Approach to identifying and managing atherogenic dyslipidemia

A metabolic consequence of obesity and diabetes

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Abstract

Objective To review the evidence for recognition and management of atherogenic dyslipidemia.

Sources of information High-quality randomized trials and meta-analyses were available to address most questions. North American and European guidelines were reviewed. Of these, the Canadian Cardiovascular Society lipid guidelines were most congruent with current literature.

Main message Atherogenic dyslipidemia is characterized by low levels of high-density lipoprotein (HDL), high levels of triglycerides, and a high low-density lipoprotein (LDL) particle number. The condition is highly associated with cardiovascular disease (CVD) and is poorly reflected in Framingham risk score and LDL measurements. Obesity, glucose intolerance, diabetes, and metabolic syndrome are rapidly becoming more common, and are often associated with atherogenic dyslipidemia, affecting long-term CVD risk. Recognition in the office is best achieved by non-HDL or total cholesterol–HDL ratio testing. Treatment success lies in optimizing diet and exercise. Of available medications, statins produce the most benefit and can be titrated to patient tolerance rather than to LDL target levels, which have a poor evidence base. The addition of fenofibrate can be considered in patients with high triglyceride and low HDL levels who have responded poorly to or have not tolerated statins.

Conclusion Growing obesity prevalence creates a CVD risk that might be missed by LDL cholesterol testing alone. Simple calculations from results of a non-fasting lipid panel produce non-HDL levels and total cholesterol–HDL ratio, both of which are superior for predicting risk in all patients. These metrics should be available in lipid panels.

EDITOR'S KEY POINTS

- Cardiovascular mortality rates have fallen almost 40% in the past several decades; however, the increasing prevalence of obesity, leading to atherogenic dyslipidemia, has begun to offset these improvements.
- In adults, half of cardiovascular events occur in patients with no conventional risk factors. Conventional short-term measures of risk are influenced overwhelmingly by fixed factors such as age and sex, and so are less predictive of events particularly in young people and in women. Patient risk can be further clarified by considering the emerging concept of the long-term risk of developing cardiovascular events.
- Ways of evaluating atherogenic dyslipidemia leading to long-term risk include modifying conventional risk scores in the context of metabolic syndrome (by a multiple of 1.5 for men and 2.0 for women); using the total cholesterol–high-density lipoprotein (HDL) ratio for calculation of treatment thresholds and targets; calculating non-HDL cholesterol from lipid panel results, and determining treatment thresholds by adding 0.8 mmol/L to levels given for low-density lipoprotein; or measuring apolipoprotein B levels if the patient has multiple emerging risk factors or low HDL or high triglyceride levels.

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The end of the human race will be that it will eventually die of civilization.
Ralph Waldo Emerson

Case description

J.E. is a 55-year-old businessman seen for follow-up of mild hypertension. He is not physically active and he admits to eating "too much." He does not abuse alcohol. He has no new complaints. His body mass index is 27 kg/m^2, and his waist circumference is now 100 cm. His blood pressure is 130/85 mm Hg while taking 25 mg of hydrochlorothiazide daily. He is a non-smoker and has no family history of heart disease. His mother died at age 71 and was overweight and had diabetes. Laboratory findings were as follows: fasting blood glucose, 5.5 mmol/L; total cholesterol (TC), 5.19 mmol/L; low-density lipoprotein (LDL) level, 3.17 mmol/L, high-density lipoprotein (HDL) level, 0.75 mmol/L; triglyceride (TG) level, 2.54 mmol/L. What would your cardiovascular disease (CVD) risk assessment and treatment recommendations be?

Many of our patients are obese and have diabetes or glucose intolerance, and it is becoming apparent that the proportion of the population with these conditions is increasing. Management of their unique risk profiles is of increased importance to family physicians. This metabolic profile consists of borderline-high LDL levels, small LDL particles, high TG levels, and low HDL levels, characterizing atherogenic or mixed dyslipidemia.[1] Evaluation of such patients is poorly served by current treatment thresholds and targets that reference LDL cholesterol alone.[2-4] These patients are at increased cardiometabolic risk, and can be identified by unique physical and laboratory parameters. Changes in management can further reduce CVD events.[5]

Cardiovascular mortality rates have fallen almost 40% in the past several decades,[6,7] with half of this reduction being the result of known risk factor modification based on targeting LDL levels.[8] Hidden in these data, however, is a trend toward a marked slowing in the rate of decline in cardiovascular events and mortality documented in the United States,[9] the United Kingdom,[10] and Australia.[11] This trend might reflect the steady increase in obesity since the 1970s in developed countries, with resulting parallel increases in diabetes and metabolic syndrome.[12] Overweight and obese individuals now represent 66% of the population in the United States, with Canada somewhat lower at 52%.[13] The prevalence of metabolic syndrome in adults is now 34.3% in the United States[14] and 19.1% in Canada.[15]

While obesity, metabolic syndrome, and diabetes can increase cardiometabolic risk through conventional risk factors, there are emerging risk factors being identified that could be playing an increasing role in residual and unrecognized CVD risk. Some of these factors are implicit in the definition of metabolic syndrome itself, which is a particularly potent predictor of risk in women.[16] A harmonized definition of metabolic syndrome is outlined in **Table 1**.[17] Additional emerging risk factors for CVD and death were identified in the INTERHEART study,[18] which compared more than 15 000 patients following myocardial infarction with matched controls. Conventional and emerging risk factors are summarized in **Table 2**.[6,7,17,18]

It has been recognized that conventional risk factors are less predictive of events in young people and in women.[18,19] Indeed, in adults, fully half of cardiovascular events occur in patients with no conventional risk factors.[20,21] Patient risk can be further clarified if we consider the emerging concept of the long-term risk of developing cardiovascular events. Conventional short-term risk scores, such as the Framingham score, are influenced overwhelmingly by fixed factors such as age and sex.[22] Over a lifetime, multiple borderline factors might interact. Among people with Framingham risk scores of 10 or less over 10 years, half to two-thirds are at high lifetime risk,[19,21] and many of these are women and young men. On the other hand, if a patient retains a low Framingham score at age 50, lifetime risk is likely to be low.[23-25] The defining features of metabolic syndrome might become particularly useful as relative indicators of lifetime risk,[6,7,26,27] as increasing obesity begins to offset the improvements in coronary artery disease mortality achieved in the past few decades.[21]

Sources of information

References provided with the existing lipid guidelines in North America and Europe[6,7,28,29] were initially reviewed. PubMed and the Cochrane database were searched using the key words *atherogenic* or *mixed* and *dyslipidemia,* restricted to English-language clinical trials, randomized controlled trials, and meta-analyses in humans. Articles referencing surrogate outcomes were excluded. References from appropriate retrieved articles were also reviewed. Good-quality evidence was available in the form of randomized trials and meta-analyses to inform most questions.

Table 1. Harmonized criteria for metabolic syndrome diagnosis: *3 of 5 positive measures are necessary for diagnosis.*

MEASURE	DIAGNOSTIC CUT POINTS	ALTERNATE INDICATIONS
Waist circumference	White Canadians, Americans, or Europeans: 94 cm (men), 80 cm (women) People from Asia, Africa, or the Middle East, or indigenous people from North and South America: 90 cm (men), 80 cm (women)	White patients (higher risk): 102 cm (men), 88 cm (women) Health Canada guideline
Triglycerides	≥ 1.7 mmol/L (150 mg/dL)	Drug treatment of high triglyceride levels
HDL-cholesterol	Men: <1.0 mmol/L (40 mg/dL) Women: <1.3 mmol/L (50 mg/dL)	Drug treatment of low HDL levels
Blood pressure	Systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg	Drug treatment of hypertension
Elevated fasting glucose	≥ 5.6 mmol/L (100 mg/dL)	Drug treatment of elevated glucose

HDL—high-density lipoprotein.
Data from Alberti et al.[17]

Table 2. Conventional and emerging cardiometabolic risk factors

RISK COMPONENT	FRAMINGHAM	METABOLIC SYNDROME	INTERHEART
Blood pressure	Hypertension and treatment	Hypertension or treatment	Hypertension
Insulin resistance	Diabetes	Elevated fasting glucose or treatment	Diabetes
Obesity	NA	Abdominal obesity	Abdominal obesity
Lipid levels	Total cholesterol Low HDL cholesterol	Low HDL cholesterol or treatment High triglycerides or treatment	Apo B–Apo A-I ratio
Behavioural factors	Smoking	NA	Smoking Low physical activity No daily vegetables and fruit No daily alcohol Psychosocial factors (eg, depression, work stress, financial stress)
Fixed factors	Age Sex Family history	NA	NA

Apo A-I—apolipoprotein A-I, Apo B—apolipoprotein B, HDL—high-density lipoprotein, NA—not applicable.
Data from Genest et al,[6] Anderson et al,[7] Alberti et al,[17] and Yusuf et al.[18]

Main message

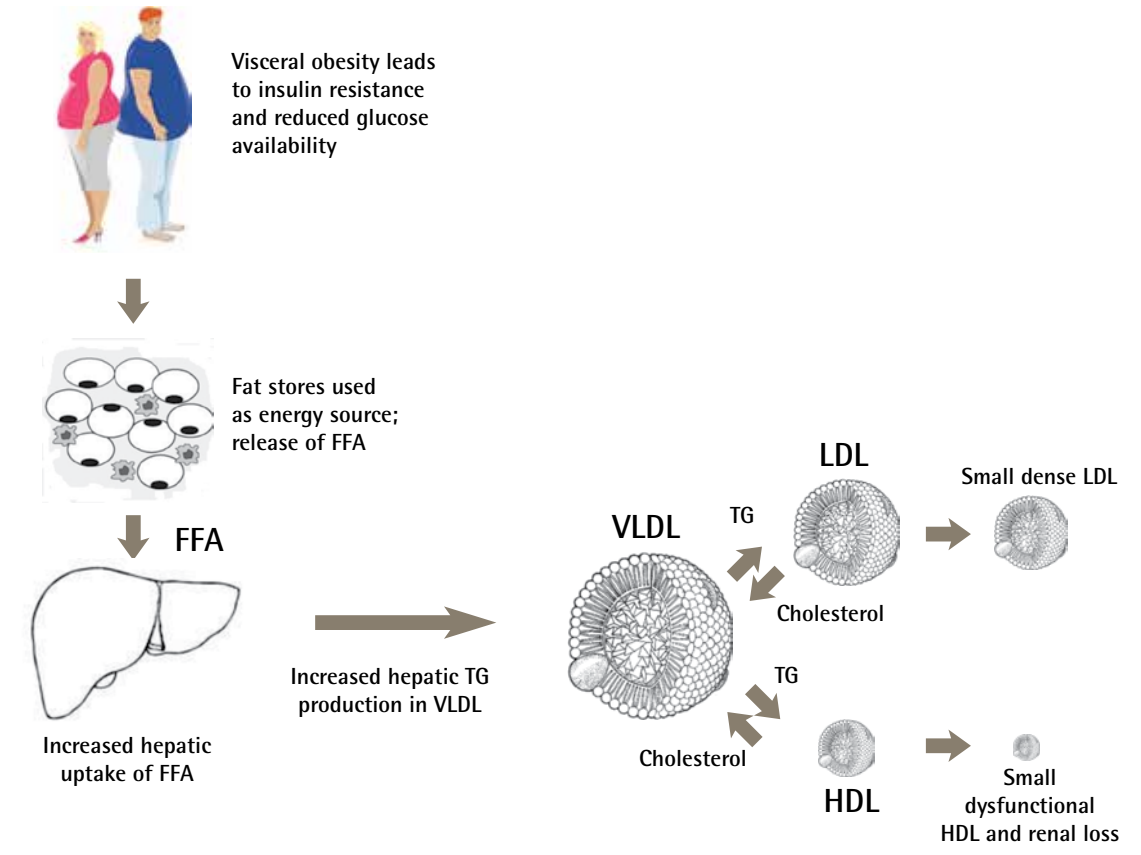
Physiology of atherogenic dyslipidemia. The lipid triad composed of elevated LDL, low HDL, and high TG levels is traditionally believed to lead to increased development of CVD. It is known, however, that as LDL levels trend lower, HDL and TG levels become relatively more predictive of CVD events.[2,4,30-32] In the presence of abdominal adiposity or diabetes, which usually accompany this lipid combination, glucose is not easily used because of insulin resistance.[33] Energy must then be obtained from fat stores, with release of free fatty acids, which prompts increased hepatic production of TGs enclosed within large, highly atherogenic, very low–density lipoprotein (VLDL) particles. The VLDL exchanges this TG for cholesterol with both LDL and HDL particles, and the TG in these smaller particles is then hydrolyzed, producing large numbers of even smaller, denser particles (**Figure 1**). Small, dense LDL particles contain less cholesterol (hence measured LDL is lower), but they easily penetrate the vascular endothelium, are easily oxidized, and are intensely atherogenic.[34-37] The low LDL level belies the importance of increased particle number, which is the parameter associated most strongly with vascular events.[31,38] Small HDL particles do not function well, leading to some loss of protective HDL function.[39-41] Because of small particle size, considerable HDL particles are lost via the kidney, resulting in reduced measured HDL levels.

The true marker of increased cardiometabolic risk then becomes the atherogenic dyslipidemia triad[42,43] of increased LDL particle number, low HDL level, and high TG level. Measured LDL might be low, however, leading to a missed appreciation of true risk. The LDL level simply reflects the amount of cholesterol in LDL particles, and it is not a reliable measure when these particles become small and more numerous, or when substantial cholesterol is carried in VLDL and remnant lipoproteins.[44]

Among the alternatives to LDL measurement are the TC/HDL ratio and non-HDL cholesterol, which reflect all cholesterol contained in particles containing apolipoprotein B (Apo B) (LDL, VLDL, intermediate-density lipoproteins, and remnant lipoproteins). The best available estimation of particle number is Apo B, as it is a constituent of all atherogenic particles.[37,44]

Office identification of atherogenic dyslipidemia. Low HDL and high TG levels suggest atherogenic dyslipidemia, and might indicate risk independent of LDL levels. Alternative estimations of atherogenic cholesterol or particle number can give more accurate information. Canadian guidelines endorse using the TC/HDL ratio or non-HDL cholesterol, which are cholesterol measurements, or Apo B, which is a measurement of particle number,[6,7] as alternatives to LDL measurement when TG levels are elevated. The US guidelines recommend non-HDL cholesterol (TC minus HDL).[28] European guidelines suggest that measurement of either Apo B or non-HDL is acceptable.[29] Measurement of Apo B, because it is actually a measure of particle number, is believed by many to be superior[31,37,38,44-48] and is supported by Canadian guidelines. However, the forthcoming and highly anticipated Adult Treatment Panel (ATP) IV guidelines might endorse calculation of non-HDL cholesterol.[3,45] The ongoing lack of harmonization among guidelines in North America and Europe might perpetuate confusion, possibly leading to poor uptake of any new recommendations.[49,50] In an effort to avoid this,

Figure 1. Physiology of visceral obesity and insulin resistance



FFA—free fatty acids, HDL—high-density lipoprotein, LDL—low-density lipoprotein, TG—triglyceride, VLDL—very low-density lipoprotein.

many authors argue that calculation of non-HDL is as sensitive as measurement of Apo B, with the advantages of requiring no additional tests, having well established treatment thresholds and goals, and being an adequate reflection of particle number.[3,51-53] All tests can be done without fasting, as, unlike with the LDL calculation, TG levels are not required (**Table 3**).[6,7,28,29]

For those who prefer to follow guideline treatment thresholds and targets (**Table 4**),[6,7,28,29] non-HDL measurement might be the preferred test. It can be readily calculated from results of a nonfasting lipid panel, and thresholds and goals are simply 0.8 mmol/L higher than LDL goals.[29] While it is only an indirect measure of particle number,[31] it does measure all of the cholesterol in particles containing Apo B. Non-HDL levels impart all the information contained in LDL measurement along with additional information on the presence of atherogenic dyslipidemia without the need to measure TG levels.[54]

Risk assignment and treatment thresholds. Conventional 10-year risk of CVD is calculated using the Framingham risk score. The Canadian Cardiovascular Society dyslipidemia guidelines[6,7] are the most evidence based,[55] and a calculator is now available for mobile devices.

A model relating the various risk factor characteristics in **Table 2**[6,7,17,18] to appropriate laboratory measurements is represented in **Figure 2**.[6,7,17,18] A desktop calculator for the Framingham score using Canadian guidelines and including optional support for this extended model is available online (**www.palmedpage.com/Framingham/Framingham%20Risk%20Calculator.htm**). This desktop tool will calculate non-HDL levels and TC/HDL ratio, estimate numbers needed to treat, and provide detection and decision support for atherogenic dyslipidemia.

In order to take into account the increased relative influence of emerging risk factors, 4 possible courses of action exist. Best evidence for each approach is evaluated in **Table 5**.[16,53,56-63]

1. Calculate the conventional risk score, and if metabolic syndrome is present increase this by a multiple of 1.5 for men and 2.0 for women. This multiple comes from a meta-analysis of prospective cohort studies[16] and

Table 3. Comparison of measurements for cardiometabolic risk

VARIABLE	LDL	NON-HDL OR TC/HDL RATIO	APO B
Measurement source	LDL cholesterol only	Cholesterol in all Apo B–based particles	Apo B lipoproteins
Composition	LDL cholesterol only	LDL, IDL, VLDL cholesterol	Number of Apo B particles of all sizes
Fasting	Yes; calculated using TG level	No	No
Availability	Lipid panel	Lipid panel	Separate laboratory order if available
Accurate at high TG levels	No	Yes	Yes
Canadian guidelines	Thresholds* and targets† well defined	Thresholds* and targets† defined for TC/HDL ratio; non-HDL levels can be calculated from recommended LDL targets	Thresholds* and targets† similar for medium and high risk
ATP III guidelines	Thresholds* and targets† well defined	Non-HDL only; secondary thresholds* and targets† derived from LDL targets	Not considered
European guidelines	No thresholds* defined; targets† well defined	Non-HDL only; secondary targets† derived from LDL targets	No thresholds* defined; different targets† for high and very high risk
Detects increased cardiometabolic risk of atherogenic dyslipidemia	Misleading when HDL levels are low and TG levels are high	Yes; this is the preferred measure in current office practice	Yes; probably the most accurate measure, but often unavailable

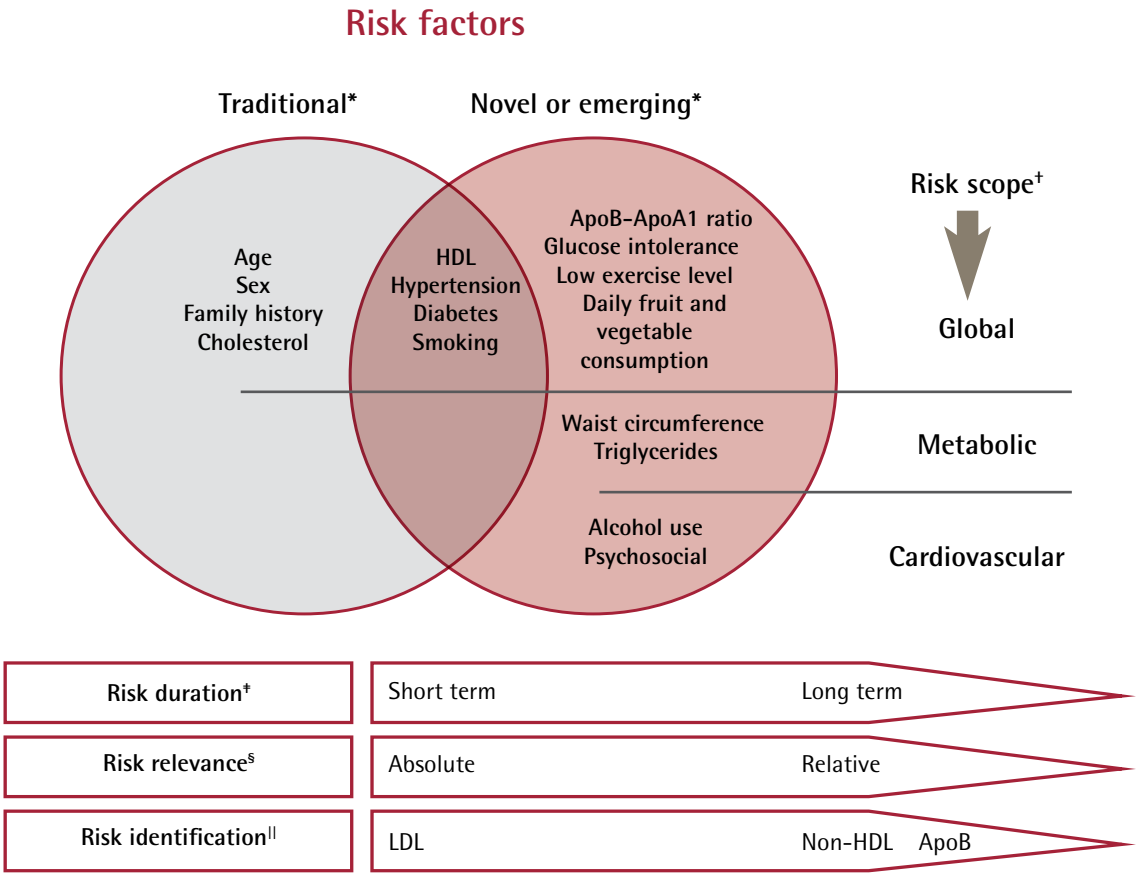
Apo B—apolipoprotein B, ATP—Adult Treatment Panel, HDL—high-density lipoprotein, IDL—intermediate-density lipoprotein, LDL—low-density lipoprotein, TC—total cholesterol, TG—triglyceride, VLDL—very low–density lipoprotein.
*Thresholds: Test levels at which drug treatment might be considered.
†Targets: Test levels used as goals of therapy.
Data from Genest et al,[6] Anderson et al,[7] Grundy et al,[28] and Reiner et al.[29]

Table 4. Guideline comparisons for treatment thresholds and targets

	THRESHOLD TO START TREATMENT		TREATMENT TARGET	
RISK LEVEL AND GUIDELINE	PRIMARY	ALTERNATE	PRIMARY	ALTERNATE
High				
• CCS	Treat all patients	Treat all patients	LDL: < 2.0 mmol/L or decrease by ≥ 50%	Non-HDL: < 2.8 mmol/L or decrease by ≥ 50% TC/HDL ratio: < 4.0 Apo B: < 0.80 g/L
• ATP III	LDL: ≥ 2.5 mmol/L; consider treating all	Non-HDL: ≥ 3.3 mmol/L; consider treating all	LDL: < 1.8-2.5 mmol/L	Non-HDL: < 2.6-3.3 mmol/L
• European*	Clinical judgment	NA	LDL: <1.8 mmol/L or decrease by ≥ 50%	Non-HDL: < 2.6 mmol/L or decrease by ≥ 50% Apo B: < 80 mg/dL
Moderate				
• CCS	LDL: > 3.5 mmol/L	Non-HDL: > 4.3 mmol/L TC/HDL ratio: > 5	LDL: <2.0 mmol/L or decrease by ≥ 50%	Non-HDL: < 2.8 mmol/L or decrease by ≥ 50% TC/HDL ratio: < 4.0 Apo B: < 0.80 g/L
• ATP III	LDL: > 2.5-3.4 mmol/L	Non-HDL: > 3.3-4.2 mmol/L	LDL: < 3.4 mmol/L	Non-HDL: < 4.2 mmol/L
• European*	Clinical judgment	NA	LDL: < 2.5 mmol/L	Non-HDL: < 3.3 mmol/L Apo B: < 100 mg/dL
Low				
• CCS	LDL: ≥ 5 mmol/L	Non-HDL: ≥ 5.8 mmol/L TC/HDL ratio: > 6	LDL: decrease by ≥ 50%	Non-HDL: Decrease by ≥ 50% TC/HDL ratio < 4.0
• ATP III	LDL: ≥ 4.0-5.0 mmol/L	Non-HDL: ≥ 4.8-5.8 mmol/L	LDL: < 4.0 mmol/L	Non-HDL: < 4.8 mmol/L
• European*	Clinical judgment	NA	LDL: < 3.0 mmol/L	Non-HDL: < 3.8 mmol/L

Apo B—apolipoprotein B, ATP—Adult Treatment Panel, CCS—Canadian Cardiovascular Society, HDL—high-density lipoprotein, IDL—intermediate-density lipoprotein, LDL—low-density lipoprotein, NA—not applicable, TC—total cholesterol, TG—triglyceride, VLDL—very low–density lipoprotein.
*European guidelines are based on a different risk scoring system.
Data from Genest et al,[6] Anderson et al,[7] Grundy et al,[28] and Reiner et al.[29]

Figure 2. Risk factor characterization



ApoA1—apolipoprotein A1, ApoB—apolipoprotein B, HDL—high-density lipoprotein, LDL—low-density lipoprotein.
*Risk type: Traditional risk factors are included in the Framingham risk calculation. Novel or emerging factors are components of the metabolic syndrome and factors identified in the INTERHEART study. There is some crossover of traditional and emerging factors.
†Risk scope: Global includes both metabolic and cardiovascular disease.
Scope is otherwise primarily metabolic or cardiovascular.
‡Risk duration: Short term is 10 years, as defined by Framingham score.
Long term or lifetime indicates emerging risk factors affecting risk of events over the entire lifespan.
§Risk relevance: Absolute is defined as a primary source of risk as defined in current guidelines.
Relative adds or subtracts an increment to primary risk.
||Risk identification: Usefulness of laboratory tests in the detection of lipid abnormalities resulting from contributing risk factors.
Data from Genest et al,[6] Alberti et al,[16] and Yusuf et al.[17]

its use is endorsed by the Canadian guidelines. The presence of metabolic syndrome will usually place the patient at high risk.

2. Use the TC/HDL ratio for calculation of treatment thresholds and targets in place of LDL values. This is supported by Canadian guidelines, and there is good support in the literature.[55,64-67]
3. Calculate non-HDL cholesterol from the lipid panel results, and decide on treatment thresholds by adding 0.8 mmol/L to levels given for LDL. This has good support in the literature and is likely to be recommended in the new ATP IV guidelines.
4. Order measurement of Apo B levels if the patient has multiple emerging risk factors or low HDL or high TG levels. A single treatment threshold and a single target are given in the Canadian guidelines for all levels of risk. Coverage of the cost of this test is inconsistent.

With the exception of option 1, these approaches require no fasting and are valid in place of LDL measurement for all patients at all risk levels. Simple calculation of non-HDL level and TC/HDL ratio could easily be done for all fasting and nonfasting lipid panels. It remains uncertain whether the ATP IV guidelines will move to use of non-HDL level as a standard.

Treatment decision. Once risk has been calculated and a treatment threshold has been generated, it is important to reach a shared, informed decision with

the patient. Understanding the numbers needed to treat might be helpful, especially as statins offer benefit at all levels of risk,[68] although benefits become vanishingly small when risk is low, especially when balanced against adverse effects and numbers needed to harm (**Table 6**).[69-80] While some high-risk patients with low LDL levels might become candidates for lipid-lowering therapy using this strategy, some patients might conversely avoid drug treatment despite higher LDL levels because of elevated HDL levels acquired through inheritance or exercise. The presence of a number of emerging risk factors, especially abdominal obesity and glucose intolerance, might add considerably to lifetime risk and should be considered as well.

Table 5. Comparing level and quality of best evidence for lipid markers in making treatment decisions

LIPID PARAMETER	GRADE*	INTERPRETATION	EVIDENCE TYPE
Metabolic syndrome	1C	Strong recommendation Low-quality evidence	Meta-analysis of prospective cohort studies[16]
TC/HDL ratio	1B	Strong recommendation Moderate-quality evidence	1 RCT[56] Meta-analysis of prospective observational studies; post hoc data analysis[57]
Non-HDL cholesterol	1B	Strong recommendation Moderate-quality evidence	Meta-analysis of RCT lipid-lowering drug studies; post hoc data analysis[58] Meta-analysis of RCT statin trials[53]
Apo B	1B	Strong recommendation Moderate-quality evidence	2 RCTs,[56,59] 1 RCT with subgroup analysis,[60] 1 RCT with post hoc analysis[61] Meta-analysis of observational studies[62]

Apo B—apolipoprotein B, HDL—high-density lipoprotein, RCT—randomized controlled trial, TC—total cholesterol.
*GRADE system for rating quality of evidence and strength of recommendations.[63]

Table 6. Adverse effects of statins in primary prevention

ADVERSE EFFECT	CLINICAL SIGNIFICANCE	NNH FOR WOMEN (MEN)*
Myopathy	Pain unrelated to CPK levels[69] Rhabdomyolysis is rare Rare autoimmune myopathy can occur[70]	39 (91) over 5 y*
Elevated transaminase levels	Hepatic damage or failure is extremely rare[71]	136 (142) over 5 y*
Withdrawal effects	Mortality and morbidity following ACS[72] or stroke[73] are increased if statins are discontinued at event onset	4 at 30 d for ACS[72] 4 at 3 mo for stroke[73]
Drug or food interactions	Levels increased with some drugs (eg, amiodarone, protease inhibitors, gemfibrozil) and with grapefruit juice	NA
Diabetes	Statins increase risk of diabetes in primary prevention trials[74] High-dose statins increase risk compared with moderate dosages[75]	255 in primary prevention trials at 4 y[74] 498 high dose vs moderate dose at 1 y[75]
Interference with exercise	Myalgia might interfere with ability to exercise[76,77] Symptomatic myopathy more common with changes in exercise intensity[78]	No data
Cognitive function	Dementia and postoperative delirium have been studied Conclusions are inconsistent	No consistent data
Renal disease	Small association with increased renal failure in a large prospective cohort study High-dose statins associated with increased acute renal injury vs low doses in patients with kidney disease[79]	434 (346) over 5 y* 1700 high dose vs low dose at 3 mo[79]

ACS—acute coronary syndrome, CPK—creatine phosphokinase, NA—not applicable, NNH—number needed to harm, NNT—number needed to treat.
*Data from Hippisley-Cox and Coupland[80]; NNTs for benefit over 5 y range from 24 to 64.

Aggressive statin therapy seems to have the strongest evidence for improvement of atherogenic dyslipidemia.[81] There has been evidence for some time from high-dose statin trials[20,82-86] and meta-analyses[83,87-91] that cholesterol lowering in patients with "normal" levels of LDL results in further CVD mortality reduction in both primary and secondary prevention. There also exists a residual 20% incidence of repeat cardiovascular events in patients who have had initial events, even though lipid levels and risk factors were thought to be controlled.[84] These findings imply that there is potential for further cardiovascular mortality improvement from statin therapy even when LDL levels are at goal levels according to current guidelines. Some of this benefit might be a result of the reduction of unrecognized risk from atherogenic dyslipidemia. There is ample evidence from large trials that patients with metabolic syndrome derive greater absolute benefit from use of statins,[92-96] perhaps in part because their initial risk of CVD events is higher.

An option for simplifying statin administration is to place less importance on targets. Statin trials have been randomized to treatment or to dose, but never to LDL targets.[87,97] Recognizing this, the main priority is to ensure that the patient is actually taking the drug,[55] as two-thirds of the benefit from statin use occurs with administration of the initial dose.[98] Once adequate compliance has been achieved, the dose can be gradually titrated to a level determined by patient tolerance[99] rather than to a treatment target.

Additions to statin therapy. Addition of a second drug to a statin might improve the lipid profile, but with one exception there is no good evidence that this improves hard outcomes. There is currently evidence supporting use of fenofibrate along with statins for reduction in cardiovascular events or mortality, but only in patients with low HDL and high TG levels.[100-103] Drug interaction with statins seems to be minimal for fenofibrate.[81,104,105] Recent combination studies with niacin, omega-3 fatty acids, ezetimibe, and cholesterol ester transfer protein inhibitors have either shown no benefit or were stopped early owing to futility (**Table 7**).[93,100,101,103,104,106-119] No combination trials have been done using resins.[119] Thus, the only evidence for reduced risk of death or CVD resulting from combination therapy with optimized statin treatment at present is for fenofibrate, and only in those with the specific mixed dyslipidemic profile.[102]

Intolerance to statin therapy. Statins confer such overwhelming benefit to high-risk patients that in patients who cannot tolerate statin therapy it is important to try changes in dosage levels and timing, and to consider alternate statins, before switching to alternative drugs. A 3-fold rise in liver enzymes can be tolerated, and in the event of high enzymes caused by hepatic steatosis, improvement can be expected with continued statin use.[120] In the absence of symptoms of myopathy, a rise of less than 10-fold in creatine kinase level can simply be followed.[69]

In the event of absolute intolerance to statins there is solid evidence from older studies of considerable benefit for both niacin and fibrates used alone. This benefit is seen for both CVD events and mortality in all patients meeting treatment criteria (**Table 7**).[93,100,101,103,104,106-119] Evidence for benefit of fish oils has come from older observational and cohort studies, but recent meta-analyses[115-117] have not been able to demonstrate improvement in outcomes. Similarly, the evidence for benefit with use of resins is weak.[119] Ezetimibe has not been studied as a single agent, nor has it been evaluated without a combined statin. All trials suggesting benefit have referenced lipid levels or other surrogate outcomes.[121] Cholesterol ester transfer protein inhibitor trials, despite remarkable elevations in HDL levels, have thus far shown no benefit in outcomes.[122]

Case revisited

J.E.'s Framingham risk score is 15.6% over 10 years according to the Canadian guideline calculator. His LDL level is 3.17 mmol/L, which is below the treatment threshold of greater than 3.5 mmol/L. He has abdominal obesity and low HDL and high TG levels, constituting metabolic syndrome and, therefore, has increased relative cardiometabolic risk. His calculated non-HDL cholesterol is 4.44 mmol/L (5.19 - 0.75 = 4.44 mmol/L). This is higher than the calculated treatment threshold for non-HDL (3.50 + 0.80 = 4.30 mmol/L). His TC/HDL ratio is 6.8, which exceeds the treatment threshold of 5 mmol/L. By either of these calculations, all cholesterol hiding in Apo B particles outside of LDL is accounted for, and treatment would be indicated even if LDL levels were normal. A decision could have been made without a fasting TG measurement.

The patient has consulted a dietitian and has begun a program under the supervision of a certified exercise trainer for the past 2 weeks. His weight is unchanged, but his waist circumference is down to 98 cm. He is informed of his moderate 10-year risk together with the relative increased longer-term risk imparted by metabolic syndrome, which places him at high 10-year and long-term risk. He agrees to a statin trial and is able to tolerate 80 mg of atorvastatin daily.

One year after the intervention he is compliant with exercise recommendations, but less so with diet. Weight and blood pressure are unchanged, but waist circumference is down to 94 cm. Laboratory results are as follows: TC, 3.5 mmol/L; HDL, 0.95 mmol/L; non-HDL, 2.55 mmol/L; TC/HDL ratio, 3.6 (nonfasting). There has been no change in liver enzymes.

Table 7. Best evidence for drugs used alone or in combination with statins

DRUG STUDIES	EFFECT* USED ALONE	EFFECT* COMBINED WITH STATIN	STRENGTH OF EVIDENCE	CONCLUSION
Niacin				
• CDP[106]	3 g/d reduced mortality by 11% on 15-y follow-up; secondary prevention following MI	NA	Large RCT in men only; follow-up for 9 y after trial ended	Significant (P=.0004) mortality benefit only on extended follow-up; only trial not confounded by other drug treatment
• HATS[107]	NA	60%-90% reduction in events or mortality for combination of simvastatin and niacin	Small RCT; confounding of niacin effect by administration with statin	Mortality reduction exceeds that expected with statin alone; trial against statin alone needed
• AIM-HIGH[108]	NA	No benefit of addition of niacin in patients maximally treated with statins; secondary prevention	Large RCT using 1.5-2.0 g of niacin; trial stopped early for futility at 3 y	No evidence for effect of niacin on event or mortality reduction with statin combination
• Bruckert et al[109]	Benefit based on the CDP trial only	Benefit, with substantial heterogeneity; old trials had variable statin use	2009 meta-analysis; did not include AIM-HIGH, which has best evidence	Probable benefit used alone; evidence for combination therapy probably no longer valid
• Duggal et al[110]	Benefit based on the CDP trial only	Small reduction in events but not mortality based on infrequent use of statins in old trials	2010 meta-analysis; did not include AIM-HIGH, which has best evidence	Probable benefit used alone; evidence for combination therapy probably no longer valid
Fibrates				
• Helsinki Heart Study[111]	Gemfibrozil produced 34% reduction in events or mortality; 71% if TG levels elevated and HDL levels low; 78% if obese	NA	Large RCT of primary prevention; no confounding from use of other drugs; benefit found on post hoc analysis	Moderate evidence for gemfibrozil used alone; especially if obese, high TG levels, low HDL levels
• BIP[112]	Benzafibrate produced 39% reduction in events if TG levels were elevated, but no effect overall	NA	Large RCT of secondary prevention; TG effect found on post hoc analysis	Moderate evidence for benzafibrate used alone if TG levels elevated
• VA-HIT[113]	Gemfibrozil produced 24% reduction in events overall	NA	Large RCT of secondary prevention	Good evidence for gemfibrozil used alone
• FIELD[114]	Fenofibrate produced no difference overall but reduced events by 11% if metabolic syndrome present; adjusted for statins	Fenofibrate gave no added benefit when given with statins	Large RCT of patients with diabetes and secondary prevention; metabolic syndrome analysis was post hoc	Moderate evidence for fenofibrate used in metabolic syndrome
• ACCORD[103]	NA	Fenofibrate showed no benefit overall when given with statins; benefit shown in subgroup with high TG and low HDL	Large RCT of patients with diabetes in primary and secondary prevention	No evidence for benefit overall; good evidence for benefit if high TG levels and low HDL levels; no fenofibrate-statin interaction
• Bruckert et al[100]	Fibrates no benefit overall, but 30% event reduction if high TG and low HDL levels	Fibrates no benefit overall, but 30% event reduction if high TG and low HDL levels	2011 meta-analysis based on post hoc subgroup analysis	Fibrates beneficial with or without statins only with high TG and low HDL levels
• Lee et al[101]	Fibrates no benefit overall, but 30% event reduction if high TG and low HDL	Fibrates no benefit overall, but 30% event reduction if high TG and low HDL	2011 meta-analysis based on post hoc subgroup analysis	Fibrates beneficial with or without statins only if TG high and HDL low
Fish oil				
• Kwak et al[115]	No evidence for benefit	No evidence for benefit	2012 meta-analysis	Insufficient evidence; largest older studies are observational or open ended
• Delgado-Lista et al[116]	Reduction of cardiovascular events by 10%; no mortality reduction	More difficult to demonstrate benefit when used with statins	2012 meta-analysis	Moderate evidence when used alone; study dosages quite variable
• Rizos et al[117]	No evidence for benefit	No evidence for benefit	2012 meta-analysis	Insufficient evidence for benefit
Resins				
• LRC-CPPT[118]	19% reduction in events or mortality with cholestyramine	NA	Large RCT	Good evidence for benefit used alone; there are no studies in combination with statins
• CDP[106]	No evidence for benefit with cholestyramine	NA	Large RCT in men only; follow-up for 9 y after trial ended	No evidence for benefit used alone
• Bucher et al[119]	Benefit for mortality using resins of "borderline significance"	NA	1999 systematic review of RCTs with mortality data	Weak evidence for benefit used alone
Other				
• Ezetimibe: None	There have been no trials evaluating hard CVD outcomes or mortality; all trials to date involved either surrogate outcomes or a fixed combination with statin; IMPROVE-IT, due in 2014, will evaluate ezetimibe against a simvastatin combination			No reliable evidence of improvement in hard outcomes
• CETP inhibitors[93,104]	Torcetrapib trial was terminated early for harm; dalcetrapib trial terminated early for futility; these drugs may lead to production of "dysfunctional" HDL with changed, and perhaps harmful, properties; anacetrapib is the subject of ongoing trials			No evidence of improved outcomes despite remarkable increases in HDL

ACCORD—Action to Control Cardiovascular Risk in Diabetes, AIM-HIGH—Atherothrombosis Intervention in Metabolic Syndrome with Low HDL and High Triglycerides, BIP—Benzafibrate Infarction Prevention, CETP—cholesterol ester transfer protein, CDP—Coronary Drug Project, CVD—cardiovascular disease, FIELD—Fenofibrate Intervention and Event Lowering in Diabetes, HATS—HDL Atherosclerosis Treatment Study, HDL—high-density lipoprotein, IMPROVE-IT—Improved Reduction of Outcomes: Vytorin Efficacy International Trial, LRC-CPPT—Lipid Research Clinics Coronary Primary Prevention Trial, MI—myocardial infarction, NA—not applicable, RCT—randomized controlled trial, TG—triglyceride, VA-HIT—Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

*Evidence presented only for hard cardiovascular end points or mortality. Surrogate end points such as lipid changes or vascular imaging are not included.

These values meet treatment goals provided he can remain compliant with diet and exercise. He is encouraged to continue taking his statin and to follow up with the dietitian. He might consider dropping to a moderate 40-mg dose of statin if he can improve his dietary compliance.

Treatment recommendations are summarized in **Box 1**.[6,7,17,18,28,29,109,123]

Conclusion

Low-density lipoprotein levels have been beneficial in calculating Framingham risk, which is a short-term estimation, heavily influenced by age. Increasing incidence of obesity is accompanied by increasing glucose intolerance and metabolic syndrome leading to a more long-term cardiometabolic risk, which is poorly predicted by LDL levels. This resulting atherogenic dyslipidemia is characterized by novel risk factors, including the diagnostic features of metabolic syndrome, atherogenic diet, and lack of exercise. These factors combine over time to increase longer-term risk of CVD, and are particularly predictive in women and younger people. Non-HDL cholesterol level or TC/HDL ratio can be used in place of LDL measurement in establishing treatment thresholds and targets, are easily calculated from non-fasting serum, and should be routinely reported on lipid panels.

Atherogenic dyslipidemia, once identified, requires renewed attention to maladaptive dietary, exercise, and smoking habits, as changes in these habits will have a potent effect on risk reduction. Drug treatment involves optimization of compliance to a statin dosage based on drug tolerance, rather than lipid targets. Fenofibrate might provide further benefit if TG levels are high and HDL levels are low. Fibrates or niacin alone have shown benefit in the event of absolute intolerance to statins.

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Competing interests
None declared

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Box 1. Treatment recommendations

Consider the following treatment recommendations:

- Optimize behaviour change such as smoking cessation and moderate exercise for at least 150 min/wk. Dietary changes should aim to reduce caloric load, simple carbohydrates, and saturated fats with a goal of cardiometabolic fitness rather than weight loss. The Mediterranean diet has the best evidence for mortality reduction.[123]
- Consider testing with a nonfasting lipid panel for patient convenience. Calculate non-HDL, and if this is high, optionally obtain a fasting TG level. Non-HDL treatment thresholds and goals are valid for all patients. Dyslipidemic patients with normal LDL levels will then not be missed. High TG and low HDL levels suggest atherogenic dyslipidemia even at normal LDL levels.
- Canadian guidelines can be followed, substituting non-HDL for LDL treatment thresholds and targets. These are calculated by adding 0.8 to the LDL value (Table 4).[6,7,28,29]
- TC/HDL ratio can be used in place of non-HDL in this protocol with equal confidence[109] using Canadian guideline treatment thresholds and targets (Table 4).[6,7,28,29]
- In addition to treatment of traditional risk factors, consider treatment for patients with metabolic syndrome or those with multiple emerging risk factors (Table 2),[6,7,17,18] especially if these include high TG and low HDL levels. Their additional risk is usually reflected in the non-HDL calculation or TC/HDL ratio.
- Younger patients with multiple emerging risk factors might be at high lifetime risk despite low levels of non-HDL. Repeated emphasis on behaviour change is important, along with periodic follow-up of lipid profiles.
- Once a patient with atherogenic dyslipidemia is identified and behaviour is optimized, treat with a high-potency statin and work up to the maximally tolerated dose if the patient concurs. No treatment target is necessary. Alternatively, treatment to non-HDL or TC/HDL ratio targets is supported in guidelines, but not by evidence.
- If problems arise with tolerance or compliance, try to reach a consensus on a lower dose or a different statin.
- If statin dose is maximized, but non-HDL levels remain above the goal, consider adding fenofibrate.
- If the tolerated statin dose is low, consider adding fenofibrate.
- If no statin is tolerated there is good evidence for use of niacin or fibrates alone. There is no information on combination of the 2.
- Repeated reference to behaviour change is important in atherogenic dyslipidemia because risk can be substantially reduced with diet and activity modification, and present drug management outcomes are suboptimal.

HDL—high-density lipoprotein, LDL—low-density lipoprotein, TC—total cholesterol, TG—triglyceride.

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