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Ancel Keys and the lipid hypothesis: From early breakthroughs to current management of dyslipidemia

Aggressive and effective lipid-lowering treatment that combines lifestyle modification and pharmacotherapy is key to preventing cardiovascular diseases.

ABSTRACT: Starting in the 1940s pioneering American physiologist Ancel Keys helped establish the epidemiological link between cholesterol and cardiovascular disease. Once Keys and others clarified the role of dietary saturated fat in disease development, early intervention studies examined the effects of diet and drug therapy. In the 1990s large trials of statins confirmed the benefits of lipid-lowering therapy for primary and secondary prevention of cardiovascular disease. As targets for therapy continue to be lowered the need for combination and novel therapies has intensified. Despite some controversy regarding the optimal method of lipid-lowering, an aggressive, intensive approach to lipid-lowering remains central in the management of cardiovascular disease.

In memoriam

We are saddened by the passing of cardiology fellow **Dr Aneez Mohamed**, whose life was tragically cut short in a hit and run accident on 7 February 2009. His in memoriam appears on page 81.

The role of dietary cholesterol in the pathogenesis of atherosclerosis and cardiovascular disease is well established in current medical science. However, as recently as 60 years ago, this important association was doubted widely in scientific and nonscientific circles. After early studies by Ancel Keys established the epidemiological link between cholesterol and cardiovascular disease (CVD), other studies followed, including intervention studies aimed at reducing cardiovascular mortality through lipid-lowering therapy and the more recent statin trials. Future directions for management of abnormal plasma lipid levels may rely on other agents now in development, including cholesterol ester transfer protein inhibitors and antagonists of apolipoprotein B.

The epidemiological link

Ancel Keys was an American physiologist, former chairman of the International Society of Cardiology, consultant to the World Health Organization and the UN Food and Agriculture Organization, and inventor of the K ration. During his professional career he founded the field of quantitative human biology, wrote the most complete account of the physiological, psychological, and cognitive effects of starvation (*The Biology of Human Starvation*, 1950), and helped establish the link between CVD and dietary cholesterol. Nicknamed Mr Cholesterol for his discoveries, he advocated for a healthy lifestyle that included a low-fat diet and regular exercise. He retired as head of the Laboratory of Physiological Hygiene at the University of Minnesota in 1972 but remained intellectually active through his 97th year. He died on 20 November 2004 at the age of 100.

Dr Keys' interest in cardiovascular disease began after the Second World War with the realization that as food supplies in northern Europe became short the death rate from coronary artery disease (CAD) dropped. This observation, coupled with reports

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of an epidemic of myocardial infarctions (MI) among American executives, motivated Keys to launch one of the first prospective studies in CVD epidemiology, the Minnesota Business and Professional Men's Study.[1] Along with Henry Taylor, Keys recruited 286 Minneapolis—St. Paul businessmen between the ages of 45 and 55 to submit to yearly physical examinations starting in 1947 in an attempt to discover the factors involved in "degeneration of the heart." Starting in 1947 the researchers recorded weight, blood pressure, ECG results, and cholesterol levels (mean 6.2 to 9.4 mmol/L). The only significant predictor of later MI was a high total cholesterol level. Initially these observations were harshly criticized by commercial interests such as the meat and dairy industry.

After a series of smaller studies, Keys examined the dietary habits of middle-aged men of Japanese origin living in either their native Japan, Hawaii, or Los Angeles in 1956.[2] This study was based on the observation that rates of CAD are significantly higher in nisei—Japanese living in Hawaii and Los Angeles—than they are for native Japanese. In Los Angeles, rates of CAD in nisei were similar to rates in "local Caucasians." For every native Japanese experiencing an MI, the Hawaiian nisei have four, and the Los Angeles nisei ten. Given the common genetic background of the subjects, Keys and his colleagues sought to examine how the "usual American mode of life" might play a role. An examination of the dietary patterns demonstrated that while native Japanese get only 13% of their calories from fats, the Hawaiian Japanese get 32% of their calories from fats, and the Los Angeles Japanese get 45% of their calories from fats. The subjects' mean total cholesterol levels corresponded to the three dietary patterns: 3.11 mmol/L for native Japanese, 4.70 mmol/L for Hawaiian Japanese, and 5.50 mmol/L for Los Angeles Japanese.

Beginning in 1957 Keys and his colleagues began what would eventually be known as the Seven Countries Study by surveying 12 000 men aged 40 to 59 from 18 areas of seven countries (Italy, the Greek Islands, Yugoslavia, the Netherlands, Finland, Japan, and the United States).[3] Study communities were chosen for their contrasting dietary patterns and the relative uniformity of their rural laboring populations. Through central chemical analysis of the foods consumed by randomly selected families as well as diet-recall measures, Keys and his colleagues were able to determine that in societies where fat was a major component of every meal (i.e., the US and Finland), both the blood cholesterol levels and the heart-attack death rates were highest. Conversely, in cultures where diets were based on fresh fruit and vegetables, bread, pasta, and plenty of olive oil (i.e., the Mediterranean region) blood cholesterol was low and heart attacks were rare. The report published in 1970 had a decisive impact on CVD prevention, as it described one of the first studies to clearly show that dietary saturated fat leads to CVD, and that the relationship is mediated by serum cholesterol.

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The early intervention studies

In the late 1960s the realization grew that prevention programs could not rely solely on protecting the most susceptible but must protect the entire population.[4] The Seven Countries Study helped confirm this and shift scientific and public attention to entire populations considered at risk.

Even though the three major preventable risk factors for CVD (elevated serum cholesterol levels, high blood pressure, and smoking) had been identified as early as 1956, the link between cholesterol and CAD required the results of large epidemiology studies before gaining widespread acceptance. As a result of corroborative evidence from prospective population studies such as the Framingham study, the scientific community refocused on systemic intervention studies to test whether reducing risk factors would reduce disease incidence.

These early trials examined the effects of diet or drug therapy in primary and secondary prevention populations. Dietary modification typically focused on a reduction of the total and

saturated fat content, although some of the trials examined fat substitution using corn or soybean oil.[5,6] At the same time, the drug therapy trials focused primarily on clofibrate and niacin, colestipol, or gemfibrozil.[5,7-13] On the whole, the drug trials were more successful at lowering cholesterol than the dietary trials. Unsurprisingly, the reduction in cardiovascular mortality and total mortality was greater in the secondary prevention trials and appeared to be dependent on the baseline cholesterol levels; that is, the higher the baseline risk the greater the obtained benefit.[5] In fact, the LRC-CPPT[5,10,11] reported a "cholesterol benefit ratio": for every 1% reduction in cholesterol a 2.5% reduction in CVD incidence was achieved.

The statin era

The mid-1990s saw the emergence of mega-trials using lipid-lowering therapy with HMG-CoA reductase inhibitors (statins). There have been numerous trials examining different statins (lovastatin, pravastatin, simvastatin, atorvastatin, and rosuvastatin) in patients with a wide variety of clinical characteristics. These trials have focused on primary prevention, secondary prevention, acute coronary syndromes (ACS), and aggressive lipid lowering.

Secondary prevention and risk equivalents

The first of these trials was the landmark 4S study,[14] which demonstrated that in patients with established CAD and a cholesterol level between 5.5 and 8.0 mmol/L, treatment with simvastatin was associated with a significant reduction in coronary mortality, all-cause mortality, stroke, and need for revascularization without a compensatory increase in noncoronary mortality. As a result this trial established the safety of cholesterol-lowering therapy and absolved it of past concerns that they would result in increased noncoronary death.[9]

The importance of treating the dyslipidemic patient with CVD or risk equivalents was reinforced in two subsequent trials with pravastatin. The LIPID trial[15] and the CARE trial[16] examined patients with established CAD and a serum cholesterol of 4.0 to 7.0 mmol/L (LIPID), and 3.2 to 6.2 mmol/L (CARE). Similar to 4S, these trials showed that pravastatin was effective at reducing CVD mortality, all-cause mortality, MI, need for revascularization, and stroke.

The largest placebo-controlled trial examining the efficacy of statin therapy was reported in 2002. The HPS study[17] examined over 20 000 high-risk patients with established CVD, diabetes, or treated hypertension and a cholesterol level greater than 3.5 mmol/L (mean total cholesterol 5.9 mmol/L, LDL-C 3.4 mmol/L) and randomized them to either simvastatin (40 mg daily) or placebo. After 5.5 years of treatment, simvastatin was associated with a significant reduction in all-cause mortality, CVD mortality, major cardiovascular events, need for revascularization, and stroke. These effects were similar among tertiles of LDL-C, suggesting that the threshold beyond which lowering LDL-C has no effect has not yet been reached.

Similarly, atorvastatin was demonstrated to be beneficial in high-risk patients with type 2 diabetes not known to have CAD in the CARDS trial,[18] where atorvastatin (10 mg daily) significantly reduced cardiovascular mortality, MI, stroke, and need for revascularization. In the AVERT trial,[19] treatment with atorvastatin was shown to be equivalent to angioplasty at reducing ischemic events in patients with one- or two-vessel CAD and an average LDL-C of greater than 3.0 mmol/L.

Primary prevention

While it is no surprise that treating the highest risk individuals (i.e., those with clinically established disease) will result in the greatest clinical benefit, these patients are estimated to make up less than 10% of the total population CVD burden. The first major trial focusing solely on primary prevention was the WOSCOPS trial,[20] which was published only 1 year after the 4S trial. Like 4S, it was a landmark trial that demonstrated a significant reduction in nonfatal MI, cardiovascular mortality, need for revascularization, and need for cardiac hospitalization in men with relatively high cholesterol levels, who received pravastatin (40 mg/day). In contrast to the earlier trials with clofibrate,[9] WOSCOPS did not demonstrate an increase in noncardiac death. As a result it established the benefit of treating dyslipidemic patients who were at high risk of developing clinically apparent CVD. This trial was followed by two others, AFCAPS/TexCAPS[21] in 1998 and ASCOT-LLA[22] in 2003, which demonstrated the efficacy of primary prevention in patients with near-normal cholesterol levels. (In the AFCAPS/TexCAPS trial, this meant total cholesterol of 5.7 mmol/L and LDL-C of 3.9 mmol/L, and in the ASCOT-LLA trial, this meant total cholesterol of 5.5 mmol/L and LDL-C of 3.4 mmol/L.)

Despite this body of evidence, some controversy remains regarding the role of statins in primary prevention for members of populations at lower baseline risk, such as women, and for patients likely to have adverse drug reactions, such as the elderly. Even though analyses of the ASCOT trial have clearly established the beneficial role of statins in these populations (an observation that was supported by secondary prevention trials such as CARE, 4S, and TNT), pharmacother-

apy remains recommended for high-risk individuals only.

Acute coronary syndromes

As discussed above, statins have been shown to be effective in patients with established, stable CAD. Given the theoretical pleotropic effects of statins on inflammation, plaque stabilization, and thrombogenicity, several studies have examined their potential utility in the immediate aftermath of an acute coronary syndrome (ACS). The first major trial to address this question was the MIRACL study,[23] which confirmed that lipid-lowering with atorvastatin (80 mg/day), when given 24 to 96 hours after admission for ACS, significantly reduced recurrent ischemic events in the first 16 weeks. PROVE-IT TIMI 22[24] elaborated on these results and demonstrated that intensive lipid-lowering reduced major cardiovascular endpoints in patients hospitalized for ACS (one-third with unstable angina, one-third with non-ST elevation MI, and one-third with ST elevation MI). Patients in the intensive arm were able to achieve an LDL-C level of 1.60 mmol/L in contrast to a level of 2.46 mmol/L achieved by those in the standard therapy arm, corresponding to a 2-year reduction in the composite of death, MI, or urgent revascularization as well as recurrent unstable angina.

Aggressive lipid-lowering

The aggressive lipid-lowering strategy was further extended to patients with stable CAD in two separate trials published in 2005. The TNT trial[25] enrolled 10 000 patients with stable CAD and a baseline LDL-C of 3.4 to 6.5 mmol/L and then randomized them to low-dose (10 mg/day) or high-dose (80 mg/day) atorvastatin. The significantly lower serum LDL-C level achieved with high-dose atorvastatin (2.0 mmol/L vs 2.6 mmol/L) was associated with a reduction in major cardiovascular events, MI, stroke, and cardiovascular mortality without affecting total mortality. Similarly, the IDEAL trial[26] demonstrated a significant reduction in nonfatal MI and need for revascularization in the intensive lipid-lowering arm, where atorvastatin (80 mg/day) was used to achieve LDL-C 2.1 mmol/L versus the standard arm, where simvastatin (20 mg/day) was used to achieve LDL-C 2.7 mmol/L. Likewise, the recently completed JUPITER trial[27] showed that rosuvastatin (20 mg/day) resulted in a significant reduction in cardiovascular morbidity and mortality in patients without evidence of CVD, a low to normal LDL-C, and an elevated C-reactive protein level compared with placebo.

These clinical results for intensive lipid-lowering therapy were supported by three surrogate endpoint studies. The SCAT Trial[28] demonstrated significantly less angiographic progression of CAD in patients with near-normal cholesterol levels (mean total cholesterol 5.2 mmol/L, LDL-C 3.36 mmol/L) who underwent intensive lipid-lowering with simvastatin versus patients on placebo. More recently the REVERSAL[29] and ASTEROID[30] trials demonstrated that lowering LDL-C to a mean level of 2.0 mmol/L with atorvastatin (80 mg) and to 1.57 mmol/L with rosuvastain (40 mg) resulted in a slowing or even regression of coronary atherosclerosis as assessed by intravascular ultrasound.

Table. Comparison of lipid guidelines: Canadian Cardiovascular Society, Adult Treatment Panel III, and European Society of Cardiology[31-33]

Risk category	CCS 2006	ATP-III-R	ESC 2007
High • 10-year FRS* ≥ 20%, CVD, peripheral vascular disease, stroke, diabetes	Treatment targets • LDL-C < 2.00 mmol/L • TChol:HDL < 4.00 mmol/L Goal apo B < 0.85 g/L†	Treatment targets 2004 • LDL-C < 2.6 mmol/L (optional goal LDL-C < 1.8 mmol/L) • Non-HDL < 3.37 mmol/L	Treatment targets • LDL-C < 2–2.50 mmol/L • TChol < 4–4.50 mmol/L
Moderate • 10-year FRS 10%–19%	Treat when • LDL-C ≥ 3.50 mmol/L • TChol:HDL ≥ 5.00 mmol/L Goal apo B < 1.05 g/L	Treatment targets • LDL-C < 3.4 mmol/L • Non-HDL < 4.15 mmol/L	Treatment targets • LDL-C < 3.00 mmol/L • TChol < 5.00 mmol/L
Low • 10-year FRS <10%	Treat when • LDL-C ≥ 5.00 mmol/L • TChol:HDL ≥ 6.00 mmol/L Goal apo B <1.25 g/L	Treatment targets • LDL-C < 4.2 mmol/L • Non-HDL < 5.00 mmol/L	

*FRS = Framingham risk score
†Apo B levels reflect the total number of LDL particles and may be a better predictor of risk with familial dyslipidemias.

Current guidelines

Owing to the demonstrated benefits of intensive lipid-lowering therapy, most major lipid guidelines were revised between 2004 and 2007 (see **Table**). These guidelines rely on risk prediction scores that estimate an individual's 10-year risk for heart disease as high, moderate, or low and recommend treatment accordingly.

The current Canadian Cardiovascular Society (CCS) guidelines[31] recommend that patients in the high-risk category be treated with a statin to achieve a reduction in LDL-C by more than 50% to a level of less than 2.0 mmol/L. The primary goal for patients in the moderate- and low-risk groups is a reduction in LDL-C of at least 40% from baseline, when levels are ≥3.5 mmol/L and ≥5.0 mmol/L, respectively.

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The current Adult Treatment Panel III (ATP-III-R) guidelines[32] are similar to the CCS recommendations with comparable targets for each risk category. A key difference however is the inclusion of patients with a Framingham risk score of less than 10% in the moderate risk category if they have two CVD risk factors (smoking, hypertension, HDL-C < 1.1 mmol/L, a positive family history of premature CAD, and age ≥ 45 years in men and ≥ 55 years in women). The low-risk category for the ATP-IIIR includes patients with a less than 10% 10-year risk and 0–1 risk factors. The risk stratification tool used by the European Society of Cardiology (ESC) is the SCORE system, which considers patients with a 10-year risk of CVD death greater than 5% as high risk.[33] The ESC lipid guidelines recognize risk equivalents as a distinct category that warrant immediate treatment to high-risk targets. For patients with a SCORE rating greater than 5%, a 3-month trial of lifestyle measures is the recommended starting point. If after 3 months lipid levels remain above moderate- to low-risk targets and the SCORE rating remains greater than 5%, then intensive therapy to reach high-risk targets is recommended.

Therapy for difficult-to-control lipid levels

As discussed, statins have been shown to be safe and effective at lowering lipid levels (especially LDL-C) and protecting against CVD. Nevertheless there are situations where despite optimal doses, lipid levels remain suboptimal. For these patients there are two established options with more in development.

The first therapeutic approach is combination therapy with niacin. Several studies have reinforced the importance of simultaneously lowering LDL-C and increasing HDL-C. Early trials focusing on the combination of colestipol and niacin (CLAS, FATS) demonstrated a significant regression in coronary atherosclerotic lesions as well as a reduction in death, MI, angina, and need for revascularization.[34,35] The more recent HATS and ARBITER-2 studies found significant effects in surrogate (CIMT, angiographic stenosis) and clinical endpoints (death, MI, stroke, or revascularization) and confirmed the beneficial effect of adding niacin to statin therapy.[36,37]

The second therapeutic approach involves combining a cholesterol absorption inhibitor such as ezetimibe with a statin. Recently the ENHANCE trial[38] confirmed the efficacy of ezetimibe at lowering LDL-C; however, it did not show any additional improvement in the surrogate endpoint of carotid vascular disease over simvasatin therapy alone. Conversly, the recent SEAS study demonstrated no effect of ezetimibe on the progression of aortic stenosis, although there was a concomitant reduction in coronary events.[39]

Future directions

In addition to the established armamentarium for lowering lipid levels, there are multiple agents in development that target novel components of the lipid pathway and atherosclerotic cascade. Perhaps the best known novel agents are in the class of the cholesterol ester transfer protein inhibitors, which are specifically designed to raise HDL-cholesterol. Their reputation was recently tainted when a phase 3 trial (ILLUMINATE) examining the safety and efficacy of torcetrapib was halted after an excess of deaths and cardiovascular events in the torcetrapib treatment group.[40] However, other novel agents in this class now being studied have not caused the same deleterious off-target effects seen with torcetrapib and appear to be safe. Other agents in development include antagonists of apolipoprotein B, the large protein that forms the backbone of all lipid molecules except HDL-C, as well as inhibitors of phospholipid A2, an enzyme that plays a critical role in the pathogenesis of atherosclerosis.

Early studies show these agents are effective at reducing LDL-C levels and decreasing inflammation without significantly increasing adverse events.

Conclusions

Over the past 50 years the lipid hypothesis has grown from an obscure theory to a central concept in the practice of cardiovascular medicine and the prevention of heart disease. The concept began with the pioneering work of Dr Ancel Keys, who helped establish the epidemiological link between dietary fats, serum cholesterol, and atherosclerotic coronary and vascular disease. But the early observations would have meant nothing if large randomized trials had not confirmed the role of dyslipidemia in cardiovascular disease and the beneficial effects of contemporary lipid management.

The key to the management of dyslipidemia remains a balanced combination of education, early prevention, lifestyle modification (including a low-fat diet and regular exercise), and tailored pharmacotherapy. While controversies continue regarding what is the most appropriate target for lipid levels and whether monotherapy should be pursued over combination therapy, the fact remains that up to 50% of ischemic heart disease worldwide can be accounted for by dyslipidemia with treatment benefits "substantially greater than those associated with hypertension therapy."[41] As such, the need for an aggressive and effective lipid-lowering treatment approach could not be more relevant.

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Competing interests

None declared.

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