Drug and Non-Drug Treatment in Lipid Control

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LEUNG: ***Drug and Non-Drug Treatment in Lipid Control.*** *Abnormal lipid level is a very strong risk factor worldwide that attributes to coronary heart disease, one of the major manifestations of atherosclerosis. Since 1990's, major trials have demonstrated that lowering cholesterol, especially lowering LDL-C, by statin, can reduce mortality and morbidity of coronary heart disease. Recent trials on statin have shown that intensive statin therapy are both safe and effective, which leads to the revision of current guidelines in treating very high risk patients. Liver function impairment and muscle enzyme elevation are more common with high dose statin, and regular blood checking and surveillance is required. A new LDL-C lowering drug that acts on cholesterol absorption pathway can be used as monotherapy in patients who do not tolerate statin, or combined with statin producing synergistic effect. Aggressive lipid lowering has also been proved effective in patients without known coronary disease but with diabetes or high Framingham risk score. Low HDL-C is another coronary risk factor, but there is yet no recommended treatment goal. Both niacin and fibrate are effective HDL-C raising drugs that can improve atherosclerosis as well as reducing cardiovascular events. Non-drug therapy plays a pivotal role in the prevention of cardiovascular disease. The benefits of exercise, smoking cessation, moderate alcohol consumption, and diet modification are well demonstrated. The time to benefit is not necessarily long, and can be as short as within 3 to 6 months. Since atherosclerosis represents the largest burden of disease for the near future, the development of novel agents for the treatment of lipid disorders will certainly continue. (J HK Coll Cardiol 2006;14(Suppl 2):B28-B35)*

Atherosclerosis, coronary heart disease, cardiac rehabilitation, lipid disorder, statin

摘要

冠心病是動脈粥樣硬化的主要臨床表現，而血脂異常是誘發冠心病的一個全球性強力危險因素。自90年代起，臨床研究表明statin可以降低膽固醇，尤其是低密度脂蛋白，從而能夠降低冠心病的死亡率和病殘率。近期的臨床研究顯示大劑量statin的治療是安全有效的，對於治療高危病人的最新指導亦因此作了修改。在大劑量使用statin時，肝功能異常和肌酶增高是常見的現象，因此需要進行常規的血液檢查和檢測。一類新的降低低密度脂蛋白的藥物能減低膽固醇吸收，它對不能耐受statin的病人可作單藥治療，亦可與statin聯合使用以增強協同作用。積極的降低血脂對於沒有冠心病，而患有糖尿病或高Framingham分值的病人同樣有效。高密度脂蛋白的下降是冠心病的另一個危險因素，但目前治療目標尚未肯定。Niacin和fibrate都是升高高密度脂蛋白的有效藥物，它們能夠改善動脈粥樣硬化、降低心血管事件。非藥物治療在預防心血管疾病中扮演著重要角色。鍛煉、戒煙、中等程度的酒精攝入、和飲食結構的調整都證實有效。達致有效所需的時間並不一定很長，它可以短至三到六個月。在不久的將來，動脈粥樣硬化將是最大的疾病負擔，因此需要不斷發展治療血脂異常的新型藥物。

關鍵詞：動脈粥樣硬化　冠心病　心臟病復康　血脂異常　statin

Introduction

Lipid disorder is one of the most studied entities in the context of atherosclerotic disease. Coronary heart disease (CHD), a major manifestation of atherosclerotic disease, causes 1 out of 10 deaths in Hong Kong. Previously considered a "western" disease, it is now clear that the general population of Hong Kong, faced with a more affluent social structure and an urbanized lifestyle, is getting more and more vulnerable to atherosclerosis. The recent Interheart study,[1] a very large case-control study of acute myocardiac infarction in 52 countries, demonstrates that traditional risk factors for CHD account for most of the risk worldwide (over 90%)

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and include abnormal lipids, smoking, diabetes, hypertension, abdominal obesity, psychosocial factors, diminished consumption of fruits and vegetables, lack of regular alcohol intake, and lack of regular physical activity. The two most potent risk factors worldwide are smoking and lipid disorder.

Lipid disorder is one of the major modifiable risk factors. Since the landmark Scandinavian Simvastatin Survival Study[2] in 1994, clinical trials have provided strong evidence that control of lipid levels can reduce mortality and morbidity of CHD. Throughout these years, reduction of low density lipoprotein cholesterol (LDL-C) levels remains the major theme in many guidelines on the secondary prevention of CHD. One example is the 2006 update of the AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease,[3] which can be used as a tool in cardiac rehabilitation for patients who are recovering from CHD. The lipid management goals are summarized in Table 1.

Lipid disorder can be treated by drugs or non-drug therapies. The use of statin to lower LDL-C has revolutionized our previous misconception that pushing LDL-C to low levels is dangerous. The questions that we are facing now turn out to be: How far should we go for LDL-C lowering? Is it safe to use higher and higher dose? Should we use the non-statin LDL-C lowering drugs? The treatment goal in the primary prevention of CHD in patients with multiple risk factors is another hot topic. There are growing evidences that a low level of high density lipoprotein cholesterol (HDL-C) is a significant risk factor. Drugs that increase HDL-C are worth discussing though there are still no specific recommendations for a target HDL-C goal. Non-drug therapies have been shown to improve lipid levels, and should not be neglected even in this era of "the lower the better". Regular exercise, dietary modifications, weight reduction and smoking cessation are all important as part of the comprehensive therapy used in cardiac rehabilitation.

Table 1. AHA/ACC secondary prevention for patients with coronary and other vascular disease: 2006 update – lipid management goals

For all patients:

- Start dietary therapy. Reduce intake of saturated fats (to <7% of total calories), trans-fatty acids, and cholesterol (to <200 mg/d).
- Adding plant stanol/sterols (2 g/d) and viscous fiber (>10 g/d) will further lower LDL-C.
- Promote daily physical activity and weight management.
- Encourage increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/d) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction.

For lipid management:

Assess fasting lipid profile in all patients, and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiate lipid-lowering medication as recommended below before discharge according to the following schedule:

- LDL-C should be <100 mg/dL and
- Further reduction of LDL-C to <70 mg/dL is reasonable.
- If baseline LDL-C is ≥100 mg/dL, initiate LDL-lowering drug therapy.
- If on-treatment LDL-C is ≥100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination).
- If baseline LDL-C is 70 to 100 mg/dL, it is reasonable to treat to LDL-C <70 mg/dL.
- If triglycerides are 200 to 499 mg/dL, non-HDL-C should be <130 mg/dL.
- Further reduction of non-HDL-C to <100 mg/dL is reasonable.
- Therapeutic options to reduce non-HDL-C are:
  - More intense LDL-C – lowering therapy, or
  - Niacin (after LDL-C – lowering therapy), or
  - Fibrate therapy (after LDL-C – lowering therapy)
- If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieve non-HDL-C <130 mg/dL if possible.

How Low is Low?

Figure 1 showed the early landmark trials in the past 20-year history of statin therapy in secondary prevention trials,[2,4,5] showing the trend that lowering of LDL-C is associated with smaller percentage of cardiovascular events. Several recent trials[6-9] (Table 2) substantiated the efficacy and safety of intensive statin therapy for patients with clinically evident CHD. With the availability of data from recent trials on intensive statin therapy, the 2004 update of the National Cholesterol Education Program – Adult Treatment Panel

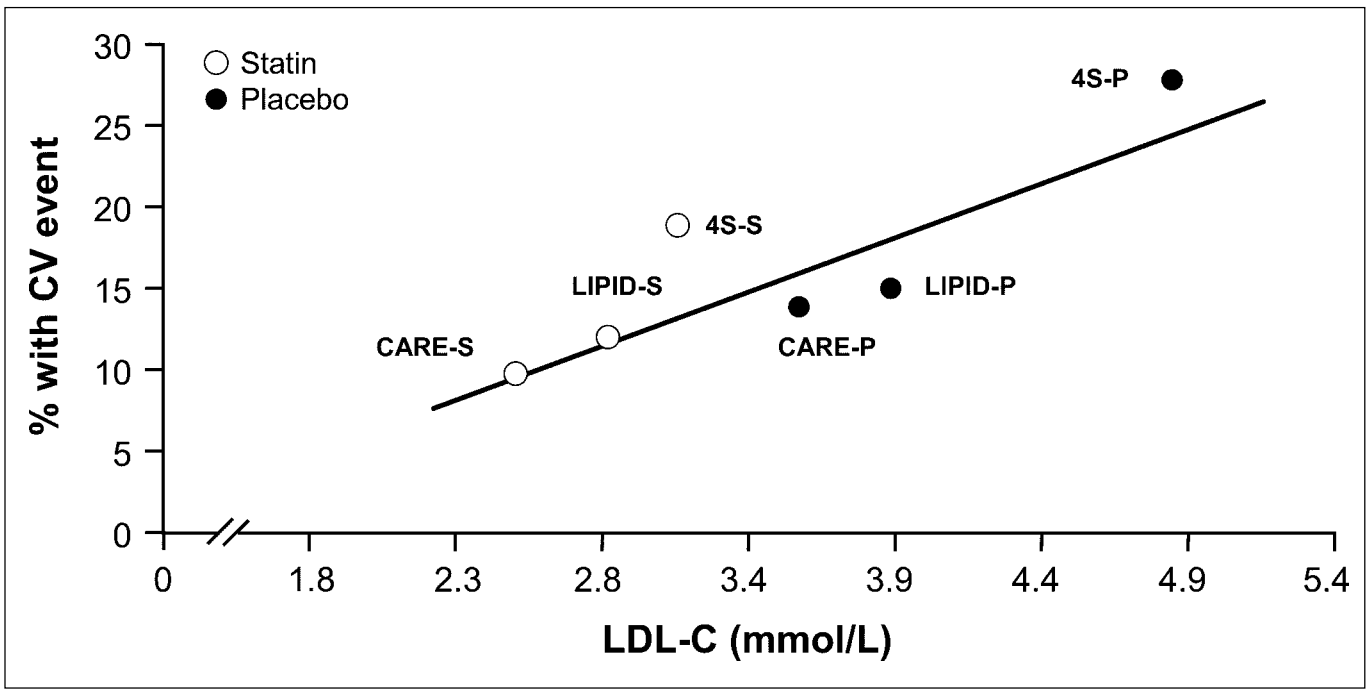

Figure 1. *Early landmark trials in the history of statin therapy. (CV events: cardiovascular events)*

Table 2. Recent trials on intensive LDL-C lowering

Trial name	Year published	Patient no.	Patient group	Medication	LDL-C achieved by study drug (mmol/L)	LDL-C reduction (mmol/L)
PROVE IT – TIMI 22 [6]	2004	4162	Acute coronary syndrome	Atorvastatin 80 mg vs pravastatin 40 mg	1.61	0.85
A to Z [7]	2004	4497	Acute coronary syndrome	Simvastatin 40/80 mg vs simvastatin 0/20 mg	1.63	0.36
TNT [8]	2005	10001	Stable CHD	Atorvastatin 80 mg vs atorvastatin 10 mg	1.99	0.62
IDEAL [9]	2005	8888	Stable CHD	Atorvastatin 80 mg vs simvastatin 20 mg	2.09	0.59

III Guidelines (NCEP/ATP III)[10] stated that the optional LDL-C goal should be ≤1.8 mmol/L for very high risk patients.

Criticism on the issue, however, is still on-going. Hayward et al[11] argued that published studies had avoidable limitations in analysis, and that current clinical evidence did not demonstrate that titrating lipid therapy to achieve proposed optional LDL-C goal of ≤1.8 mmol/L by NCEP/ATP III was beneficial or safe. Another argument is that additional benefits of statins may relate to mechanisms other than LDL-C lowering, such as lowering inflammation, as reflected by C-reactive protein levels.[12,13]

Is High Dose Statin Safe?

Intensive statin therapy requires the use of higher doses of available statins or the use of newer but more potent statins on the market. A meta-analysis on the effect of statins on LDL-C levels had showed the dose effects on LDL-C of all available statins, which are not linear and decrease at near peak doses (Table 3).[14] The major risks of statin use are myositis and abnormal liver function tests (LFTs). Liver failure is very rare. The Treating to New Targets (TNT) study[8] showed that the group given 80 mg of atorvastatin, when compared to the group given 10 mg of atorvastatin, had significantly higher rate of treatment-related adverse events, and higher rate of persistent impairment in liver function tests (LFTs). However, there were no persistent elevations of creatine phosphokinase (CPK) in both groups. The Cholesterol Treatment Trialists (CTT) meta-analysis[15] reported that rhabdomyolysis occurred in 9 (0.023%) of 39884 patients treated with statins against 6 (0.015%) of 39817 patients treated with placebo, and the excess was nonsignificant.

In general, statin use causes approximately 0.5-2% incidence of LFT elevations >3 x the upper limit of normal (ULN). Elevation is dose dependent but can be idiosyncratic. LFTs should be checked 4-6 weeks after any significant change in statin dosage, or change to another statin. A mild to moderate increase in LFTs (<3 x ULN) is not a contraindication to initiate or continue statin use, but LFTs should be followed closely. If LFT elevation is >3 x ULN, then statin dose should be decreased or discontinued.[16]

Myositis is another important concern. Baseline creatine phosphokinase (CPK) is helpful, since elevations in CPK in asymptomatic individuals before initiation of statin treatment is common. CPK should be checked if patients develop symptoms indicative of myositis. Drug treatment should be discontinued if CPK elevation is >10 x ULN. For lesser CPK elevations it is reasonable to decrease dosage to see if symptoms abate. Sometimes symptoms cannot be tolerated by patient but there is no CPK elevation, and treatment should be discontinued.

If toxicity develops after a statin is used, it is reasonable to rechallenge patients with a different statin. Rechallenging with a hydrophilic statin (pravastatin or rosuvastatin) at a lower dose may prove beneficial.

Non-Statin LDL-C Lowering Drugs?

Statin extenders that decrease LDL-C effectively include bile acid-binding resins and inhibitors of

Table 3. LDL-C reduction by percentage change according to statin and daily dose (adapted from Law et al. [14])

Statin	Percentage reduction in LDL-C				
	5 mg	10 mg	20 mg	40 mg	80 mg
Lovastatin (Mevacor)		21%	29%	37%	45%
Pravastatin (Pravachol)	15%	20%	24%	29%	33%
Fluvastatin (Lescol)	10%	15%	21%	27%	33%
Simvastatin (Zocor)	23%	27%	32%	37%	42%
Atorvastatin (Lipitor)	31%	37%	43%	49%	55%
Rosuvastatin (Crestor)	38%	43%	48%	53%	58%

cholesterol absorption. Bile acid-binding resins (cholestyramine and colestipol) can decrease LDL-C by about 15-30%. But they have important adverse events including abdominal fullness and constipation, malabsorption of fat soluble vitamins, and drug interaction through reducing absorption of other drugs. Popularity of use is reducing.

Ezetimibe is a new drug that inhibits absorption of cholesterol at the brush border of the small intestine. It decreases LDL-C by 15-18%. Its major advantage is it acts synergistically with statins, allowing an additional 25% reduction in LDL-C. Using a statin alone, this additional 25% reduction can be achieved only when the statin dose has been doubled three times (i.e. increasing from 10 mg to 80 mg). Ezetimibe can be used as monotherapy in patients who do not tolerate statins, but long term reduction in atherosclerotic events has not yet been demonstrated.

Statin in Multiple Risk Group?

The concept of aggressive lipid lowering has also landed on the platform of the primary prevention. According to the NCEP/ATP III guidelines,[17] high risk patients included those with diabetes and those with 10 year Framingham risk >20%. (Risk is calculated based on Framingham risk score which incorporates age, total cholesterol, smoking status, HDL-C, and systolic blood pressure to determine the Framingham 10 year risk of coronary events. The European counterpart is called the European SCORE system[18] that assesses 10 year risk of total fatal vascular events.) These patients should have their LDL-C reduced to <2.6 mmol/L. More evidence is demonstrated in the Anglo-Scandinavian Cardiac Outcomes Trial - Lipid-Lowering Arm (ASCOT-LLA)[19] in which the studied patients had at least 3 coronary risk factors, and in the Collaborative AtoRvastatin Diabetes Study (CARDS)[20] in which the studied patients had type 2 diabetes. Both studies excluded those with established coronary disease or high cholesterol levels, and both showed significant reductions in major cardiovascular events and procedures by the daily use of 10 mg of atorvastatin as compared to placebo. Indeed some of the patients in both studies belonged to the moderately high risk group according to the NCEP/ATP III guidelines. Their results will therefore have implications for future lipid management guidelines.

When and How to Increase Low HDL?

HDL-C transport excess cholesterol from peripheral tissues to liver for excretion, a process known as reverse cholesterol transport. Low HDL-C is associated with an increased risk of CHD, especially in diabetics. Often, persons with low HDL-C have other risk factors, such as diabetes or hypertension. The NCEP/ATP III guidelines[17] do recognize low HDL-C as a significant risk factor for CHD, but the guidelines do not specifically recommend that HDL-C be a target of control, and do not specify a goal for raising HDL-C. This is because, without trials designed to isolate the effects of drugs on changes in HDL-C levels and on coronary outcomes, it is difficult to determine how much of the treatment benefit in reducing the rates of CHD are due to changes in HDL-C levels.

Niacin is the most effective medication to raise HDL-C levels, causing increases of 20-35%. It inhibits hepatic uptake of apolipoprotein A-I (apo-Lp A-I) and increases plasma pre-β HDL-C levels. The Coronary Drug Project[21] demonstrated a significant reduction in the incidence of death and myocardial infarction after 5 years of niacin treatment among men with a history of myocardial infarction. The side effects include cutaneous flushing, dyspepsia, and elevation of plasma glucose and uric acid levels. Flushing is minimized with the use of a newer extended-release formula; with the concurrent consumption of a low-fat snack at bedtime, 30 minutes after ingestion of an aspirin; and with a regime that begins with a low dose (e.g., 350 or 500 mg each night) and increases gradually.

Fibrate therapy results in an increase in HDL-C levels of 10-25%. Fibrates activate peroxisome-proliferator-activated receptor α (PPARα), which stimulates expression of the hepatic apo-Lp A-I gene. The Helsinki Heart Study[22] and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[23] demonstrated increases in HDL-C and reductions in cardiovascular events in asymptomatic

men and those with primary dyslipidemia or CHD, respectively, when they received gemfibrozil 1200 mg daily. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[24] compared micronised fenofibrate 200 mg daily with placebo in patients with type 2 diabetes. Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events, but reduced total cardiovascular events. But those allocated placebo had a higher rate of starting statin therapy, which might have masked a moderately larger treatment benefit. Important side effects of fibrates include myositis, which is rare but occurs more in patients with renal impairment and concomitant treatment with statins.

Statins can raise HDL-C levels by 2-15% by increasing apo-Lp A-I synthesis. Different agents vary in efficacy. Rosuvastatin, fluvastatin and simvastatin can probably raise HDL-C levels better, the range being from 5% to 15%.[25] Combination therapy has also been tried in patients with low HDL-C levels. The HDL Atherosclerosis Treatment Study (HATS)[26] demonstrated that a combination of low dose simvastatin and high dose niacin significantly increased HDL-C levels and reduced coronary stenosis in patients with low HDL-C, average LDL-C, and average triglyceride levels. In the newer Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study,[27] addition of extended-release niacin to existing statin therapy in subjects with established coronary disease increased HDL-C levels by 21% and showed no progression in carotid intima thickness when compared to placebo.

Several new therapies to increase HDL-C levels are being studied, including inhibitors of cholesteryl-ester-transfer protein (CETP) and PPARα activators. A kind of bioengineered molecule called recombinant apo-Lp A-I Milano has been shown to cause regression of plaques in animal models.[28]

Non-Drug Therapy Still Effective?

Paying additional effort on non-drug therapy of lipid disorder in this era is challenging. We have to face critics from layman as well as the medical profession. Examples are: lifestyle modification is tedious and slow; it is difficult to follow; the effect is small; etc. It is prudent to clarify some of the misconceptions on non-drug therapy.

As much as 70% of cardiovascular disease can be prevented or delayed with dietary choices and lifestyle modifications.[29] Cardiovascular mortality is still having an upward trend globally, especially in the developing countries, because of a growing epidemic of obesity, decreasing physical activity and persistent cigarette smoking.

The benefits of **exercise** on lipid profiles and cardiovascular disease have been clearly demonstrated. A meta-analysis of 52 exercise training trials lasting more than 12 weeks achieved an average 4.6% increase in HDL-C levels and 5.0% reduction in LDL-C levels.[30] Only minimal adherence to current physical activity guidelines, which yield an energy expenditure of about 1000 kcal/wk, is associated with a significant 20-30% reduction in risk of all-cause mortality in the general population.[31] A meta-analysis of 48 randomized controlled trials demonstrated that exercise-based cardiac rehabilitation (for patients with CHD) was associated with significant reduction in all-cause mortality as well as total cholesterol levels.[32]

Tobacco smoke contains many cardiotoxic substances, of which nicotine is probably the most important. Cigarette smoking increases triglyceride and lowers HDL-C levels.[33] Cessation of smoking yields a 50% reduction in the risk of a coronary event in the first year or two after quitting, and the risk approaches that of non-smokers after 5-15 years. Patients who quit smoking have a 36% reduction in relative risk of mortality compared with those who continue smoking.[34]

Obesity is associated with low HDL-C and high triglyceride levels. A meta-analysis demonstrated that HDL-C levels increased by 0.006-0.009 mmol/L per kilogram of weight reduction.[35] The proportional reduction in LDL-C levels is, however, even smaller.

Moderate **alcohol** consumption, defined as one or two drinks daily, raises HDL-C levels,[33] and reduces cardiovascular events by as much as 20-45%.[36] However, the potential risks may outweigh the benefits in persons with hepatic dysfunction, hypertension, the potential for addiction, or a family history of breast and colon cancer.

There are ample evidences that **diet** therapy can improve lipid levels. Reduction in LDL-C levels remains a major goal of CHD risk management. Saturated and trans fatty acids results in high LDL-C levels.[37,38] The greatest increases result from lauric, myristic and palmitic fatty acids found in dairy fat, meat and tropical oils. Trans monounsaturated fatty acids found in baked food, stick margarine and French fries have equivalent changes. Dietary cholesterol is found in foods of animal origin that are also high in saturated fat (except egg yolk and shellfish). An increase of dietary cholesterol will increase total serum cholesterol slightly, of which 70% is in the LDL fraction. In general, adoption of diets low in saturated fat and cholesterol will reduce LDL-C levels in the range of 5-10%. Such diets also lower HDL-C levels, but the effect can be overcome by the concomitant decrease in LDL-C levels. Native Alaskan populations that eat a diet rich in n-3 polyunsaturated fatty acids have high HDL-C levels.[39]

It is generally believed that the time to benefit of non-drug therapy is rather slow, which defeats the eagerness of those under treatment. However, a recent meta-analysis on 5 important dietary therapy trials (published in 1985-1993) on secondary prevention demonstrated that the benefit on cardiovascular events can be observed in 1-2 years after commencement of therapy.[40] Two of these studies, each including n-3 polyunsaturated acids as part of the dietary intervention, reported a more rapid time to benefit (within 3 to 6 months).

Conclusion

This is an updated summary of available data on the effect of drug and non-drug therapies on lipid disorder, with the aim of preventing cardiovascular disease. The development of novel agents for the treatment of lipid disorders will certainly continue, because atherosclerosis represents the largest burden of disease for the near future. The use of existing drugs, such as high dose statins, combination therapy, or drugs that increase low HDL-C, has proved to be effective in reducing cardiovascular events. Non-drug therapy, such as exercise, anti-smoking program, or diet modification, is an essential adjunct in high risk patients, as well as an effective initial treatment modality for those in the low and medium risk groups. Indeed, who can ascertain that he/she can avoid being involved in the global epidemic of atherosclerosis?

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