ 7.5% used as threshold for intervention for those aged 40 to 75 y as primary prevention • Decision needed for high- or low-dose statin
Use of hsCRP levels to further refine treatment threshold	Not used	Treatment suggested if intermediate risk, LDL < 3.5 mmol/L, and hsCRP ≥ 2 mg/L in certain age groups	• No trials exist using the hsCRP variable as an independent risk modifier or in a dosing study • No better than FRS on meta-analysis9	Not part of risk assessment
Established CVD (secondary prevention)	All treated	All treated	Maximum intervention used in established disease	All patients with established CVD treated with high-intensity statins
LDL levels > 5.0 mmol/L	Treatment recommended; look for FH or secondary cause of high lipid levels	Treatment recommended; look for FH or secondary cause of high lipid levels	• Alternate treatment might help if a secondary cause is found • High lipid levels owing to FH might require consultation	Consider high-dose statins in this group
Diabetes	Those with type 2 diabetes aged 40 to 75 y with risk factors present or with 10-y risk ≥ 7.5% should receive high-intensity statin therapy; they should receive moderate-dose statins if no risk factors are present	Patients with diabetes aged > 40 y, or with > 15-y duration of diabetes, or with microvascular disease should be treated as high risk	Patients with diabetes evaluated by 10-y risk as usual, but become high-risk equivalent if risk factors are present	Treat those aged 40 to 75 y with high-dose statins if risk factors are present; treat with moderate-dose statins if no risk factors are present
Chronic kidney disease	Treat according to 10-y risk status with exception of dialysis patients	Treat as high-risk equivalent with exception of dialysis patients	Not addressed as a separate group	Treat according to 10-y risk unless undergoing dialysis
Non-HDL or Apo B levels as alternate targets	No recommendation	Specific goals for non-HDL cholesterol and Apo B levels	No randomized trials exist to show benefit for lipid level or particle number goals	No lipid level or particle number goals for therapy
Alternative drugs to statins	None	Drugs added to achieve target LDL levels	No evidence for benefit of other drugs added to statins	Statins are the only recommended lipid-lowering agents

ACC—American College of Cardiology, AHA—American Heart Association, Apo B—apolipoprotein B, CCS—Canadian Cardiovascular Society, CVD—cardiovascular disease, FH—familial hypercholesterolemia, FRS—Framingham risk score, HDL—high-density lipoprotein, hsCRP—high-sensitivity C-reactive protein, LDL—low-density lipoprotein.

Table 2. Treatment groups likely to benefit from statin therapy

TREATMENT GROUP	RECOMMENDATIONS
Secondary prevention for those aged ≤ 75 y with CVD	High-dose statin therapy or maximally tolerated statin dose
Primary prevention for those aged ≥ 21 y with LDL cholesterol > 5.0 mmol/L	High-dose statin therapy or maximally tolerated statin dose Look for secondary cause or family history
Primary prevention for patients with diabetes aged 40 to 75 y with LDL cholesterol levels between 2.0 and 5.0 mmol/L	If no risk factors are present, use moderate-intensity statins If risk factors are present or 10-y CVD risk is ≥ 7.5%, use high-intensity statins or maximally tolerated statin dose
Primary prevention for those aged 40 to 75 y with no CVD or diabetes who have LDL cholesterol levels between 2.0 and 5.0 mmol/L	With 10-y CVD risk of ≥ 7.5%, moderate- or high-intensity statin depending on level of risk

CVD—cardiovascular disease, LDL—low-density lipoprotein.
Data from Stone et al.[1]

Table 3. Practical application of evolving guidelines in primary prevention

RECOMMENDATION	DISCUSSION
Install a desktop calculator having characteristics congruent with your practice	CCS algorithms using FRS might be most appropriate for Canada[8,10] Quantification of dietary, exercise, and statin interventions are helpful Tool should include the following: • real-time display of changes in risk factors and interventions that are turned on and off; • graphics capability to display effects of risk factor changes on CVD risk; • ability to generate cardiovascular age, which might improve patients' understanding11,12; and • decision support option for age thresholds, diabetes, and family history
Use 10-y CVD risk as threshold for treatment in place of LDL level	LDL levels are referenced only as extremes of the primary prevention spectrum and are no longer used as thresholds for intervention
Abandon treatment goals	In place of treatment goals ... • maximize change in dietary pattern with patient input; • maximize exercise interventions with patient input; • optimize exercise and assess myalgia before statin introduction; • use statin therapy according to degree of FRS; and • consider dispensing with LDL follow-up unless you think it will motivate the patient. This concept might have to be introduced gradually
Use statin dosing according to level of FRS and patient tolerance	If intolerant, remember that a low-dose statin can give two-thirds of maximal lipid lowering[13] High-risk patients require high-intensity dosing or maximally tolerated dosing Myalgia might respond to changes in dosing, timing, statin type, or dosing intensity[14]
Abandon hsCRP measurement as part of risk assessment	No longer part of treatment decision
Treat all patients with diabetes aged 40 to 75 y according to recommendations	Treat with moderate-intensity statin if no risk factors are present Treat with high-intensity statin if risk factors are present or the 10-y CVD risk is ≥ 7.5%
Treat all adults with LDL ≥ 5.0 mmol/L according to recommendations	Consider a secondary cause or familial hyperlipidemia Consider consultation
Make the patient part of the intervention decision	A lifestyle commitment can modify risk and reduce need for drug use[15] Patients' understanding of absolute risk reduction using statins might influence treatment threshold A 10-y CVD risk treatment threshold of 7.5% is always negotiable

CCS—Canadian Cardiovascular Society, CVD—cardiovascular disease, FRS—Framingham risk score, hsCRP—high-sensitivity C-reactive protein, LDL—low-density lipoprotein.

Table 4. Effect of interventions on CVD or mortality

INTERVENTION	CVD RISK REDUCTION, %	STUDY INTERVALS, Y	TYPE OF EVIDENCE
Mediterranean diet	30	4.5	1 large RCT[30]
Moderate-intensity exercise	15	4-32	Multiple large prospective cohorts[31-33]
High-intensity exercise	30	4-32	Multiple large prospective cohorts[31-33]
Moderate-dose statin	30	Up to 10	Multiple RCTs[1,17]
High-dose statin	45	2-10	Multiple RCTs[1,23]

CVD—cardiovascular disease, RCT—randomized controlled trial.

Table 5. Dose therapy capable of relative CVD risk reduction rates: *Statin drugs used in randomized controlled trials.*

DRUGS	DOSE INTENSITY	RELATIVE CVD RISK REDUCTION, %
Atorvastatin, 10-20 mg		
Rosuvastatin, 5-10 mg		
Simvastatin, 20-40 mg		
Pravastatin, 40-80 mg		
Lovastatin, 40 mg		
Fluvastatin, 40 mg	Moderate	30
Atorvastatin, 40-80 mg		
Rosuvastatin, 20-40 mg	High	45

CVD—cardiovascular disease.
Data from Stone et al.[1]

olive oil, resulted in a relative reduction in events of 30% over 4.5 years as compared with a cohort following a low-fat diet. This result was obtained without calorie restriction or change in level of physical activity. Rather than specific nutrient or calorie restriction, the new guidelines actually recommend conversion to a pattern of eating, as seen in the DASH [Dietary Approaches to Stop Hypertension] or AHA dietary plans.[30] Although the evidence for benefit in surrogate outcomes for the latter approaches is very strong, there is thus far no evidence for the hard CVD outcome benefits seen for the Mediterranean dietary pattern.

Although the evidence for benefit of exercise is based, at best, on prospective cohort data, the results are consistent, are coherent with overall science, and display a reliable dose response[34] in the prevention of hard cardiovascular end points. Three meta-analyses[31-33] have indicated a relative benefit of approximately 15% for moderate and 30% for more vigorous exercise over an average follow-up of 13 years. A large prospective cohort of more than 400 000 people followed for 8 years showed a mortality benefit for as little as 15 minutes of moderate-intensity activity daily.[35] On the other end of the spectrum, there is substantial evidence that, in runners, activity levels exceeding current recommendations (150 minutes of moderate exercise weekly) can continue to further reduce probability of CVD events at distances up to 80 km per week.[34] The association of exercise with benefit is a compelling one, but causation will never be proven in a randomized controlled trial owing to unavoidable issues with selection bias, blinding, and crossover.

Statin therapy is now the only recommended drug intervention. Moderate-dose therapy is capable of a 30% relative reduction in 10-year event rates, and high-intensity dosing can increase this to 45%. Doses of drugs evaluated in randomized controlled trials are listed in **Table 5.**[1]

Because it is now possible to quantify alternatives to statin therapy, it is also possible to present a comparison of interventions to patients in terms of graphic representations, percentages of risk reduction, or numbers needed to treat. A computerized tool that is capable of continuously showing changes as events (ie, risk factors or interventions) are turned on and off can be helpful in shared decision making.

Drug side effects and interactions are reduced. There is no longer any recommendation for lipid-lowering drugs to be used in addition to statins. Myalgia and myopathy related to combination with fibrates and niacin[36] are thus avoided. Statin dosage and type can be changed without the confusion of having to question whether other lipid-lowering drugs are contributing to symptoms. Myalgia might respond to switching to a hydrophilic statin, longer intervals between dosing, or changing from a high-dose, low-potency drug to a moderate-dose, high-potency drug.[14] Statin myalgia might adversely affect the ability to exercise,[37,38] so an exercise intervention should be optimized before instituting a drug intervention.

The patient is involved in informed decision making. The AHA-ACC guidelines have put increased emphasis on participation of an informed patient in intervention decisions. While physicians might use odds ratios or numbers needed to treat as useful decision points, patients might be more comfortable with graphic representation[39] or calculation of "cardiovascular age," which can be derived from CCS algorithms.[11,12] This approach might help to temper the effect of a move to lower drug treatment thresholds, particularly if lifestyle options are initially presented as alternatives to drug therapy, and the effect of these options is quantified in some way. Calculators with the ability to follow incremental changes with introduction and elimination of both risk factors and interventions can be helpful. Examples of such calculators can be found at **www.palmedpage.com/calculators.html** and **http://bestsciencemedicine.com/chd/calc2.html**.

Conclusion

Graphic representations that display the quantification of the effects that lifestyle alternatives have on CVD risk can improve patients' understanding and promote informed decision making. As has been the case with smoking, repeated reference to and reinforcement of these alternatives might eventually affect the causative factors of CVD. When drug therapy must be added, the choice has become much simpler. Simplified understanding of evidence and interventions might be liberating for both the patient and the physician.

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Competing interests
None declared

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