The good and the bad: what researchers have learned about dietary cholesterol, lipid management and cardiovascular disease risk since the Harvard Egg Study

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SUMMARY

Background: The prevalence of cardiovascular diseases, while lower than it once was, remains a significant health consideration. Aims and Methods: To review the evolving evidence with respect to what role various factors play in the aetiology of coronary heart disease (CHD). Results: While total cholesterol and low-density lipoprotein cholesterol (LDL-C) were previously believed to play central roles, it has now become clear that neither in isolation is highly significant. For example, some people with very high LDL-C levels do not develop CHD, while others with very low LDL-C levels do. Furthermore, there is a difference between dietary cholesterol and serum cholesterol. Dietary cholesterol, which is found in animal-based foods, raises blood cholesterol in only approximately one-third of people. Conversely, intake of saturated fatty acids and trans fatty acids can result in dyslipidaemia. Furthermore, obesity - particularly abdominal obesity - and metabolic syndrome both are strong independent risk factors for development of cardiovascular disease. Conclusions: Statin therapy and a diet comprising a portfolio of plant sterols and viscous fibres can both significantly reduce LDL-C levels and C-reactive protein. The latter is a key marker of inflammation and of elevated risk for cardiovascular disease.

The role of cholesterol

In 2004, a standardised case–control study of acute myocardial infarction (MI) in 52 countries, comprising 15,152 cases and 14,820 controls, was published (4). It helped quantify the relative effects of various modifiable risk factors that were gender- and age-related in all regions of the world (Figure 1). This study demonstrated that many markers need to be examined in total to determine a patient’s risk, rather than one or two markers in isolation such as cholesterol or hypertension, and that having more than one risk factor can exponentially increase risk of having a heart attack (Figure 2).

Physicians continue to be taught that checking serum cholesterol, and initiating treatment if high, is the best course of action for reducing a patient’s coronary heart disease (CHD) risk. This is based on data from the Framingham Heart Study, which showed the presence of a linear relationship between serum cholesterol and CHD risk (5). However, as discussed by other authors in this supplement, new...
evidence shows that the situation is considerably more complex, with many factors at play. This also holds true for low-density lipoprotein cholesterol (LDL-C), elevated levels of which are a risk factor for atherosclerosis and CHD (6). Research has uncovered many different sub-types of LDL-C, some of which are more atherogenic than others, and which only contribute to CHD risk when present together with other factors (7). Moreover, LDL-C on its own is a poor marker of risk in individuals who have not had a CHD event. This was shown by a prospective examination of 2103 middle-aged men from Quebec. In this study, a reduced plasma high-density lipoprotein cholesterol (HDL-C) concentration had a greater impact than raised LDL-C on the atherogenic index (8). Indeed, some subjects with very high LDL-C levels did not develop CHD during the 5 years of follow-up, while others with very low LDL-C levels did. Thus, basing treatment and management solely on reducing LDL-C levels is of limited value.

Unfortunately, many physicians relate information pertaining to secondary prevention (i.e. preventing the reoccurrence of an event in a patient) to primary prevention (i.e. preventing the initial occurrence of an event in a patient) with regard to MI or other CHD event. For example, one widely believed notion is that reductions in LDL-C in primary-prevention patients through the use of statins drastically reduce the risk of a stroke or an MI. This is only true in individuals who previously experienced an event or who have several risk factors (9). The mechanisms regulating levels of LDL-C, HDL-C and overall cholesterol homeostasis are very complex – as are, in turn, those that lead to the development of heart disease. Clinicians must take the lead in emphasising fact over fiction, such as that there is a difference between dietary cholesterol and serum cholesterol and that dietary cholesterol, which is found in animal-based foods, raises blood cholesterol in only approximately one-third of people (10).

### Table 1 Cardiovascular risk factors (2,3)

<table>
<thead>
<tr>
<th>Non-modifiable risk factors</th>
<th>Modifiable risk factors</th>
<th>Emerging risk factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Cigarette smoking</td>
<td>Metabolic syndrome</td>
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<tr>
<td>Gender</td>
<td>Hypertension</td>
<td>Triglycerides</td>
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<tr>
<td>Heredity</td>
<td>Dyslipidaemia</td>
<td>Lipoprotein (a)</td>
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<td></td>
<td>Obesity</td>
<td>Lipoprotein-associated phospholipase A2</td>
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<td></td>
<td>Glucose intolerance</td>
<td>Remnant lipoproteins</td>
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<td></td>
<td>Diabetes</td>
<td>Small, dense LDL</td>
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<td></td>
<td>Left ventricular hypertrophy</td>
<td>Fibrinogen</td>
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<td></td>
<td>Stimulant drugs (e.g. cocaine)</td>
<td>Homocysteine</td>
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<td></td>
<td>Behavioural factors (stress)</td>
<td>Urine albumin/creatinine ratio</td>
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<tr>
<td></td>
<td>Poverty</td>
<td>High-sensitivity C-reactive protein</td>
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<td>Impaired fasting glucose</td>
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### Figure 1 Risk factors for acute myocardial infarction (4)

![Figure 1](image1.png)

### Figure 2 Metabolic syndrome independently increases risk for coronary heart disease (CHD) and type 2 diabetes (20)

![Figure 2](image2.png)

### Figure 3 Cardiovascular disease mortality is significantly increased in individuals with the metabolic syndrome (25)

![Figure 3](image3.png)
The complexity of cholesterol homeostasis

Two facts that have held up to decades of scientific scrutiny are that: (i) intake of saturated fatty acids increases the total LDL-C levels and (ii) that intake of polyunsaturated fatty acids decreases total LDL-C in most individuals. There is also a consensus that substituting poly- or mono-unsaturated fat for saturated fat reduces LDL-C levels while leaving HDL-C levels largely unchanged, which makes individuals more sensitive to insulin and less likely to develop type 2 diabetes. Furthermore, a number of controlled metabolic studies have shown that trans fatty acids, which are found in stick margarine, vegetable shortening, commercial baked goods and deep-fried foods, raise LDL-C levels and lower HDL-C levels. The result is an increase in total cholesterol to HDL-C that is approximately twice as large as that occurring with the ingestion of saturated fatty acids. Thus, trans fatty acids promote insulin resistance and increase the risk of type 2 diabetes (11). The concerted effort to reduce trans fat content in food products is a positive development in the risk reduction of CHD events.

There remains much work to be performed. The ability to analyse what levels of cholesterol are beneficial in various individuals remains to be elucidated. For example, eggs are associated with higher glycaemic values, especially in vulnerable individuals such as those with metabolic syndrome or diabetes (12). But as shown by the Harvard Egg Study (12), the results of which were discussed in detail in the article by Dr Jones, the majority of people do not have an increased risk of CHD even when consuming more than one egg per day. Thus, increases in LDL-C levels with intake of eggs appear to be associated with higher levels of the large, more buoyant forms of LDL-C, which are less atherogenic than their smaller counterparts (13). In addition, the ratio of total cholesterol to HDL-C is not increased in most individuals when they consume even large numbers of eggs (14).

The complex interplay of factors involved in cholesterol homeostasis comes into sharp focus when examining the progression of CHD risk factors to endothelial injury and clinical events. These risk factors, such as smoking and hypertension, create oxidative stress in artery walls, which in turn lead to endothelial dysfunction (15). Endothelial dysfunction is a preclinical precursor of atherosclerosis (15). A host of other biochemical moieties and events must come into play and interact with the risk factors before clinical events can occur (15). At least one randomised, controlled study has shown that consumption of many eggs for short periods of time does not lead to endothelial dysfunction (16). Thus, it would appear that only vulnerable individuals, such as those with several serious risk factors, are most likely to develop endothelial dysfunction – and, if other factors exist, CHD.

Not all commonly used recommendations and guidelines utilise current evidence. For example, the data needed to calculate the Framingham score – and to calculate target LDL-C and total cholesterol: HDL-C levels – are age, gender, current smoking status, total cholesterol level, HDL-C level and systolic blood pressure (3). Neither the presence of metabolic syndrome nor the family history of CHD is taken into account. Efforts are under way to bring these and other emerging risk factors into the equation. Furthermore, the 2006 Canadian Dyslipidemia Guidelines recommend that treatment begin in low-risk patients when LDL-C level exceeds 5 mmol/l and in high-risk primary care patients when LDL-C level exceeds 2 mmol/l (9). Robust evidence does not exist to support these recommendations.

The National Cholesterol Education Program Adult Treatment Panel III recommendations (3) state that secondary-prevention patients should consume < 200 mg/day of cholesterol, and that primary-prevention individuals should consume ≤ 300 mg/day of cholesterol – the equivalent of > 1 egg/day. Primary-prevention patients are those with risk factors for development of CHD, while secondary-prevention patients have already had a CHD event such as an MI. The restrictions are more stringent, quite appropriately, when it comes to saturated fat. In all patients, this form of fat should comprise < 7% of total caloric intake and fat of all kinds may provide 25–35% of total calories. Polyunsaturated fat should represent no more than 10% of total calories, and monounsaturated fat up to 20% of total calories. Carbohydrates may contribute 50–60% of total calories via foods rich in complex carbohydrates such as whole grains, fruits and vegetables. In addition, individuals should consume 20–30 g of dietary fibre daily and protein should account for approximately 15% of total calories.

Obesity and the metabolic syndrome

What should be the most important focus of research and guidance to family physicians in continuing to reduce the risk of CHD? LDL-C is clearly one risk factor that contributes to CHD, but evidence points to a much larger portion of the risk being attributable to the metabolic complications associated with obesity, diabetes and the metabolic syndrome (17).
The obesity epidemic has reached unprecedented proportions in Western society and represents a growing threat to health in an increasing number of countries worldwide (18,19). Approximately 220,000 deaths in the US and Canada, and 320,000 deaths in Western Europe per year can be attributed to obesity (18,19). Obesity – abdominal obesity even more than body mass index – represents a strong independent risk factor for CVD and is associated with the metabolic syndrome. This is because the metabolic syndrome, in turn, is associated with many other risk factors for CVD including dyslipidaemia, hypertension and insulin resistance – all of which tend to cluster in abdominally obese individuals (18,19). Type 2 diabetes is also highly prevalent in those with features of the metabolic syndrome, but insulin resistance per se is not sufficient to cause diabetes (20). Only when the pancreas fails to compensate for insulin resistance is there a risk of developing diabetes (21).

The National Cholesterol Education Program Adult Treatment Panel III criteria for identification of the metabolic syndrome are a waist circumference of > 102 cm (40 inches) in men and > 88 cm (35 inches) in women plus any two of the following: triglycerides of $\geq 1.7$ mmol/l (150 mg/dl); HDL-C of < 1.04 mmol/l (40 mg/dl) in men and < 1.3 mmol/l (150 mg/dl) in women; blood pressure of $\geq 130/85$ mmHg; and a fasting blood glucose of $\geq 6.1$ mmol/l (110 mg/dl) (3). Europe has more stringent criteria, such as a smaller waist circumference cut off [94 cm (37 inches) in men and 80 cm (31.5 inches) in women] (22). Measurement of waist circumference is recommended as a simple method of identifying the body weight component of the metabolic syndrome. Some men may be prone to development of several metabolic risk factors when the waist circumference is only marginally increased – for example, to 94–102 cm (37–39 inches) (3). Such persons may have a strong genetic predisposition to insulin resistance (3). These men should benefit from changes in lifestyle, as recommended for individuals with categorical increases in waist circumference (3).

Elevated serum triglycerides are most frequently observed in patients with the metabolic syndrome, although secondary or genetic factors also can elevate triglyceride levels (23). Low HDL-C may also have several causes, but is frequently present in the metabolic syndrome (23). In addition, a fasting glucose level of $\geq 110$ mg/dl is commonly associated with insulin resistance (23). It should be kept in mind, however, that while the metabolic syndrome is associated with both CHD and type 2 diabetes, not everyone with type 2 diabetes has the metabolic syndrome (24). The 2001 National Cholesterol Education Program Adult Treatment Panel III recommendations suggested that the metabolic syndrome might independently predict the development of both type 2 diabetes and CHD (3,25).

Evidence suggests that the presence of metabolic syndrome increases the risk of developing CVD to a greater extent than any other single factor. Finnish researchers who followed slightly more than 1000 men for 10 years uncovered a 3.55-fold increased risk for CVD mortality among those with metabolic syndrome (Figure 3; 26). Other studies, such as a National Health and Nutrition Examination Survey analysis, suggest that diabetes alone is not associated with as great a risk of CHD as the metabolic syndrome alone, but that the combination of diabetes and metabolic syndrome is associated with a very high risk of a future vascular event (20). As a result, the rate of hospitalisation of those with diabetes for such vascular events as MI is increasing (23). And, as a corollary, statin therapy reduces the mortality rate of people with suspected metabolic syndrome far more than it does in individuals with other risk factors such as isolated high LDL-C (Figure 4; 27).

**Figure 4** Reduction of coronary heart disease (CHD)-related mortality by statins among individuals with metabolic syndrome vs. those with isolated elevated low-density lipoprotein cholesterol (LDL-C) (27)
Conclusion
Protection of the heart and maintaining healthy cholesterol levels can be optimised by limiting consumption of foods high in saturated and trans fatty acids, which are the leading culprits behind high LDL-C levels. It is important to limit intake of foods such as high-fat dairy products, fatty cuts of red meat, hydrogenated margarine, vegetable shortening, processed foods and fried foods, but it is not feasible to forbid certain foods. However, patients can be cautioned regarding the potential harm these foods may cause.

Compelling evidence from metabolic studies, prospective cohort studies and clinical trials conducted in the last 20 years indicates that at least three dietary strategies are effective in preventing CHD: substituting non-hydrogenated, unsaturated fats for saturated and trans fats; increasing consumption of omega-3 fatty acids from fish, fish oil supplements or plant sources; consuming a diet high in fruits, vegetables, nuts and whole grains and low in refined grain products. Such diets, together with regular physical activity, avoidance of smoking and maintaining a healthy weight may prevent the majority of CVD in Western populations.

Discussion
Q – Dr Ward: How do you define the point at which a person becomes a secondary-prevention patient when it is clear that there is a gradual accretion of risk factors that could result in CHD?
A – Dr Constance: It appears that inflammation is a key to this. We see some young patients who are dying of heart disease, and on the other hand we see a lot of elderly individuals who have atherosclerosis but who have never had a vascular event. It is clear that dietary and serum cholesterol are not the whole story and LDL-C also will not tell you who is going to have a vascular event. Evidence shows that if a patient begins to gain weight and stops exercising and if he also has metabolic syndrome, then his C-reactive protein titres will begin to increase rapidly.

This means that there are individuals in primary prevention who should be treated more aggressively than the current guidelines suggest, but that, conversely, not everyone who may be developing atherosclerosis should be treated with medication. The guide should be the number of risk factors an individual has. Indeed, a study dubbed JUPITER has shown that even with very moderate-risk patients – and without high total cholesterol or high LDL-C – if you can identify those with an inflammation burden as shown by elevated hsCRP, and treat them with statins, this is very beneficial (28).

Q – Dr Lau: I don’t think C-reactive protein will displace concern about cholesterol completely. In the JUPITER study, they were still using a statin to lower the C-reactive protein. So it’s not just a pure story of reducing inflammation and ‘let’s forget about cholesterol’. I don’t think those days will ever come. But I think our paradigms are shifting in terms of broadening our understanding of atherosclerosis and also diabetes, as diseases of inflammation.

Q – Dr Lau: What is the role of diet, particularly dietary cholesterol, in patients who are on statin therapy?
A – Dr Constance: Aggressive diet changes can be beneficial because most patients in secondary-prevention have the metabolic syndrome. Studies have shown that if these individuals increase their exercise and reduce intake of cholesterol, trans fatty acids and saturated fatty acids, their total serum cholesterol will drop by 10–20% (29). It is still unknown, however, whether reduction of serum cholesterol by statins results in a compensatory increase in absorption of dietary cholesterol, in other words a shift to becoming a hyper-responder to cholesterol. We’re not likely to know the answer any time soon because the sad fact is that when patients do change their diets after a heart attack, it’s not for a very long time. They go back to their bad habits, and we count on drug therapy, which is not the right thing, but that’s the reality.

Q – Dr Jones: Could eggs potentially be a significant part of a low-energy, low-fat diet aimed at weight reduction in primary- or secondary-prevention patients?
A – Dr Constance: Everything in moderation works. The most important thing is to have them lose weight, then you can help the blood pressure control, the LDL-C values and the glycaemic values. Now, whether you’re going to recommend a particular type of diet is another story. Weight loss does not change the lipid profile as much as we’d like to see, so statin therapy is the still the most important intervention. And while a person can probably then go back to eating eggs regularly, they probably shouldn’t eat bacon with it, because saturated fat is a huge contributor to increased LDL-C.

A – Dr Jones: The study published in 2003 in the *Journal of the American Medical Association* asks exactly your question, which is: can you do it by diet, or do you need a statin? And it showed that a ‘portfolio’ diet high in plant sterols, soy protein, viscous fibres and almonds has a similar effect on hyperlipidaemic adults’ lipid and C-reactive protein levels as a statin, at least initially (29). However, the
subsequent studies by that group indicated that it’s a tough ride (and compliance suffers) because you don’t get to eat bacon, you don’t get to eat ice cream, you have to Chow down on soy protein and nuts and all that stuff. And so the effect dies away, and actually you see the extinction of the effect after several months (30). We’re involved in a multicentre trial using the portfolio diet, and we’ve really had trouble keeping people on this trial. So maybe some day there will be a modified portfolio diet that will be easier to deal with. Maybe it will contain eggs for satiety and taste. But right now it’s a tough ride (for patients to stay compliant with it).

A – Dr Constance: This is still a grey area, because there has not been a prospective, randomised trial involving egg consumption in primary- and secondary-prevention patients. I would say in healthy individuals, a healthy lifestyle is much more important than anything else, and up to six eggs a week could be part of that. If you’re a diabetic or if you have insulin resistance, high egg consumption is an issue. If you have coronary disease, you can have up to six eggs a week, but not more than that and I certainly wouldn’t label eggs a forbidden food for anyone.

References