

An International Atherosclerosis Society Position Paper: Global Recommendations for the Management of Dyslipidemia

Full Report

Introduction

The International Atherosclerosis Society (IAS) has developed a guide for dyslipidemia intervention. This guide is based on deliberations of an IAS committee with international representation. Its recommendations are based on an interpretation of available data from a majority of the panel members. The Position Paper was developed as follows. Fifteen committee members were nominated by the IAS Executive Committee and were invited to participate on the writing panel. They were both experts and representative of different regions of the world. Timely questions relating to lifestyle and drug management of dyslipidemia were selected and shared with the panel. Responses were organized as IAS panel deliberations. From the deliberations, key recommendations were abstracted. Before each deliberation, a background section was developed for perspective. A draft document was constructed and shared with IAS panel members. Responses were incorporated and a revised draft was again shared. The second draft was also provided to the IAS Executive Board. All comments were collated and incorporated into a final draft; this was provided to the IAS Executive Committee for approval. Finally, the document was shared with IAS member societies for their comment and ratification. Many member organizations provided useful comments that led a final modification of the document.

The recommendations are based on international consensus. Three major lines of evidence underpinned the recommendations: epidemiological studies, genetic studies, and clinical trials. Where appropriate, the recommendations were further informed by pathological studies, pharmacology, metabolic studies, smaller clinical trials, meta-analyses of clinical trials, animal studies, and the basic sciences. Each line of evidence contains strengths and weakness. Epidemiological studies are worldwide in scope. A vast database of population research relates cholesterol and lipoproteins to ASCVD. The consistency and strength of these relationships make it possible to determine optimal cholesterol levels for ASCVD prevention. Although epidemiology is subject to confounding factors, consistency of results from many studies helps to overcome this weakness. Genetic epidemiology reduces the possibility of confounding factors by having single variables—genetic mutations. Although genetic data are limited, they are highly informative for linking cholesterol levels to risk for ASCVD. Finally, clinical trials, especially randomized clinical trials (RCTs), allow testing of single variables—usually drug

therapies. This fact has led many guideline panels to give priority to RCTs over other lines of evidence. Most RCTs however are drug trials. Allowing RCTs to dominate guideline development largely restricts them to drug recommendations; reliable RCTs for lifestyles therapies are few. Drug RCTs moreover have not been carried out in a diversity of populations. Volunteers for RCTs commonly do not reflect the population at large. And finally, RCTs are mostly sponsored by the pharmacological industry. They are designed primarily to obtain regulatory registration, not to answer critical questions in clinical intervention. The IAS panel recognized the enormous fund of useful information provided by RCTs; but it also has placed RCTs in the context of epidemiological and genetic findings.

Most investigators in the lipid field contend that atherosclerosis is largely a lifestyle problem. This belief derives from epidemiology and not RCTs. Creating guidelines exclusively from drug RCTs makes pharmacology a solution to unhealthy life habits. Drug treatment may of necessity supersede lifestyle in secondary prevention; but a drug paradigm may not be the best for primary prevention. Some investigators are promoting the concept that drugs should be used as public health measures in primary prevention. The IAS panel instead favored using lifestyle intervention to reverse unhealthy life habits. Drugs are reserved for higher risk patients.

Although RCTs are limited, their results are largely congruent with epidemiological evidence. Epidemiology shows that high levels of serum cholesterol impart increased risk for coronary heart disease (CHD) whereas low levels coincide with low rates of CHD (Pooling Project Research Group 1978; Stamler et al. 1986; Anderson et al. 1987; Law et al. 1994). In accord, RCTs demonstrate that reducing serum cholesterol lowers risk for both CHD and stroke (Lipid Research Clinics Program 1984; Rossouw et al. 1990; Scandinavian Simvastatin Survival Study Group 1994; Shepherd et al. 1995; Lewis et al. 1998; Downs et al. 1998; The Long-Term Intervention With Pravastatin In Ischemic Disease Study Group 1998; Schwartz et al. 2001; Heart Protection Study Collaborative Group 2002; Serruys et al. 2002; Shepherd et al. 2002; Holdaas et al. 2003; Sever 2003; Colhoun et al. 2004; de Lemos 2004; Grundy et al. 2004; Pedersen et al. 2005; LaRosa et al. 2005; Ray et al. 2005; Amarenco et al. 2006). These congruent findings are the cornerstone of cholesterol guidelines.

The writing panel recognized different populations can differ in many important ways. Although the panel attempted to make the recommendations as uniform as possible, adjustments were made as needed for particular countries or populations.

Other organizations likewise have crafted treatment guidelines for dyslipidemia. For over 25 years the National Heart Lung and Blood Institute in the USA sponsored a National Cholesterol Education Program (NCEP). Its major product has been the reports of the Adult Treatment Panel (ATP). The most recent report is ATP III (Expert Panel 2001, NCEP 2002). ATP IV preparation has been suspended. The American Heart Association (AHA) and American College of Cardiology Foundation also issues guidelines; among these, secondary prevention guidelines are the most recent (Smith et al. 2011). The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) publish joint dyslipidemia guidelines (Catapano 2011). Organizations in other countries have developed guidelines both on lipid management and on cardiovascular risk reduction. The IAS stores all of these guidelines on its website (www.athero.org); they provide a treasure trove of information for those interested.

Primary Prevention

Introduction

Primary prevention seeks to prevent new onset atherosclerotic cardiovascular diseases (ASCVD). These diseases include coronary heart disease (CHD), stroke, and other atherosclerotic vascular diseases. ASCVD constitutes the leading cause of death in the world (Bonow et al. 2002); ASCVD morbidity and mortality moreover increase when countries become urbanized and industrialized (Global Atlas on Cardiovascular Disease Prevention and Control 2011). Since the prevalence of ASCVD rises with advancing age, the reduction in early deaths from infections and malnutrition increases ASCVD prevalence later in life. To reduce the worldwide burden of ASCVD, new onset disease must be decreased.

Pathogenesis of atherosclerosis. Some elevation of LDL seemingly is required for atherogenesis and hence ASCVD (NCEP 2002; De Backer et al. 2003; Genest et al. 2003). LDL accounts for more than 75% of atherogenic lipoproteins, the others being cholesterol-enriched remnants of triglyceride-rich lipoproteins. The latter play a larger role when triglycerides are elevated. When LDL infiltrates into the arterial wall, it initiates and promotes atherosclerosis; indeed an elevated LDL acting alone can cause ASCVD. The role of LDL is best exemplified by familial hypercholesterolemia (FH) (Brown and Goldstein 1976). Persons with FH commonly develop premature atherosclerosis and clinical ASCVD even in the absence of other risk factors (Goldstein et al. 2001). No other risk factor can do the same. In populations with low levels of LDL, the presence of other risk factors—cigarette smoking, hypertension, low HDL, or diabetes—does not lead to premature ASCVD (Grundy et al. 1990). These other risk factors appear to accelerate atherogenesis when LDL is high enough to initiate atherosclerosis. For this reason, the prime focus of prevention of ASCVD must be on lowering LDL and keeping it low throughout life. LDL promotes atherosclerosis in several ways. After entering the arterial wall, LDL is trapped and modified in a variety of ways; this leads to its uptake by macrophages (Tabas et al. 2007). Lipid-engorged macrophages are called foam cells. Expansion of regions of foam cells creates a fatty streak. The latter initiates smooth muscle proliferation, and this response forms a fibrous cap (fibrous plaque) (Wang et al. 2012). But continued LDL infiltration creates superficial lipid-rich areas in fibrous plaques. These areas are prone to breaking through the surface of the plaque; this breakage is called plaque rupture (Falk et al. 2013). When rupture occurs, plaque contents exude and precipitate a thrombosis. Plaque rupture and thrombosis in coronary arteries are responsible for acute coronary syndromes (ACS). Ruptures of carotid artery plaques produce strokes. All of these steps occur in patients with FH and demonstrate how elevated LDL alone can cause clinical ASCVD.

Since LDL is the predominant cholesterol-carrying lipoprotein, it has received the most attention in the atherosclerosis field. Yet very low density lipoproteins (VLDL) also are cholesterol enriched and have atherogenic potential (Chung et al. 1994; Rapp et al. 1994; Havel 2000; Veniant et al. 2000; Twickler et al. 2005; Varbo et al. 2013). The most atherogenic form of VLDL consists of partially degraded VLDL, called remnants. The atherogenic component of VLDL is its cholesterol, not its triglyceride. VLDL remnants are particularly enriched in

cholesterol. The importance of VLDL as an atherogenic lipoprotein is greatest in persons with hypertriglyceridemia (Jeppesen et al. 1998).

Risk factors for ASCVD accelerate the process described above. The *major risk factors* include cigarette smoking, hypertension, low HDL-C, and diabetes (NCEP 2002). They act at one or more steps in atherogenesis to enhance the formation of plaques or cause plaque rupture. The *emerging risk factors* are those that relate to atherosclerosis or its complications, although their mechanistic linkage to ASCVD is less well understood. These factors include proinflammatory and prothrombotic states, and some forms of dyslipidemia. *Underlying risk factors* are atherogenic diets, obesity, physical inactivity, and genetic tendencies. They underlie the development of major and emerging risk factors. *Advancing age* is usually listed as a major risk factor; but age per se is not a cause of atherosclerosis. Since atherogenesis progresses throughout life, a person's age commonly reflects atherosclerotic burden; importantly, however, the extent of atherosclerotic burden at a given age varies greatly from one individual to another. Age therefore is an imprecise indicator of risk for individuals.

Besides cholesterol lowering, primary prevention aims to reduce the accelerating risk factors—both major and emerging risk factors. Public health approaches to prevention focus on identifying and treating individuals with risk factors, especially smoking and hypertension. Primary prevention promotes lifestyle behaviors to prevent the development of accelerating risk factors as well as elevated LDL-C (Lloyd-Jones et al. 2010). When any of the major risk factors are identified, they too become targets for clinical intervention.

Lipoprotein classes. Three major classes of lipoproteins are LDL, VLDL, and high density lipoproteins (HDL). VLDL, derived from liver, carries both triglycerides and cholesterol. An elevated VLDL occurs with hypertriglyceridemia. Clinically LDL is identified as LDL cholesterol (LDL-C). Calculation of LDL-C is as follows: $L = C - H - kT$ where L is LDL cholesterol, C is total cholesterol, H is HDL cholesterol, T are triglycerides, and k is 0.20 if the quantities are measured in mg/dL and 0.45 if in mmol/L (Friedewald et al. 1972). LDL is derived from the catabolism of VLDL and exits the circulation mainly via LDL receptors on the surface of liver cells. Another triglyceride-rich lipoprotein is the chylomicron; this lipoprotein carries triglycerides derived from dietary fat. Although chylomicrons apparently are not atherogenic, chylomicron remnants may be. The sum of LDL-C and VLDL-C is called non-HDL-C (calculated as non-HDL-C = total-C minus HDL-C). Several studies show that non-HDL-C is more strongly related to risk for ASCVD than LDL-C (Cui et al. 2001; Farwell et al. 2005; Ridker et al. 2005; Liu et al. 2006; Holme et al. 2008; Robinson et al. 2009). In this document, the term *atherogenic cholesterol* can be applied to either LDL-C or non-HDL-C. It should be noted that total cholesterol (TC) is often used in risk assessment algorithms. TC is less reliable as a target of therapy, but it can be used if lipoprotein cholesterol values are not available.

HDL is derived in part through products released during triglyceride catabolism; other components are made by liver and gut. Epidemiological evidence suggests that HDL may protect against ASCVD (Gordon DJ et al. 1989; Fruchart et al. 2008; Chapman et al. 2011). A low HDL-C is widely recognized as a major risk predictor for ASCVD (NCEP 2002; Catapano et al. 2011; Teramoto et al. 2013). Several mechanisms are proposed whereby a high HDL-C may protect against ASCVD (Barter 2011). Clinical trials are currently underway to determine whether HDL-raising drugs will reduce risk of ASCVD. Regardless of outcome, HDL is a powerful indicator of risk and plays a key role in global risk assessment.

Lifestyle Influence on Lipoproteins and ASCVD Risk

Prevalence of ASCVD differs greatly in different regions of the world (Global Atlas on Cardiovascular Disease Prevention and Control, 2011). Although these differences may be due in part to genetic/racial factors, most investigators believe that lifestyle influences predominate (Keys 1980; Stamler 1982; Blackburn et al. 1987; Pietinen et al. 1996; Zhou et al. 2003; Knoop et al. 2004; Menotti et al. 2008; Fung et al. 2009). These influences include the composition of diet, total caloric intake and body weight, physical activity levels, and smoking habits (Lloyd-Jones et al. 2010; Mozaffarian et al. 2011). The former three affect LDL or other lipoproteins. If healthy life habits were to be adopted in high-risk populations, the prevalence of ASCVD almost certainly would decline.

Dietary lipids. Dietary fats in particular affect lipoprotein levels (Baum et al. 2012). Diets rich in saturated fatty acids and *trans* fatty acids raise LDL-C levels, as does a high cholesterol intake (NCEP 2002). In populations in which dietary saturated fatty acids and cholesterol are high, serum cholesterol levels are 10-25% higher than where intakes are low (Pietinen et al. 2001; Kok and Kromhout 2004). Unsaturated fatty acids (monounsaturated and polyunsaturated) do not raise LDL-C levels and represent an alternative to saturated fatty acids (Mensink et al. 2003). Diets high in carbohydrates will cause mild-to-moderate increases in VLDL and often reduce HDL levels. Unsaturated fatty acids do not affect LDL-C levels relative to carbohydrates. Replacement of carbohydrates with monounsaturated fatty acids has the advantage that it does not lower HDL-C (Grundy 1986). But there is little evidence that a higher VLDL and lower HDL-C on high carbohydrate diets are atherogenic; populations consuming low-fat, high-carbohydrate diets often have low rates of ASCVD, especially CHD.

Epidemiological studies indicate that countries having high intakes of saturated fats and cholesterol carry an increased prevalence of CHD (Keys et al. 1984; Peoples Republic of China-United States Cardiovascular and Cardiopulmonary Epidemiology Research Group 1992; Kromhout et al. 2000). In contrast, when intakes of saturated fats and cholesterol are low, whether from diets low in total fats or high in unsaturated fats, rates of CHD are relatively low. A few RCTs have evaluated the effects of saturated fats and unsaturated fats on incidence of CHD; those on a diet high in unsaturated fats had fewer CHD events (Dayton et al. 1969; Miettinen et al. 1972; Gordon 1995).

Cardioprotective foods and food patterns. Other dietary factors have been implicated in ASCVD risk (or protection there from). These include fruits and vegetables, fish, n-3 fatty acids, nuts, seeds, moderate alcohol intake, low sodium/high potassium intakes (Jenkins et al. 2000; Kris-Etherton et al. 2008; Banel and Hu 2009; Fraser 2009; Sabaté et al. 2010; Sofi et al. 2010; Mozaffarian et al. 2011; van den Brandt 2011;). In particular, available evidence indicates that increased consumption of some natural foods, such as tree nuts and peanuts, legumes, whole grains rich in soluble fiber like oats and barley, and cocoa products like chocolate, can reduce blood cholesterol by themselves, independently of the background diet (Ros and Hu 2013). Part of the cholesterol-lowering effects of seeds may be due to fiber content. It has been demonstrated that high intakes of soluble fiber will reduce serum cholesterol levels (Jenkins et al. 1993; Brown et al. 1999). Another category of plant products that reduce cholesterol levels are the plant sterols/stanols (Grundy et al. 1969; Miettinen et al. 1995; Gylling and Miettinen 1999; Blair et al. 2000; Katan et al. 2003). Intakes of about 2 gm

per day of these products will reduce serum LDL-C levels about 10%.

None of these factors have been subjected to rigorous RCTs except for n-3 fatty acids. In the JELIS study, a primary and secondary prevention study in patients with hypercholesterolemia, eicosapentaenoic acid (EPA) reduced risk for major coronary events when combined with a statin (Yokoyama et al. 2007). Recently, an important RCT has tested the effects of a Mediterranean-type diet on CHD risk (Estruch et al. 2013). This was enriched with virgin olive oil or mixed nuts, thus high in unsaturated fats. A test of this diet showed that it protected against ASCVD (Estruch et al. 2013).

Obesity. Excess body fat adversely affects all of the lipoproteins. In some people, obesity raises LDL-C levels; but it more consistently raises VLDL and lowers HDL-C (Wolf and Grundy 1983). HDL-C can decline during active weight loss, with a typical return to baseline, or increase above baseline longer term if weight loss is maintained. In addition to improvement in lipid blood levels with nutritional and physical activity interventions, overweight, dyslipidemic patients may simultaneously experience improvement in lipid blood levels with fat weight loss promoted by weight management drug therapies as well as bariatric surgery (Bays et al. 2013). Epidemiological studies show that obesity is an underlying risk factor for ASCVD (Hubert et al. 1983; Park and Kim 2012); this risk is mediated largely through major risk factors, but possibly through emerging risk factors as well.

Physical inactivity. Epidemiological studies indicate that physical inactivity associates with increased risk for ASCVD (Thompson et al. 2003). Regular physical activity helps to prevent obesity with the accompanying beneficial effects on lipoproteins (Bays et al. 2013). Vigorous physical activity appears to independently lower triglycerides and raise HDL-C (Vanhees et al. 2012). Beyond effects on plasma lipids, physical activity may protect against ASCVD in a variety of ways (Physical Activity Guidelines Advisory Committee 2009; Li and Siegrist 2012).

Metabolic syndrome. Adverse risk factors induced by obesity and physical inactivity can aggregate to produce a multiplex risk factor for ASCVD and diabetes called the metabolic syndrome. This syndrome consists of atherogenic dyslipidemia (high triglyceride and low HDL-C), high blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. In many countries the prevalence of the metabolic syndrome ranges between 20% and 30% of the adult population; in some populations, the prevalence can be even higher (Grundy 2008). A clinical diagnosis of the metabolic syndrome based on consensus was recently published (Alberti et al. 2009). The criteria are shown in Table 1.

Table 2 lists country specific recommendations for waist circumference thresholds for abdominal obesity. The presence of the metabolic syndrome essentially doubles the risk for ASCVD (Gami et al. 2007; Mottillo et al. 2010). Of clinical importance, all of the risk factors associated with syndrome can be improved by lifestyle intervention (Orchard et al. 2005; Goldberg et al. 2012).

Tobacco use. Another lifestyle consideration is tobacco use, particularly cigarette smoking. This is a major cause of ASCVD worldwide and a high priority must be given to prevention or cessation of cigarette smoking as a lifestyle intervention (Global Atlas on Cardiovascular Disease Prevention and Control 2011).

Measure	Categorical Cut Points
Elevated Waist Circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	< 40 mg/dL (1.0 mmol/L) in males < 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol.

*It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.

†The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose n-3 fatty acids presumes high triglycerides.

‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

		Recommended Waist	
Population	Organization (Reference)	Men	Women
Europid	IDF (Alberti et al. 2005)	≥ 94	≥ 80
Caucasian	WHO (World Health Organization 2000)	≥ 94 cm (increased risk)	≥ 80 cm (increased risk)
		≥ 102 cm (still higher risk)	≥ 88 cm (still higher risk)
United States	AHA/NHLBI (ATP III*) (NCEP 2002)	≥ 102 cm	≥ 88 cm

Region	Source	Men	Women
Canada	Health Canada (Health Canada 2003; Khan et al. 2006)	≥ 102 cm	≥ 88 cm
European	European Cardiovascular Societies (Graham et al. 2007)	≥ 102 cm	≥ 88 cm
Asian (including Japanese)	IDF (Alberti et al. 2005)	≥ 90 cm	≥ 80 cm
Asian	WHO (Hara et al. 2006)	≥ 90 cm	≥ 80 cm
Japanese	Japanese Obesity Society (Oka et al. 2008)	≥ 85 cm	≥ 90 cm
China	Cooperative Task Force (Zhou 2002)	≥ 85 cm	≥ 80 cm
Middle Eastern, Mediterranean	IDF (Alberti et al. 2005)	≥ 94 cm	≥ 80 cm
Sub-Saharan African	IDF (Alberti et al. 2005)	≥ 94 cm	≥ 80 cm
Ethnic Central and South American	IDF (Alberti et al. 2005)	≥ 90 cm	≥ 80 cm

*Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for CVD and diabetes at waist-circumference thresholds of ≥ 94 cm in men and ≥ 80 in women and identify these as optional cut points for individuals or populations with increased insulin resistance (Grundy et al. 2005; NIH 1998; WHO 2000; Health Canada 2003; Khan et al. 2006; Graham et al. 2007; Hara et al. 2006; Oka et al. 2008; Examination Committee of Criteria for “Obesity Disease” in Japan; Japan Society for the Study of Obesity 2002; Zhou et al. 2002; Alberti et al. 2005).

Lipid Lowering Drugs and ASCVD Risk

Statins are powerful LDL lowering drugs. They block cholesterol synthesis in the liver and raise LDL receptors, which remove LDL from the blood stream. Statins also lower VLDL, the other atherogenic lipoprotein. These agents reduce LDL-C by 25-55%. A wealth of RCT evidence demonstrates that statins decrease risk for ASCVD events in both primary and secondary prevention (Grundy et al. 2004; Cholesterol Treatment Trialists’ (CITT) Collaboration et al. 2010, 2012). In 5-year RCTs they reduced risk for ASCVD events by 25-45%; it is estimated that long-term treatment will produce even greater risk reduction (Law et al. 2003). Statins are first-line drug treatment in both primary and secondary prevention.

Statins have proven to be safe for most patients (Pasternak et al. 2002; McKenney et al. 2006; LaRosa et al. 2013). They do not cause liver disease, cataracts, or hemorrhagic stroke. Rare patients experience muscle damage characterized by marked elevations of creatine kinase, rhabdomyolysis, hemoglobinuria and acute renal failure. This is most likely to occur in who have complex medical problems and/or who are taking multiple medications. Predisposing medications are cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs. The combination of gemfibrozil with a statin is more likely to cause myopathy than is fenofibrate.

The most common side effect of statins is myalgia. Up to 10% of patients taking statins complain of muscle aches, weakness or other symptoms (Bruckert et al. 2005; Rosenbaum et al. 2012); consequently some people are unable or unwilling to continue their statin. The extent to which myalgias are actually due to statins is disputed (Thompson et al. 2003; Parker et al. 2013). For patients who complain of myalgias on statin therapy, alternative approaches thus must be employed to obtain the needed LDL reduction. These include maximizing lifestyle therapies or using other lipid-lowering drugs. In some patients, statins can cause moderate rises in transaminases, which are not a sign of true hepatotoxicity but may require reassurance (Bader 2010). Recently statins have been linked to new onset diabetes (Sattar et al. 2010; Preiss et al. 2011). The risk seems small, is of questionable clinical relevance, and is far outweighed by benefit of risk reduction for ASCVD. Most cases of diabetes appear in to occur in patients who already have borderline diabetes. Occasional patients complain of cognitive dysfunction while taking statins (Wagstaff et al. 2003; Golomb et al. 2008; Rojas-Fernandez et al. 2012). The possibility of these side effects indicates that statin therapy must balance benefit versus risk. Fortunately, the risk for serious side effects is low whereas the benefit for patients at risk for ASCVD can be great.

Ezetimibe is another LDL-lowering drug. It blocks the absorption of cholesterol by the intestine. This only moderately lowers LDL-C (15-25%) (Bays et al. 2001). Ezetimibe appears to be safe but has not been tested in RCTs against placebo in monotherapy for either safety or for efficacy to reduce ASCVD. The rationale for use of ezetimibe therefore is predicated on its ability to lower LDL levels. One use of the drug is for LDL lowering in patients with statin intolerance. Another is in combination with statins in patients with familial hypercholesterolemia. It can further be used with statins to achieve very low LDL-C levels in very high risk patients (Cannon et al. 2008). Recently the combination of ezetimibe and simvastatin was shown to reduce cardiovascular events in patients with chronic kidney disease (Baigent et al. 2011).

Fibrates are primarily triglyceride-lowering agents that also lower VLDL-C. Clinical experiences attests to their utility for treatment of severe hypertriglyceridemia to prevent development of acute pancreatitis. They also have been tested in many RCTs for prevention of CHD. A meta-analysis of these trials shows reduction for CHD morbidity of about 10% (Jun et al. 2010); however, there was not a reduction in total mortality. Another meta-analysis in patients with hypertriglyceridemia found a CHD risk reduction of approximately 25%. (Lee et al. 2011). Moreover, RCTs have shown that fibrates, specifically gemfibrozil, reduce risk when used as the sole lipid-lowering drug (Frick et al. 1987; Rubins et al. 1999); they therefore represent an alternative in people who cannot tolerate statins. The combination of a statin + a fibrate is attractive for mixed hyperlipidemia because of a favorable effect on the lipoprotein pattern; however, RCT evidence of incremental risk reduction when a fibrate is added to a statin is lacking. There is a need for a specific clinical trial to test the efficacy of add-on fibrate therapy in patients with mixed hyperlipidemia.

Niacin effectively lowers triglycerides and moderately raises HDL-C. It also moderately reduces LDL-C. In one secondary prevention trial niacin reduced CHD events and total mortality (Canner et al. 1986, 2005). Imaging studies further show that niacin combined with a statin reduces subclinical atherosclerosis (Brown et al. 2001; Taylor et al. 2005). In two large secondary RCTs, however, addition of niacin to maximal statin therapy failed to further reduce ASCVD events (AIM-High investigators 2011, HPS II THRIVE 2013). It is well known that niacin is accompanied by a variety of side effects; of note, in HPS II THRIVE, the combination

of niacin and simvastatin was accompanied by an increased risk of myopathy in the Chinese population (HPS2-THRIVE 2013). On the other hand, for patients with statin intolerance, the combination of niacin + ezetimibe can effectively lower LDL-C levels (Jelesoff et al. 2006); this represents an alternative to statin therapy but without proof of risk reduction.

LDL Cholesterol and Non-HDL Cholesterol as Major Targets of Therapy

Background. Most dyslipidemia guidelines recognize LDL as the major atherogenic lipoprotein and consequently identify LDL-C as the primary target of therapy (NCEP 2002; Catapano et al. 2011). In addition strong evidence points to VLDL as being atherogenic like LDL (NCEP 2002; Varbo et al. 2013); thus the claim can be made that combining LDL and VLDL makes non-HDL-C a preferred target in patients with dyslipidemia. Since the major apolipoprotein of both LDL and VLDL is apolipoprotein B (apoB), some investigators propose using total apo B as an alternative to non-HDL-C (Barter et al. 2006). These investigators cite studies suggesting that total apo B (or lipoprotein particle number) is more highly correlated with ASCVD risk than is LDL-C (Lamarche et al. 1996; Moss et al. 1999; Walldius et al. 2001; Blake et al. 2002; Rosenson et al. 2002; Talmud et al. 2002; Corsetti et al. 2004; Jiang et al. 2004; Shai et al. 2004; St-Pierre et al. 2005) and other reports suggest that apo B is more strongly correlated with ASCVD risk than is non-HDL-C (Sniderman et al. 2010, 2011, 2012). Therefore some workers contend that total apo B is the preferred target of lipid-lowering therapy. Other reports suggest that non-HDL-C equals or exceeds the predictive power of apo B (Ridker et al. 2005; Boekholdt et al. 2012; Robinson et al. 2012). Thus if total apo B is more predictive than non-HDL-C, the difference is small. A recent analysis of contemporary statin trials moreover demonstrated that on-treatment levels of non-HDL-C are more strongly associated with future risk of ASCVD events than either apo B or LDL-C (Boekholdt et al. 2012). In the same analysis non-HDL-C explained a larger proportion of the atheroprotective effects of statin therapy than either apoB or LDL-C (Boekholdt et al. 2012). These findings favor the use of non-HDL-C over LDL-C as targets of therapy. Other reasons to place primacy on non-HDL-C are that it is less expensive to measure than apo B and does not require fasting as does LDL-C.

As for HDL-C, epidemiological studies show that levels of this lipoprotein are inversely associated with risk for ASCVD (Gordon et al. 1989). These studies suggest that HDL may be protective. Clinical trial evidence indicates that risk for ASCVD is modulated by HDL-C levels even when statin treatment has reduced LDL-C levels to below 70 mg/dL (1.8 mmol/L) (Barter et al. 2007). But because of a lack of evidence that raising HDL-C reduces risk for ASCVD, current treatment guidelines do not make a low HDL-C concentration a primary target of drug therapy. They do however support maximizing lifestyle therapies in an effort to raise HDL-C concentrations.

IAS panel deliberations. For historical and conceptual reasons, most panel members recognized LDL-C as the first target of clinical intervention for reducing ASCVD risk. Non-HDL-C (reflecting all atherogenic lipoproteins) was considered an equal target in patients with or without hypertriglyceridemia. Several panel members in fact favored replacing LDL-C with non-HDL-C as the primary treatment target. Others found apo B attractive as an alternative to non-HDL-C. They nonetheless recognized the increased cost of measuring apo B; most felt that any superiority of apo B over non-HDL-C is not sufficient to justify its routine measurement in either risk assessment or as a target of therapy (Ramjee et al. 2011). An optimal apo B level for primary prevention remains to be defined. According to one study, in untreated, high risk patients, an apo B level of < 90 mg/dl is roughly equivalent to an LDL-C level < 100 mg/dl and

a non-HDL-C level < 130 mg/dl; but during statin therapy, to consistently reach an apoB target of < 90 mg/dl it is necessary to reduce non-HDL-C to < 100 mg/dl or to reduce LDL-C to < 70 mg/dl (Ballantyne et al. 2008). A final issue with apo B in routine clinical management is a lack of standardization (Grundy et al. 2011). Since measurement of apo B is an immunoassay it suffers from inconsistencies in measurement technique. Finally, the panel counted a low HDL-C as a major risk factor and recommended it be a component of global risk assessment; moreover a low HDL-C was considered a reasonable target of lifestyle intervention but not of drug therapy.

Recommendation. Since LDL is the major atherogenic lipoprotein, LDL-C is accepted as the major target of lipid-lowering therapy. Non-HDL-C nonetheless is an alternate target and has growing advantages. Notably it includes atherogenic cholesterol-rich VLDL remnants; and it does not require fasting for accurate measurement. Thus, in this document, the term *atherogenic* cholesterol is used interchangeably with LDL-C and non-HDL-C. It is expected that in future guidelines non-HDL-C will replace LDL-C as the better target of treatment. Total apo B is an optional target, but is not recommended as a primary target treatment. Issues of cost, lack of standardization, and lack of consensus on its use stand in the way of making apo B the primary treatment target. A low HDL-C is a target of intervention, but predominately through lifestyle therapies. Since HDL-C is independently and inversely related to ASCVD risk, it is useful as a component of global risk assessment.

Other Lipid Measures in Primary Prevention

Background. Other lipid-related measures are either predictors of ASCVD or they are potential targets of therapy. Among these are triglycerides, lipoprotein subfractions, total cholesterol/HDL-C ratios, triglyceride/HDL-C ratios, lipoprotein (a) (Lp[a]), and lipoprotein-associated phospholipase A(2) (Lp-PLA2). Elevated serum triglycerides are a positive risk predictor for ASCVD (Austin 1991; Assmann et al. 1996; Jeppesen et al. 1998; Iso et al. 2001); however, except in cases of severe hypertriglyceridemia, they are not a direct target of therapy. High triglycerides are associated with elevated non-HDL-C, and for risk prediction and therapy, they are subsumed by the latter. Small, dense LDL particles likely carry ASCVD prediction (Austin et al. 1988; Gardner et al. 1996; St-Pierre et al. 2001; Blake et al. 2002; Kuller et al. 2002; Rosenson et al. 2002). Although positive prediction is undeniable, more small LDL particles occur in the presence of higher non-HDL-C. Effective treatment of the latter probably is sufficient. The total cholesterol/HDL-C ratio was previously promoted by Framingham investigators as a predictor of CHD (Castelli et al. 1992). Similarly the apo B/apo A1 ratio has been shown to be a strong predictor of CHD (Yusuf et al. 2004; O'Donnell et al. 2010). Both total cholesterol and HDL-C appear in Framingham global risk assessment, and so the predictive power of the ratio adds nothing to risk assessment. To date apolipoproteins and their ratios have not been incorporated into Framingham risk scoring. The triglyceride/HDL-C ratio has been shown to correlated with insulin resistance and risk for ASCVD (McLaughlin et al. 2003; Bhalodkar et al. 2006; Bittner et al. 2009; Hadaegh et al. 2009; Gasevic et al. 2012; Kang et al. 2012); its major usefulness is as a component of the metabolic syndrome. An elevated Lp(a) almost certainly is associated with a greater risk for ASCVD; thus, Lp(a) may have some utility in risk assessment (Nordestgaard et al. 2010). But except for a modest effect of niacin, there are no efficacious drugs currently available for reducing Lp(a). Lp-PLA2 is an inflammatory enzyme expressed in atherosclerotic plaques. A collaborative meta-analysis of 32 prospective studies showed that Lp-PLA2 is positively correlated with risk for ASCVD (Lp-

PLA2 et al. 2010). At present, however, its use as a predictor of ASCVD has not been fully developed.

IAS panel deliberations. The panel recognized that a variety of other lipid risk factors have predictive power for ASCVD. To date, however, these factors have not been incorporated into standard risk assessment tools such as the Framingham risk scoring. Their utility thus is either limited or uncertain. Furthermore their measurements add expense to routine risk assessment. Consequently they cannot be recommended for routine testing. In the hands of lipid specialists some of these tests may provide useful information. For example the panel recognized that the EAS recommends screening for elevated Lp(a) in those at moderately high or high ASCVD risk, and in selected patients, niacin therapy can be employed.

Recommendations. Estimation of fasting triglycerides is useful for calculating LDL-C levels; elevated triglycerides further support use of non-HDL-C as a treatment target. Determination of small dense lipoproteins is an option, but usefulness in prediction or therapy is largely subsumed by non-HDL-C. The total cholesterol/HDL-C ratio adds nothing to global risk assessment because the ratio is already part of the latter. Similarly, the triglyceride/HDL-C ratio is contained in the metabolic syndrome. An elevated Lp(a) signifies a greater risk in patients with multiple risk factors; its presence points to a need for more intensive management of other risk factors, notably atherogenic cholesterol. A high Lp-PLA2 appears to be predictive of ASCVD; but at present the test is not widely available.

Non-Lipid Emerging Risk Factors

Background. There are several so-called emerging risk factors for ASCVD (Ridker 2007; Casas et al. 2008; Catapano et al. 2011; Davidson et al. 2011). Among these are C-reactive protein (CRP), fibrinogen, plasma insulin, Lp-PLA2, homocysteine, and microalbuminuria. Among these CRP has received the most attention. Without doubt CRP carries predictive power. Some investigators contend that elevated CRP signifies need for statin therapy in a person otherwise at borderline risk (Wilson et al. 2008). One algorithm uses CRP along with other risk factors to calculate absolute risk; this is the Reynolds risk algorithm (Cook et al. 2012), (<http://www.reynoldsriskscore.org/>). Other researchers contend that emerging risk factors carry little utility in global risk assessment (Emerging Risk Factors Collaboration 2012). They argue that even if risk prediction with CRP (or other biomarkers of risk) is positive, the number of people who would benefit from screening is too small to justify the financial investment into routine measurement (Emerging Risk Factors Collaboration 2012).

IAS panel deliberations. Among the several non-lipid risk factors, only CRP was considered worthy of use in risk-assessment algorithms. There was not full agreement on its value, although it was acknowledged that an elevated CRP associates with increased risk for ASCVD. Measurement of CRP is an option in moderate risk patients as a guide the risk-reduction therapy. If CRP is to be measured, use of the Reynolds risk score deserves consideration.

Recommendations. C-reactive protein (CRP) measurement is an option in patients at moderate lifetime risk. If CRP is used, the most acceptable risk assessment tool is the Reynolds risk score.

Identifying Persons at Risk for ASCVD

Short-term risk assessment with major risk factors. Most guidelines adjust intensity of LDL-lowering therapy (and LDL-C goals) to absolute, short-term risk as determined by major risk factors and age. For primary prevention, several categories of risk are defined. Most algorithms estimate 10-year risk for CHD or ASCVD. In the USA, ASCVD is about one-third higher than CHD (2012 NHLBI Morbidity and Mortality Chart Book). (<http://www.nhlbi.nih.gov/resources/docs/cht-book.htm>). Although risk categories vary somewhat in different guidelines, risk typically is divided into three categories of 10-year risk: high, intermediate, and low. ATP III guidelines defined *high risk* as 10-year risk for CHD to be > 20%, *intermediate risk* is 5-20%, and *low risk*, < 5%. Intermediate risk was subdivided into *moderately high risk* (10-20) and *moderate risk* (2+ risk factors or ~ 5-9%). The EAS/ESC (Catapano et al. 2011) classifies risk according to 10-year risk for fatal cardiovascular disease: *very high* (> 10%), *high* (5-10%), *moderate* (intermediate) ($\geq 1\%$ and < 5%), and *low* (< 1%). EAS/ESC's high risk corresponds approximately to 10-year risk for ASCVD events of 15-30%. The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice propose similar risk assessment (Perk et al. 2012). In recent Canadian guidelines, risk categories were defined in terms of 10-year risk for CHD: high: $\geq 20\%$; intermediate: 10-19%; and low: < 10%. Brazilian guidelines used the same classification. Other countries propose similar although not identical categories. Australian guidelines categorized risk for CHD as high: > 15%/5 years (>~ 30%/10 years); moderate: 10-15%/5 years (~ 20-30%/10 years); and low: <10%/5 years (<~ 20%/10 years). Japanese guidelines defined three categories of 10-year risk for CHD death: high: > 2.0%, moderate: 0.5-< 2.0%; and low: < 0.5%.

ATP guidelines have used the Framingham risk algorithm to classify risk for hard CHD (myocardial infarction and coronary death) (NCEP 2002). The prevalence in the USA of three categories of 10 year risk for CHD ($\geq 20\%$; 10-19%; and < 10%) by age is shown in Figure 1.

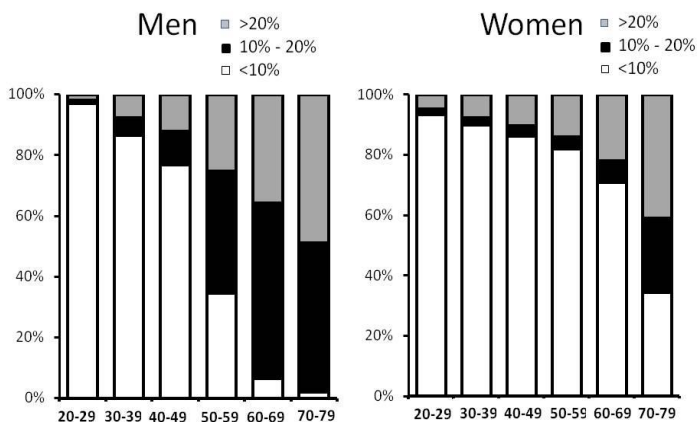


Figure 1. 10-year risk for CHD by age decade based on NHANES III data. Risk levels include high (> 20%), intermediate (10-20%), and low (<10%). (Modified from Ford et al. 2004)

The EAS/ESC employs an algorithm called SCORE to determine risk for fatal CVD. Another risk algorithm available in Europe is PROCAM (Assmann et al. 2007). The latter is similar to Framingham, except that it is adjusted for the European population (<http://www.chd-taskforce.de>). The question has been raised whether Framingham scoring and SCORE over-estimate the risk for CHD (Ramsay et al. 2011). This is a reasonable question because of the decline in CHD rates in higher risk populations. Available evidence indicates that Framingham scoring over-estimates risk in many countries (see below).

Risk assessment with major + emerging risk factors. As discussed before, a host of emerging lipid and non-lipid risk factors has been studied. Surprisingly few studies attempted to incorporate them into global risk assessment (including major risk factors). One exception is the metabolic syndrome which includes both emerging and major risk factors. In US populations, patients with the metabolic syndrome appear to be at moderately high risk for CHD (Lorenzo et al. 2007). In fact, postmenopausal women with metabolic syndrome appear to be at higher risk than predicted by Framingham scoring (Pelletier P et al. 2009). Several authors have emphasized the need to incorporate the metabolic syndrome into global risk assessment (Patt et al. 2003; Correll et al. 2006; Jaumdally et al. 2006; Arsenault et al. 2009). Framingham investigators have further reported that the trajectory for increasing risk is greater in persons with the metabolic syndrome than in those without (Franco et al. 2009). Thus, the presence of the metabolic syndrome may signify greater lifetime risk for a given Framingham risk score for 10-year risk. In a word, it is doubtful that risk associated with the metabolic syndrome is entirely subsumed by Framingham risk scoring. Moreover, there is little doubt that the metabolic syndrome is a stronger predictor of type 2 diabetes than is Framingham risk scoring (Wannamethee 2008; Wannamethee et al. 2005).

Framingham risk scoring does not include triglycerides as one of its components. Another risk assessment tool (PROCAM) does in fact include triglycerides in global risk assessment (http://www.chd-taskforce.com/procam_interactive.html) (Assmann et al. 2002). PROCAM investigators have reported that unadjusted Framingham scoring over-estimates risk in European populations (Hense HW et al. 2003). This seems to be a well-defined discrepancy between the populations of some European countries and that of the United States.

Small LDL particles associate with risk for ASCVD (Gardner et al. 1996; Austin et al. 1988; Arai et al. 2013). Framingham investigators have examined the relation between small LDL particles and ASCVD risk in their population (Kathiresan et al. 2006). They found small LDL particle number is elevated in the patients with the metabolic syndrome, with increases with the number of metabolic syndrome components, and most prominently with triglycerides and HDL-C. Whereas increased small LDL particle number identified the metabolic syndrome with high sensitivity, a higher number of small LDL particle number was not associated with greater CVD event rates in those with the metabolic syndrome. They made no attempt to integrate LDL particle number into Framingham risk scoring.

Finally, there has been much interest in integrating CRP into Framingham risk assessment. One approach has been to use CRP as a “tie-breaker” to decide whether to use cholesterol-lowering drugs for a given Framingham risk score. Framingham investigators indicate that this approach has promise (Wilson et al. 2008). But perhaps more promising is the inclusion of CRP values into multivariate analysis so as to produce a risk assessment tool that incorporates this measure. The Reynolds risk score is the best example of this approach (Cook et al. 2012), (<http://www.reynoldsriskscore.org/>).

In summary, there is promise for combining emerging risk factors with the major risk factors for estimating risk. To date, however, no consensus has gelled on how best to merge the two categories of risk factors. Consequently until a consensus has developed, it is preferable to use algorithms that incorporate only the major risk factors. This does not detract from the usefulness of metabolic syndrome as a long-term predictor of ASCVD and type 2 diabetes. Moreover for those who desire to use CRP as a component of risk assessment, Reynolds risk scoring is an option.

Risk assessment by atherosclerosis imaging. One promising approach to improved risk assessment is through atherosclerosis imaging. Measurement of coronary artery calcium (CAC) is the most widely used approach (Greenland et al. 2007). CAC is strongly correlated with coronary artery plaque burden (Rumberger et al. 1994, 1995; Budoff et al. 1996; Guerci et al. 1997; Schmermund et al. 1998). Carotid artery sonography is another methodology, although it does not have as much predictive power for CHD events as does CAC (O’Leary et al. 1999; Folsom et al. 2008; Nambi et al. 2010). Nonetheless, carotid artery imaging with ultrasound and other imaging modalities can be useful for identification at high risk for stroke (Wardlaw et al. 2009; U-King-Im et al. 2009). These modalities can be a useful guide for stroke prevention. There is little doubt that CAC adds predictive power when combined with Framingham risk scoring (Grundy 1999; Greenland et al. 2004; Sung et al. 2008; Elias-Smale et al. 2010; Okwuosa et al. 2011; Tota-Maharaj et al. 2012; Yeboah et al. 2013; Youssef et al. 2013).

According to a recent expert committee report, CAC testing can be used as an adjunct to risk-factor scoring in intermediate risk (moderate-to- moderately high patients (Greenland et al. 2007). CAC measurement in these patients could be a guide to intensity of statin therapy. Nonetheless, CAC testing is not widely available and is relatively expensive. How to use it appropriately in risk assessment is not well understood by most physicians. Therefore, CAC testing has not become a part of routine risk assessment.

Long-term risk assessment. The use of 10-year risk assessment as a sole indicator of risk is problematic because the purpose of primary prevention is to reduce lifetime risk, not 10-year risk. Estimates of 10-year risk, of course, underestimate lifetime risk except in the elderly population. This fact has led to increased interest in estimating lifetime risk (Lloyd-Jones et al. 2004; Pencina et al. 2007, 2009; Hippisley-Cox et al. 2010; Berry et al. 2012). Donald Lloyd-Jones has spear-headed interest in lifetime risk estimation (Lloyd-Jones et al. 1999, 2003, 2004, 2006, 2007; Marma 2010, Allen et al. 2012; Berry et al. 2012; Wilkins et al. 2012; Karmali and Lloyd-Jones 2013). A seminal report by Lloyd-Jones et al. (2006) was based on Framingham data. Risk factors included total cholesterol, systolic blood pressure, cigarette smoking, and diabetes. Four risk levels of cholesterol and blood pressure were identified. Cigarette smoking and diabetes were named major risk factors. Atherosclerotic CVD events were defined by the occurrence of myocardial infarction, coronary insufficiency, death resulting from coronary heart disease, angina pectoris, atherothrombotic stroke, intermittent claudication, or other cardiovascular death. This risk-assessment tool will hence be designated the *Lloyd-Jones/Framingham algorithm* (Table 3).

Risk Factor	Minor*	Moderate*	Major
Cholesterol (mg/dL)	180-199	200-239	≥ 240
Systolic blood pressure (mmHg)	120-139	140-159	≥ 160
Cigarette smoking	0	0	+++
Diabetes	0	0	+++

* The term minor refers to *not desirable* and moderate refers to the *elevated* used by Lloyd-Jones et al. (2006).

Table 4 provides an estimation of total CVD morbidity by age 80 from age 50 based on these four risk factors in the Framingham Heart Study (Lloyd-Jones et al. 2006).

Risk Factor	Men	Women
None	5%	8%
≥ 1 minor	25%	10%
≥ 1 moderate	38%	22%
1 major	45%	25%
≥2 major	60%	45%

A potential weakness of this algorithm is that it is based on estimated risk from age 50. However, it can reasonably be assumed that an individual's risk factors (other than age) will remain constant throughout middle age and into older years. Consequently basing the estimate of long-term risk starting at age 50 should give a fairly good estimate of absolute long-term risk.

In a more recent publication from The Cardiovascular Lifetime Risk Pooling Project (Berry et al. 2012), the same risk factors were used to estimate CVD mortality by age 80 from age 55 based on these same four risk factors as in the Lloyd-Jones/Framingham Risk Algorithm.

In another long-term risk predictor from the Framingham Heart Study, investigators (Pencina et al. 2009) related the number of major risk factors to 10-year and 30-year risk for CVD morbidity and mortality in 45-year-old men and women. This algorithm is similar to that developed by Lloyd-Jones et al. (2006).

Another risk predictor to estimate lifetime risk of ASCVD is the QRISK model (Hippisley-Cox et al. 2008; Hippisley-Cox et al. 2010; Collins and Altman 2012). This model was derived from a prospective cohort study with data collected from 563 general practices in the UK between 1994 and 2010. The study included 2,343,759 subjects in the derivation dataset and 1,267,159 in the validation dataset. Measures included smoking status, ethnic group, systolic blood pressure, total cholesterol/high density lipoprotein cholesterol ratio, body mass index (BMI), and family history of CHD disease in first degree relative aged < 60 years. CVD was defined as coronary heart disease, stroke, and transient ischemic attack. The QRISK2 lifetime risk calculator is available at www.qrisk.org/lifetime/. This calculator has the advantage that it is ethnic specific, at least for the ethnicities represented in the UK.

Risk assessment calibration. Risk factors affect total risk differently in various populations. This is because of differences in baseline population risk. The latter can be defined as the inherent risk of a population beyond traditional risk factors. A multitude of factors likely contribute to baseline population risk. In an effort to adjust risk scoring for different populations, Framingham Heart Study investigators and others have attempted to recalibrate Framingham scoring for several populations (Laurier et al. 1994; Liao et al. 1999; Menotti et al. 2000; D'Agostino et al. 2001; Thomsen et al. 2001; Diverse Population Collaborative Group 2002; Brindle et al. 2003; Empana et al. 2003; Hense et al. 2003; Marrugat et al. 2003; Liu et al. 2004; Asia Pacific Cohort Studies Collaboration et al. 2007; Eichler et al. 2007; Chow et al. 2009; Marques-Vidal et al. 2009; Rodondi et al. 2012). Recalibration coefficients derived from

available data are shown in the table below. In the United States, D’Agostino et al. (2001) found that Framingham scoring similarly predicted CHD risk in whites and blacks. However, the Framingham algorithm over-estimated risk in Japanese-Americans. Likewise in several studies, Framingham scoring over-predicted risk in several European countries and in China. It correctly estimated risk in rural Indians but under-predicted risk in Indians living in urban settings. It further correctly predicted risk in other Asians, including a predominance of Koreans (Asia Pacific Cohort Studies Collaboration et al. 2007). Relative to QRISK scoring, Framingham generally over-predicts risk (Hippisley-Cox et al. 2008; Collins and Altman 2012). These findings emphasize the importance of not using Framingham scoring without recalibration for determining who is a candidate for cholesterol-lowering drugs. When using one of the long-term, risk-assessment algorithms based on Framingham risk scores, the absolute risk can be approximated by multiplying the estimated risk by the recalibration coefficient (Table 5).

In some countries (e.g. Italy, China, and Japan), baseline population risk appears to be unusually low (Menotti et al. 1993; Campbell et al. 1998; Yokokawa et al. 2011). This may be due in part to a lifetime of relatively low LDL-C levels, but other poorly defined factors likely account for the low population risk. In Asian countries, hypertension appears to be the dominant risk factor, and stroke incidence rivals that of CHD (Singh et al. 2000). Nonetheless, all of the major risk factors contribute to risk and all deserve clinical attention in proportion to their severity.

Reference	Cohort	Men	Women	Combined
Eichler et al. (2007)	Italy			0.37
	Scotland			0.91
	Germany			0.43
	France			0.41
	UK			0.76
	Ireland			0.76
	Australia			0.90
	New Zealand			1.15
Murrugat et al. (2003)	North East Spain			0.37
Marques-Vidal et al. (2009) (2009)	Switzerland	0.48	0.44	
Brindle et al. (2003)	Britain	0.57		
Chow et al. (2009)	Rural India	1.0	0.8	
	Urban India	1.81	1.54	
Asia Pacific Cohort Studies Collaboration (2007)	“Asian” (enriched in Korean)	1.02	0.96	

Liu et al. (2004)	China	0.36		
D'Agostino et al. (2001)	Japanese American	0.50		
	Native American	0.80	0.70	

IAS panel deliberations. For primary prevention, the panel generally favored moving to a lifetime (long-term) risk prediction for clinical intervention on LDL-C (and atherogenic lipoproteins). At least four algorithms are available: two from Framingham, The Cardiovascular Lifetime Risk Pooling Project, and QRISK. With QRISK, risk can be estimated on-line. QRISK is attractive because it is ethnic specific. The committee identified the following categories of risk for ASCVD to age 80 years. Outcomes are those defined by Framingham (myocardial infarction, coronary insufficiency, death resulting from coronary heart disease, angina pectoris, atherothrombotic stroke, intermittent claudication, or other cardiovascular death). QRISK should slightly under-predict these outcomes because it includes fewer endpoints than Framingham.

The panel emphasized that without absolute risk projections for different populations, absolute risk estimations for individuals will be open to some question. It is clear from Framingham studies in different populations that the relative impact of risk factors on absolute risk is highly consistent. Since European risk assessment is based on CVD mortality, the results of Berry et al. (2012) could be employed to classify long-term CVD mortality risk as follows: low risk (< 10%), moderate risk (10-15%), moderately high > 15-29%, and high risk (\geq 30%). But the IAS panel favored using the Framingham total CVD data to estimate long-term risk (Lloyd-Jones et al. 2006). Since risk factors worsen ASCVD risk, attention must always be given to the management of risk factors themselves. This is particularly the case when risk factors are present in young adults; standard risk algorithms underestimate the long-term impact of major risk factors present in young adults. Indeed, regardless of age, all accelerating risk factors—whether cigarette smoking, hypertension, or diabetes—deserves clinical intervention. The same is true for elevated LDL-C. Once intervention is initiated, global risk will change. Therefore global risk calculations are not fixed entities. For example, treatment of any risk factor will lower the risk and can downgrade a person to a lower risk category. There is a tendency to pigeon-hole a person based on a single risk assessment. The fact that risk category is modifiable along with changes in risk factors illustrates the weakness of global risk assessment for defining a person's true risk status. One advantage of the QRISK algorithm is that it allows for adjustment of absolute risk based on changes in risk factor status.

Recommendation: For primary prevention, risk to age 80 for ASCVD can be stratified into high (\geq 45%), moderately high (30-44%), moderate (15-29%), and low (< 15%) (Table 6).

Table 6. Long-term Risk for ASCVD by age 80 (from age 50)	
Long-Risk Category	Absolute Risk for ASCVD
Low	< 15%
Moderate	15-30%
Moderately high	30-44%
High	≥ 45%

Four risk assessment tools are available (see above). Three estimate long-term risk for CVD morbidity (Lloyd-Jones et al. 2006; Pencina et al. 2009; QRISK) and one gives risk for CVD mortality (Berry et al. 2012). The QRISK has the advantage that it is ethnic specific (at least for the UK). QRISK may be reliable for all of Western Europe. Estimation of Framingham long-term risk allows for recalibration of risk in many countries. Therefore for world populations the IAS recommends using the Lloyd-Jones/Framingham algorithm (Lloyd-Jones et al. 2006) for estimating absolute risk for total ASCVD to age 80. The calculated risk should then be recalibrated based on the coefficients determined by national comparisons with Framingham estimates. If recalibration values are not available, it may be more prudent to focus treatment on individual risk factors.

Optimal levels of LDL-C (or non-HDL-C) for Primary Prevention

Background. What constitutes an optimal LDL-C (or non-HDL-C) for lifetime prevention of ASCVD? Cholesterol-lowering RCTs were not specifically designed to test efficacy at various goals for LDL-C (or non-HDL-C); according to some researchers the optimal LDL-C for lifetime prevention in persons without ASCVD therefore cannot be known. Some thus propose eliminating LDL-C goals altogether from treatment recommendations (Hayward et al. 2010). Considerable data can be used to inform optimal cholesterol ranges. Epidemiological studies in several populations show that risk for CHD falls progressively down to a total cholesterol of approximately 150 mg/dL (3.9 mmol/L) (Stamler et al. 1986; Law et al. 1994) (Figure 2). In populations, a total cholesterol of 150 mg/dL corresponds to an LDL-C of about 100 mg/dL (2.6 mmol/L) (or non-HDL-C of 130 mg/dL (3.4 mmol/L) (NCEP 2002).

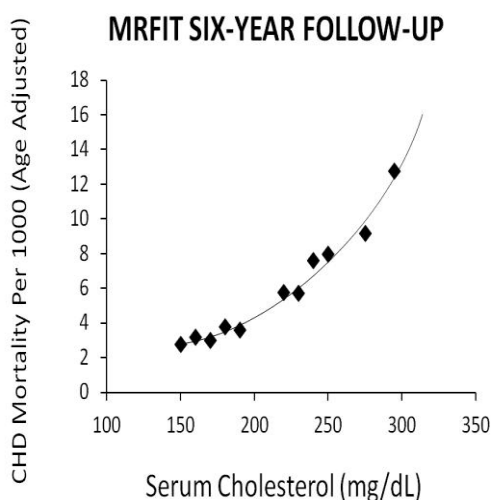


Figure 2. CHD mortality in the MRFIT study after 6 years of follow-up. The figure shows the curvilinear relationship between serum cholesterol levels and CHD mortality (from Stamler et al. 1986)

Genetic studies further show that genetic variants causing lifetime LDL-C levels of approximately 100 mg/dL (2.6 mmol/L) associate with very low rates of CHD (Cohen et al. 2006; Kathiresan 2008; Ference et al. 2012) (Figure 3). Third, clinical trials demonstrate that reducing LDL-C levels to near 100 mg/dL (2.6 mmol/L) or less over 5 years substantially reduces ASCVD events in primary prevention (Figure 4). Based on evidence of these types, ATP III (Expert Panel 2001) defined an LDL-C level < 100 mg/dL (2.6 mmol/L) as being optimal, whereas 100-129 mg/dL was called near optimal.

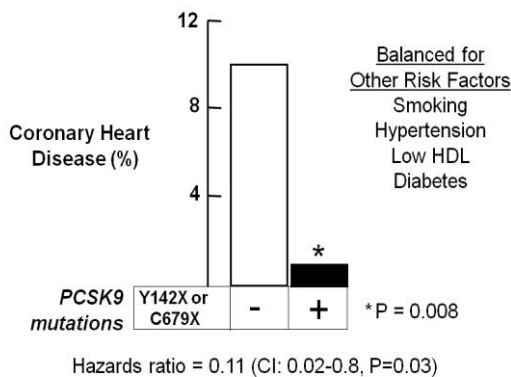
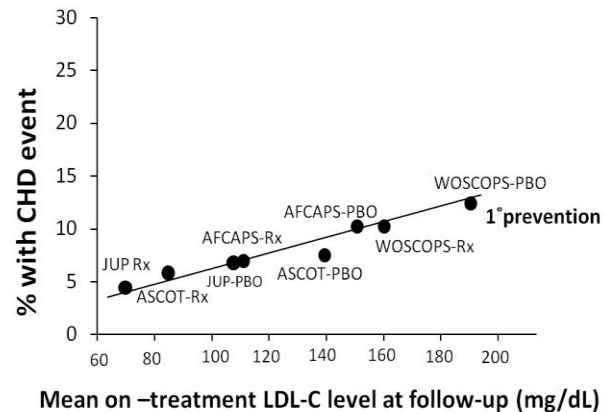


Figure 3. Benefit of lifetime of low LDL levels in patients with and without mutations in PCSK9. Those with mutations (+) had low LDL levels (< 100 mg/dL) and those without mutations (-) had higher levels (138 mg/dL). Otherwise they were balanced for risk factors--smoking, hypertension, low HDL, and diabetes. Those with mutations were virtually free of CHD whereas those without mutations had the expected prevalence of CHD. (Modified from Cohen et al. 2006)

Figure 4. Relation between LDL-C levels and prevalence of CHD in randomized clinical trials. Results are shown for placebo (PBO) vs. on-treatment (Rx) for WOSCOPS, AFCAPS-TextCAPS, ASCOT, and JUPITER. Although reduction of LDL-C to near 70 mg/dL appears to reduce lower risk compared to 100 mg/dL, the absolute beneficial effect of the lower level compared to 100 mg/dL is small (Abstracted from major primary prevention trials).



Most evidence for optimal LDL-C comes from higher risk populations. Some lower risk populations may well tolerate somewhat higher levels of LDL-C. In the Seven Countries Study, for example, baseline risk varied greatly from one country to another. CHD rates were much higher in northern Europe and USA than in southern Europe and Japan (Menotti et al. 1993). Lower CHD rates in the latter areas may have been due in part to a paucity of ASCVD risk factors, or in the case of Japan, to racial as well as environmental factors. Regardless, low-risk populations may be able to sustain ATP III's near-optimal LDL-C (100-129 mg/dL; 2.6-3.4 mmol/L) without higher ASCVD rates (Teramoto et al. 2013).

Beyond the concept of an optimal LDL-C, various guideline committees have set LDL-C goals according to risk category. For primary prevention, ATP III (NCEP 2002) set an LDL-C treatment goal of < 160 mg/dL (4.1 mmol/L) for persons at low risk; of < 130 mg/dL (3.4 mmol/L) for moderate or moderately high risk, and of < 100 mg/dL (2.6 mmol/L) for high risk. For Japanese, who have a lower population risk, national guidelines set LDL-C goals for three categories of risk are < 160 mg/dL (low risk), < 140 mg/dL (moderate to moderately high risk),

and < 120 mg/dL (high risk) (Teramoto et al. 2013). In 2004, an ATP III subpanel (Grundy et al. 2004) modified the LDL-C goal for moderately high-risk individuals to be < 100 mg/dL (2.6 mmol/L). EAS/ESC guidelines (Catapano et al. 2011) recommend an LDL-C goal of < 100 mg/dL (2.6 mmol/L) for high risk subjects and a goal of < 115 mg/dL (3.0 mmol/L) for moderate (intermediate) risk individuals. Recent Canadian guidelines recommended an LDL-C goal of < 80 mg/dL (2.0 mmol/L) for patients at moderately high-risk or high risk (Anderson et al. 2013); these guidelines, however, are heavily weighted to pharmacotherapy and do not discuss the relative benefits of different lower goals for LDL-C in primary prevention.

It is important to distinguish between optimal levels and goals of therapy. For primary prevention, the former refer to levels that minimize risk for ASCVD over a lifetime; the latter refer to concentrations that impart an acceptably lower risk at any given risk level. The concept of optimal level places the emphasis on strategies to maintain low cholesterol concentrations over a lifetime. Therapeutic goals are for persons who are already at a defined risk level. Existing epidemiological and genetic evidence support an optimal LDL-C of < 100 mg/dL. RCT evidence is congruent with this level even though trials were not designed to test for specific goals. Different national guidelines have identified various LDL-C goals in primary prevention at different risk levels. For persons at high risk, it is possible that goals of therapy will be even lower than optimal levels for lifetime prevention, e.g. for secondary prevention or high-risk primary prevention (Anderson et al. 2013). Less than optimal goals may be set for reasons of cost; in some countries it may not be practical to achieve optimal levels in spite of their desirability.

IAS panel deliberations. The majority of the IAS panel favored setting an optimal LDL-C for primary prevention to be a level of < 100 mg/dL (2.6 mmol/L) (or non-HDL-C of < 130 mg/dL [3.4 mmol/L]). This position is based on evidence from epidemiology and genetics augmented by limited RCT data. This conclusion however does not rule out the acceptability of attaining near-optimal LDL-C levels in people at low-lifetime risk due either to a paucity of other risk factors or because of a low baseline population risk. Neither does it rule out the setting of still lower cholesterol goals in patients with high accumulated risk, as is done in some national guidelines (Anderson et al. 2013).

Recommendation. The optimal LDL-C level for lifetime primary prevention is < 100 mg/dL (2.6 mmol/L) (or non-HDL-C of < 130 mg/dL). This level is especially desirable in high-risk populations. Near-optimal LDL-C levels (100-129 mg/dL [2.6-3.3 mmol/L]) (or non-HDL-C of < 130-159 mg/dL [3.4-4.1 mmol/L]) may be acceptable in low-risk populations or in individuals with a paucity of other risk factors. The IAS does not specifically prescribe “treatment goals” for atherogenic lipoproteins for different circumstances. Instead it identifies optimal levels and makes the general statement that the intensity of lipid-lowering therapy should be adjusted to long-term risk. Because of the great variety of circumstances affecting use of lipid-lowering therapy, these guidelines leave to clinical judgment and national recommendations on intensities of therapies.

Statin Therapy vs Treatment to LDL-C Goals

Background. Some authors dispute the use of LDL-C goals because of alleged lack of RCT evidence-specific goals (Hayward et al. 2012). They assert that LDL-C goals should be eliminated altogether; decisions about cholesterol-lowering drugs instead should depend entirely on estimated risk. This view makes statins the be-all and end-all of risk management.

Non-statin RCTs are considered insufficient to serve as the basis of recommendations (Ledford 2013).

Another view holds the following: The introduction of statins has created a “crisis” in preventive strategies. Potent statins are now inexpensive and largely safe. Would it not be better to ignore lifestyle factors and instead employ statins widely in the population (Wald and Law 2003)? This idea is known as the “polypill” approach because it includes drugs to lower both LDL and blood pressure (Lonn et al. 2010; Elley et al. 2012; Wald et al. 2012). The use of the polypill as a public health measure remains a possible approach for the future. Preliminary trials to test the strategy have been initiated (Indian Polycap Study (TIPS) et al. 2009; PILL Collaborative Group 2011). Still it is too soon to know whether the public and medical profession will accept the polypill model. Among unresolved issues are costs, drug side effects, and long-term compliance. The polypill idea casts the benefits of lifestyle interventions in a dim light. Many investigators in the atherosclerosis community do not share this pessimism towards lifestyle efficacy.

A commonly held view is that statins exert risk reduction through multiple actions (pleiotropic actions) (Mihos et al. 2010; Ma and Ma 2011; Porter and Turner 2011; Davignon 2012). Yet their primary mechanism of action is to reduce LDL (and atherogenic lipoproteins). RCTs with statins show that ASCVD reduction is proportional to LDL lowering (Baigent et al. 2005 (Figure 5). Statins seemingly are like other LDL-lowering agents and are not unique except in LDL-lowering potency. Other dietary and drug cholesterol-lowering agents show a similar risk reduction for a given degree of LDL cholesterol lowering (Figure 6). The strong relation between reductions in LDL reduction and ASCVD risk allows for the defining of optimal LDL-C levels; and this relation justifies defining treatment efficacy in terms of LDL-C levels achieved.

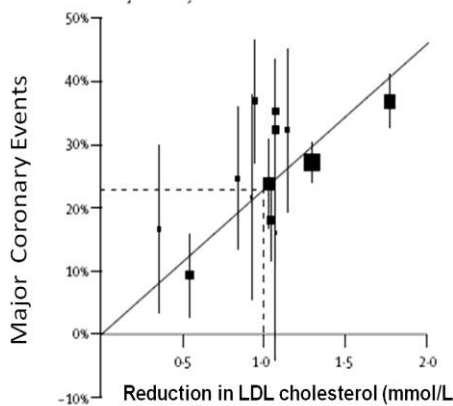


Figure 5. Results from the Cholesterol Treatment Trialists’ Collaboration. The data show that an absolute reduction in LDL-C levels produces a constant risk reduction in major coronary events across all absolute levels of LDL-C. (from Baigent et al. 2005)

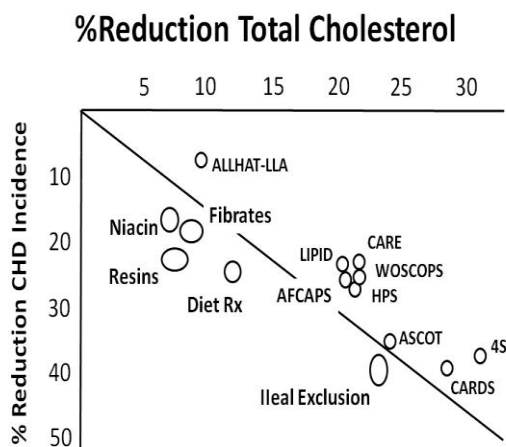


Figure 6. Comparison of percent reduction in total cholesterol and percent reduction in CHD incidence. Data abstracted from RCTs of statin trials and non-statin therapies for cholesterol lowering (NCEP 2002; Rossouw et al. 1990; Gordon 1995).

IAS panel deliberations. The majority of the IAS panel favored defining therapeutic efficacy in terms of the lipoprotein response and relative to an optimal atherogenic cholesterol level. The panel concluded that use of the polypill as a public health measure is premature.

Recommendations. For clinical cholesterol guidelines, levels of atherogenic cholesterol are the cornerstone for defining efficacy of therapy. Statin therapy undoubtedly represents first-line therapy when risk is high enough to warrant cholesterol-lowering drugs.

IAS Lifestyle Recommendations

The prime aim of lifestyle intervention is to reduce levels of atherogenic cholesterol. A secondary aim is to decrease other risk factors. The IAS panel made the following recommendations for maximal lifestyle therapy (MLT) to be used in the clinical setting.

LDL-raising lipids. Reduce intake of saturated fatty acids to < 7% of total calories, and at least to < 10%. Lower intake of *trans* fatty acids to < 1% of total calories (or even more) and dietary cholesterol to < 200 mg/day

Other dietary factors. Maintain a relatively high intake of fruits, vegetables, and fiber. Replace excess saturated fatty acids with either complex, fiber-rich carbohydrates (with emphasis on whole grains) or monounsaturated/ polyunsaturated fatty acids. The latter can be obtained through vegetable oils and nuts. Consume some fish rich in omega-3 fatty acids. Eat foods low in sodium and high in potassium. Processed meats and sugar-sweetened beverages, sweets, grain-based desserts and bakery foods should be limited. For individuals who choose to consume alcohol up to 2 servings daily for men and 1 serving daily for women is advised.

Consider using plant sterols/stanols (2 g/day) as a dietary adjunct along with soluble/viscous fiber (10 to 25 g/day) to further lower LDL-C levels. Several nations place limits on amounts of plant sterols/stanols that are allowed as nutritional supplements (because of questions about potential benefits vs. possible side effects). However, if plant sterols/stanols are available, they are a useful adjunct to lowering of LDL-C by dietary means.

Total fat. The IAS recommends flexibility in the intake of total fat depending on cultural preferences; alternatives are lower fat intakes of 20-25% of calories or even lower (as is typical in Pacific Rim countries), or higher fat intakes of 30-35% of calories or even higher (as is typical in Mediterranean countries). Any fat intake above that recommended for saturated and *trans* fatty acids should be in the form of unsaturated fatty acids. In addition, irrespective of the total fat content of the diet, nutrient needs must be met and energy intake be appropriate for maintenance of a healthy body weight.

Total calories. One ideal aim of dietary intervention is to achieve and maintain a desirable weight. The latter can be defined by either BMI or waist circumference. The World Health Organization defines two categories of overweight/obesity: BMI 25-29.9 kg/m² (overweight) and ≥ 30 kg/m² (obesity) (<http://www.who.int/mediacentre/factsheets/fs311/en/>). However, in some populations, such as South Asians, lower BMI cutpoints for overweight/obesity are recommended (Misra et al. 2009). For South Asians, normal BMI was defined as 18-22.9 kg/m², overweight as 23-24.9 kg/m², and obesity as ≥ 25 kg/m². These same thresholds may

apply to other areas of Asia. If a normal BMI cannot be achieved in obese individuals, achieving a 10% reduction in body weight is desirable. The latter has been shown to reduce the risk for diabetes and to improve the metabolic syndrome in patients with pre-diabetes (Eriksson and Lindgarde 1997; Pan et al. 1997; Tuomilehto et al. 2001; Knowler et al. 2002; Orchard et al. 2005; Goldberg et al. 2012).

An alternate indicator of obesity status is waist circumference. As noted before, waist circumference thresholds to define abdominal obesity have been identified for different countries.

Weight reduction can be facilitated by professional nutritional assistance when such is available.

Physical Activity. Engage in approximately 30 minutes of moderate intensity physical activity daily. The activity should be aerobic, 40-75% of aerobic capacity, for 5-7 days a week, for 30-60 minutes per day. For individuals trying to lose weight it is recommended that these individuals eventually progress to higher amounts of exercise (e.g. 250-300 min/week or > 2000 kcal/week of leisure-time physical activity) (American College of Sports Medicine 2013).

The metabolic syndrome is a multiplex risk factor for ASCVD and type 2 diabetes (Grundy 2007). It is becoming increasingly common throughout the world (Grundy 2008). It essentially doubles the risk for ASCVD (Gami et al. 2007; Mottillo et al. 2010). The syndrome deserves identification in routine clinical practice (Alberti et al. 2009). Patients with metabolic syndrome should receive maximal lifestyle therapy with increased emphasis on weight reduction and increased physical activity.

Tobacco use. The goal of clinical intervention is complete cessation of tobacco use. Quit rates are related to intensity of counseling. Components of effective counseling include problem-solving guidance for smokers and provision of social support. More intense practices are motivational interviewing, assessing readiness to change, referrals to smoking-cessation clinics, telephone "quit lines," and pharmacotherapy. Detailed national guidelines are available in many countries or can be obtained through the internet.

Practical suggestions for a healthy lifestyle. The American Heart Association Nutrition Committee (2006) has created a table of suggestions for a healthy lifestyle. The following is a summary of their suggestions (Table 7).

Table 7. Practical Tips for a Healthy Lifestyle (American Heart Association Nutrition Committee, 2006)
<ul style="list-style-type: none">• Limit your intake of saturated fat to 7% of energy, trans fat to 1% of energy, and cholesterol to 300 mg per day by<ul style="list-style-type: none">— choosing lean meats and vegetable alternatives;— selecting fat-free (skim), 1%-fat, and low-fat dairy products; and— minimizing intake of partially hydrogenated fats.• Know your caloric needs to achieve and maintain a healthy weight.• Know the calorie content of the foods and beverages you consume.• Track your weight, physical activity, and calorie intake.• Prepare and eat smaller portions.

**Table 7. Practical Tips for a Healthy Lifestyle
(American Heart Association Nutrition Committee, 2006) (con't)**

- Track and, when possible, decrease screen time (e.g., watching television, surfing the Web, playing computer games).
- Incorporate physical movement into habitual activities.
- Do not smoke or use tobacco products.
- If you consume alcohol, do so in moderation (equivalent of no more than 1 drink in women or 2 drinks in men per day).
- Food choices and preparation
Use the nutrition facts panel and ingredients list when choosing foods to buy.
- Eat fresh, frozen, and canned vegetables and fruits without high-calorie sauces and added salt and sugars.
- Replace high-calorie foods with fruits and vegetables.
- Increase fiber intake by eating beans (legumes), whole-grain products, fruits, and vegetables.
- Use liquid vegetable oils in place of solid fats.
- Limit beverages and foods high in added sugars. Common forms of added sugars are sucrose, glucose, fructose, maltose, dextrose, corn syrups, concentrated fruit juice, and honey. Some investigators contend that high fructose intakes are a risk factor for fatty liver disease and type 2 diabetes.
- Choose foods made with whole grains. Common forms of whole grains are whole wheat, oats/oatmeal, rye, barley, corn, popcorn, brown rice, wild rice, buckwheat, triticale, bulgur (cracked wheat), millet, quinoa, and sorghum.
- Cut back on pastries and high-calorie bakery products (e.g., muffins, doughnuts).
- Select milk and dairy products that are either fat free or low fat.
- Reduce salt intake by
 - comparing the sodium content of similar products (e.g., different brands of tomato sauce) and choosing products with less salt;
 - choosing versions of processed foods, including cereals and baked goods, that are reduced in salt; and
 - limiting condiments (e.g., soy sauce, ketchup).
- Use lean cuts of meat and remove skin from poultry before eating.
- Consume fish, especially oily fish, at least twice a week.
- Limit processed meats that are high in saturated fat and sodium.
- Grill, bake, or broil fish, meat, and poultry.
- Incorporate vegetable-based meat substitutes into favorite recipes.
- Encourage the consumption of whole vegetables and fruits in place of juices.

(American Heart Association Nutrition Committee, 2006)

IAS Cholesterol-lowering Drug Recommendations

When a decision is made to initiate LDL-lowering drugs, *statins* are first-line therapy. The choice of statins depends on availability and costs. The dose of statins should be adequate to

achieve optimal levels of atherogenic cholesterol. In patients who are statin intolerant, several options are available: switching to an alternate statin, reducing statin dose, every other day statins, use of alternate drugs (ezetimibe, bile acid resins, niacin) alone or in combination, and maximizing lifestyle changes. Combined drug therapy, i.e. statin + other cholesterol-lowering drug (ezetimibe and/or bile acid resin) is a reasonable option in patients with severe hypercholesterolemia.

Specific Forms of Dyslipidemia in Primary Prevention

The IAS panel made the following consensus recommendations for special circumstances.

Very high LDL-C levels constitute a higher risk condition and deserve more intensive LDL lowering therapy. About one in 500 patients has a monogenic cause for of hypercholesterolemia. Most such patients will have a mutation in one of three genes: LDL receptors (familial hypercholesterolemia); PCSK-9; or apolipoprotein B. Because of the high lifetime risk of patients with familial hypercholesterolemia, attention must be given from an early age to effective cholesterol lowering (National Institute for Health and Clinical Excellence 2008; Daniels et al. 2011; Goldberg et al. 2011; Watts et al. 2011). Other cases of severe hypercholesterolemia likely will have polygenic hypercholesterolemia. In some patients with severe hypercholesterolemia, it may not be possible to achieve optimal LDL-C concentrations with the combination of lifestyle and statin therapies; in this circumstance, combination drug therapy (e.g. statins + ezetimibe and/or bile acid resins and/or niacin) may prove efficacious. In patients with extremely high LDL-C, e.g. homozygous familial hypercholesterolemia, LDL apheresis may be required to retard atherogenesis (Thompson 2010; Stefanutti et al. 2013). Finally, recently in the USA, the FDA approved use of lomitapide and mipomersen as adjunct to diet and drugs in severe familial hypercholesterolemia. Both of these drugs inhibit the production of lipoproteins containing atherogenic cholesterol.

Hypertriglyceridemia. Observational evidence strongly suggests that mixed hyperlipidemia (elevated LDL-C + elevated VLDL-C) raises risk more than high LDL-C alone (Frick et al. 1987; Wiesbauer et al. 2009). Therapy of mixed hyperlipidemia is simplified by making non-HDL-C the treatment target. This is particularly so when the serum triglycerides is < 500 mg/d (5.7 mmol/L). An optimal non-HDL-C for primary prevention will be a level of < 130 mg/dL (3.4 mmol/L). Statins lower non-HDL-C as effectively as they lower LDL-C. Whether the combination of statins with fibrates or niacin is efficacious in primary prevention is uncertain.

Patients with severe hypertriglyceridemia (TG > 500mg/dL; 5.7 mmol/L) are at increased risk for acute pancreatitis (Murphy et al. 2013). The higher the triglyceride level, the greater is the risk. Clinical experience shows that use of fibrates or niacin in patients with severe hypertriglyceridemia will reduce risk for acute pancreatitis. High intakes of omega-3 fatty acids are an alternative to drug therapy for treatment of severe hypertriglyceridemia.

Adjusting Intensity of Cholesterol-lowering Therapy to Absolute Risk

Background. As mentioned before, some researchers hold that decisions about lipid treatment should be based exclusively on calculated risk for ASCVD; accordingly LDL-C levels should be ignored both at baseline and on-treatment (Hayward et al. 2006; Krumholz and Hayward 2010; Hayward et al. 2011). In this opinion, risk itself is the target of therapy. An alternate view identifies elevations of atherogenic cholesterol as the underlying cause of ASCVD. If

true, treatment intensity should not be independent of atherogenic-cholesterol levels. Hence all persons without ASCVD ideally would achieve optimal atherogenic-cholesterol levels. Since most people in high-risk populations have atherogenic-cholesterol levels above optimal, most should benefit by some form of cholesterol-lowering intervention. Whether to drive atherogenic cholesterol to optimal levels depends on cost-benefit-safety factors. Available therapeutic options are therapeutic lifestyle changes and cholesterol-lowering drugs (i.e. statins or other drugs). Most agree that lifestyle intervention is the first option of therapy and is universally needed for maximum risk reduction; nonetheless drug therapy will be warranted in some persons to attain optimal atherogenic-cholesterol levels. Once the decision is made to use drugs, the aim should be to achieve optimal atherogenic-cholesterol concentrations. Considerations for each risk category can be briefly reviewed.

For practical purposes, high risk can be defined as one of the following: (a) a risk for ASCVD \geq 45% up to age 80, (b) diabetes plus other risk factors (Solano and Goldberg 2006), (c) familial hypercholesterolemia (Civeira 2004), and possibly chronic kidney disease (Polonsky and Bakris 2012). For primary prevention, current guidelines generally agree cholesterol levels in high-risk persons should be lowered to the optimal range (Grundy et al. 2004; Catapano et al 2011; Anderson et al. 2013). Although drug therapy may be required to achieve optimal atherogenic-cholesterol levels, use of maximal lifestyle intervention will make it possible to use lower doses of drugs and will reduce risk in ways other than cholesterol reduction.

Moderately high risk can be defined as (a) a risk for ASCVD to age 80 of 30-44%, (b) diabetes without other risk factors (Adler 2008; Wannamethee et al. 2011), (c) chronic kidney disease (Tonelli et al. 2012), and (d) metabolic syndrome in higher risk populations (Lorenzo et al. 2007; Hoang et al. 2008). For persons at moderately high-risk, several guidelines endorse reduction of atherogenic cholesterol to the optimal range, i.e. LDL-C of < 100 mg/dL (2.6 mmol/L) (Grundy et al. 2004; Catapano et al. 2011, Anderson et al. 2013). These same guidelines allow use of cholesterol-lowering drugs combined with lifestyles therapies to achieve these low levels. Even so, use of cholesterol-lowering drugs in moderately high risk persons to achieve a low LDL-C is not universally accepted (Teramoto et al. 2007). In some countries, use of drugs in this risk category is considered too expensive for the health care system to support.

Moderate risk is here defined as risk for ASCVD to age 80 year of 15-29%. Maximal lifestyle therapy is generally advocated for this risk range. Whether to recommend cholesterol-lowering drugs is disputed. Some investigators oppose treatment of lower risk individuals with statins (Mascitelli and Goldstein 2012; Newman et al. 2012). A recent meta-analysis of RCTs nonetheless suggests some benefit can be attained in moderate risk persons (Cholesterol Treatment Trialists' (CITT) Collaboration et al. 2012). Long-term treatment of such people moreover might magnify benefit (Brown and Goldstein 2006; Steinberg and Grundy 2012). To resolve this question to everyone's satisfaction, a clinical trial may be required (Domanski et al. 2011). One factor to consider in persons at moderate risk is the baseline level of atherogenic cholesterol. There is almost universal agreement that those with very high LDL-C concentrations (> 190 mg/dL) should be treated with drug therapy; in these individuals, LDL-C should be reduced as much as possible (NCEP 2002; Catapano et al. 2011). For those with high LDL-C (160-190 mg/dL), treatment with cholesterol-lowering drugs seems reasonable. Whether statin treatment in moderate-risk individuals with marginally high LDL-C (130-159 mg/dL) is warranted is uncertain. Although such individuals might achieve some risk reduction from statin therapy, maximizing lifestyle therapies should provide a similar benefit.

Some investigators have questioned whether statins will reduce risk in women without ASCVD; they note a lack of benefit in reducing total mortality (Walsh and Pignone 2004; Kendrick 2007; Bukkapatnam 2010). Even reports that LDL-lowering therapy does not reduce ASCVD mortality note that morbidity is decreased. Evidence for reduction in ASCVD morbidity with statin therapy has been strengthened by the JUPITER trial and follow-up meta-analysis of all primary prevention trials in women (Ridker et al. 2008; Mora et al. 2010). On the basis of RCT data it is reasonable to treat women similarly to men, provided they fall into the same risk categories. By these criteria, many fewer women will qualify for cholesterol-lowering drugs than men.

Next must be considered the question of employing statin therapy in older persons (> 65 years). Risk assessment tools for older persons are limited. A reasonable approach is to estimate 10-year risk using Framingham scoring (recalibrated for country). The on-line calculator (<http://hp2010.nhlbi.nih.net/atp/iii/calculator.asp?usertype=prof>) estimates risk for hard CHD. The resulting value can be elevated by approximately one-third to obtain total ASCVD. The resulting estimate will give a rough estimate of long-term risk category. The result should assist in deciding whether to use statin therapy. There is RCT evidence that statin therapy will reduce ASCVD risk in older persons (Shepherd et al. 2002).

IAS panel deliberations. The IAS panel favored efforts to achieve optimal levels of atherogenic cholesterol in primary prevention. However, the intensity of this effort should be conditioned by considerations of long-term risk, costs of intervention, and safety. The panel emphasized that all persons at risk deserve maximal lifestyle therapy. Use of statins generally should be reserved for persons at high or moderately high risk. The judicious use of lifestyle therapies plus the availability of generic statins nonetheless will make it possible to inexpensively attain optimal LDL-C levels in most patients. Whether to use statins in moderate-risk individuals depends on clinical judgment and national policies. Their use should be considered for persons with high or very high LDL-C concentrations. Women should be treated similarly to men when long-term risk is similar. Statin therapy has been shown to reduce risk in older persons; they should not be excluded from therapy when risk is moderately high or high. Nonetheless, clinical judgment is required for decisions about drug therapy in older persons. They frequently are treated with multiple drugs, and the costs and possibilities of drug interaction must be kept in mind (Grundy 2006).

Recommendations. To reduce long-term risk for ASCVD in primary prevention it is ideal to achieve atherogenic cholesterol in the optimal range. Several factors must be kept in mind when deciding how low to drive atherogenic cholesterol. Lifestyle therapies are first-line intervention; but depending on risk status, drug therapies may be necessary. A general recommendation for adjusting intensity of therapy to absolute risk is shown in Table 8.

Risk Level to age 80 yrs	Low (<15%)	Moderate (15-24%)	Moderately High (25-40%)	High (>40%)
Therapeutic Intensity		Moderate	Moderately High	High
Specific therapy	Public health recommendation ^a	MLT ^b +CLD ^c optional ^d	MLT ^b +CLD ^c consideration ^e	MLT ^b +CLD ^c indicated ^f

^a Persons at low risk for ASCVD should be treated according to national recommendation for the general public. These recommendations should accord with IAS recommendations for lifestyle therapies.

^b MLT = maximal lifestyle therapies

^c CLD = cholesterol-lowering drug, usually a statin

^d Cholesterol-lowering drug therapy usually reserved for patients with high levels of atherogenic cholesterol.

^e Statin therapy is widely recommended for this risk category, although it is not accepted in many countries because of cost considerations. If drugs are employed, the dose should be adequate to achieve optimal atherogenic-cholesterol levels.

^f Cholesterol-lowering drug therapy is usually indicated in this category. The dose should be adequate to achieve optimal atherogenic-cholesterol levels.

Management of Non-lipid Risk Factors in Primary Prevention

Every major risk factor deserves clinical attention. Non-lipid risk factors either accelerate atherogenesis or predispose to thrombotic events. It is true that cholesterol-lowering therapy will reduce risk for ASCVD events in the presence of all other risk factors. This fact is behind the concept of treating “risk” with LDL-lowering therapy. In primary prevention, however, attempting to treat non-lipid risk factors with LDL lowering alone fails to achieve the benefit that can be obtained by therapy directed at other major risk factors. For instance, using cholesterol-lowering drugs to treat cigarette smoking or hypertension in young adults is inappropriate management.

Cigarette smoking is a major risk factor for ASCVD, but has many other adverse effects (e.g. lung cancer, chronic obstructive pulmonary disease and other cancers). The World Health Organization (WHO) gives a grim picture of tobacco-induced illness worldwide (WHO Fact sheet N°339 May 2012) (<http://www.who.int/mediacentre/factsheets/fs339/en/index.html>). Tobacco kills approximately 6 million people per year. About half of those who use tobacco are killed by it. The world has approximately one billion smokers, and most live in low- and middle-income countries. Tobacco use is increasing throughout the world. Thus clinical management of cardiovascular risk must stress smoking cessation or preventing tobacco use. Cessation of tobacco use should be an integral part of maximal lifestyle therapy.

Hypertension. Raised blood pressure is a major risk factor for coronary heart disease, stroke, peripheral vascular disease, and kidney failure (http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/index.html)http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/index.html). Hypertension causes about 13% of all deaths (7.5 million deaths per year). It occurs in

approximately 40% of people over age 25. Almost 1 billion people have uncontrolled hypertension. Among the major risk factors for ASCVD, hypertension is the foremost cause of disability (Ezzati et al. 2002). Lifestyle factors (obesity, high salt intakes, alcohol) contribute importantly to development of hypertension; but once hypertension takes hold, it can usually be controlled by judicious use of inexpensive anti-hypertensive agents.

Diabetes is widely recognized as a major contributor to ASCVD. According to the WHO, 347 million people have diabetes; and in 2004, 3.4 million died from this disease. Most diabetes occurs in low- and middle-income countries; but high-income countries with a high prevalence of obesity are by no means immune. The WHO projects that the presence of diabetes will rise by 2/3 in the next 20 years. An elevation of plasma glucose predisposes to microvascular disease, notably kidney failure and blindness; but there is considerable evidence that hyperglycemia either accelerates atherosclerosis or underlies ASCVD events. Most diabetes is type 2 and is often accompanied by other cardiovascular risk factors. The combination of hyperglycemia and other risk factors is commonly designated a high-risk condition for ASCVD events. In some populations the risk associated with type 2 diabetes approaches that of established ASCVD (NCEP 2002). But in other populations this is not true. Whereas hyperglycemia per se may be a risk factor, it cannot be universally identified as a CHD risk equivalent. When combined with other risk factors, the combination clearly enhances risk. Since the relation of diabetes and ASCVD is complex for different populations throughout the world, it is difficult to simplify the connection. To date there is limited evidence that treatment of hyperglycemia will reduce risk for macrovascular ASCVD (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008; Skyler et al. 2009). Even so, control of hyperglycemia will reduce microvascular disease. The most effective means to reduce ASCVD events in patients with diabetes is through the use of LDL-lowering drugs (Jellinger et al. 2012). Patients with type 1 diabetes are at increased risk for ASCVD (Orchard et al. 2006). Current guidelines indicate that patients with type 1 diabetes should be treated with cholesterol-lowering drugs similarly to those with type 2 diabetes when their risk factor profiles are similar (American Diabetes Association 2012).

Chronic kidney disease is associated with increased likelihood for ASCVD events and is generally considered to be a higher risk condition (Tonelli et al. 2012). The efficacy of statin therapy for reducing risk has been a subject of some uncertainty. However, a recent clinical trial showed clearly the benefit of intensive LDL-lowering therapy in patients with chronic kidney disease (Baigent et al. 2011). The value of statin therapy in patients with chronic kidney disease is supported by two recent meta-analyses (Barylski et al. 2013; Hou et al. 2013). Whether statins are useful in patients on hemodialysis is uncertain. For example, in the 4D trial, atorvastatin therapy showed no benefit in patients with diabetes who were undergoing hemodialysis (Wanner et al. 2005). This report however may not be the last word on the question; another trial suggested benefit in end-stage renal disease (Baigent et al. 2011).

Secondary Prevention

Secondary prevention extends to all patients with established ASCVD. These conditions include a history of CHD, stroke, peripheral arterial disease, carotid artery disease, and other forms of atherosclerotic vascular disease.

Identifying Optimal Levels of Atherogenic Cholesterol in Secondary Prevention

Background. In patients with existing ASCVD there is a wealth of RCT evidence showing that statin therapy reduces recurrent cardiovascular events (NCEP 2002; Grundy et al. 2004; Smith et al. 2011; Baigent et al. 2005; Cholesterol Treatment Trialists' (CTT) Collaboration et al. 2010). The CTT collaboration consisted mainly of secondary prevention trials (Figure 5). The relationship between LDL-C levels and CHD incidence is summarized in Figure 7 below. This fact has led some researchers to hold that statins should be used in secondary prevention without reference to baseline levels of atherogenic cholesterol or to goals of therapy. Nonetheless most evidence supports the view that the major benefit of statin therapy is achieved through lowering of LDL-C (or non-HDL-C). Earlier statin RCTs showed substantial CHD risk reduction following lowering LDL-C to the range of 100-125 mg/dL (Sacks et al. 2000).

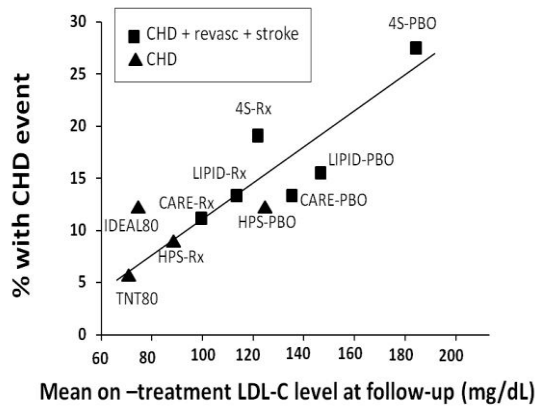


Figure 7. Relation between LDL-C lowering and % CHD in secondary prevention trials. The finding supports a constant relationship, even to LDL-C levels < 80 mg/dL. Rx = on-treatment arm of study; PBO = placebo arm. 80 = 80 mg atorvastatin. These data support an optimal LDL-C being near to or below 70 mg/dL in secondary prevention. (Figure abstracted from secondary prevention trials)

More recent RCTs reported that further reduction of LDL-C to a mean of 70-80 mg/dL causes additional falls in CHD events (Heart Protection Study, 2002; LaRosa et al. 2005, 2007; Pedersen et al. 2005; Cannon et al. 2004, 2005, 2006). These results are summarized in Figures 8-10.

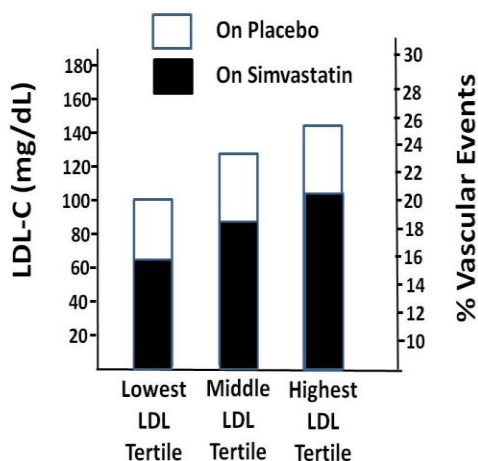


Figure 8. Risk reduction in the Heart Protection Study with simvastatin therapy at 3 levels of baseline LDL-C. The total height of the bars gives the LDL-C level and % vascular events on placebo by LDL-C tertile. The heights of the black bars give the LDL-C levels and % vascular events on simvastatin therapy. In the lowest tertile, starting simvastatin therapy with baseline level of 100 mg/dl lowered LDL-C to near 60 mg/dL and produced a corresponding lower % of vascular events. This finding supports an optimal LDL-C of < 70 mg/dL in secondary prevention. (From Heart Protection Study, 2002)

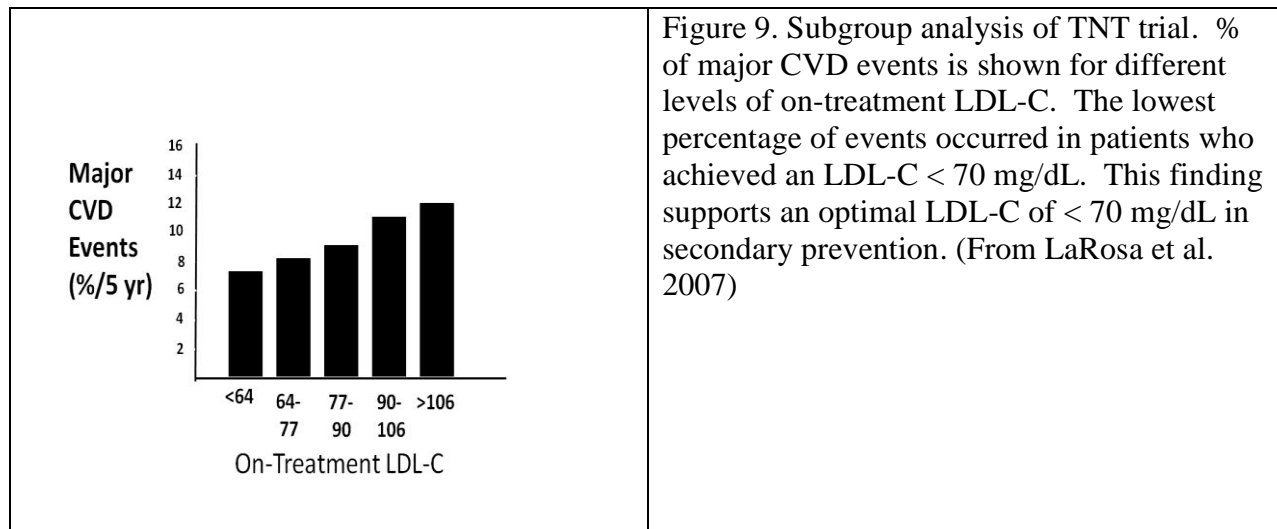


Figure 9. Subgroup analysis of TNT trial. % of major CVD events is shown for different levels of on-treatment LDL-C. The lowest percentage of events occurred in patients who achieved an LDL-C < 70 mg/dL. This finding supports an optimal LDL-C of < 70 mg/dL in secondary prevention. (From LaRosa et al. 2007)

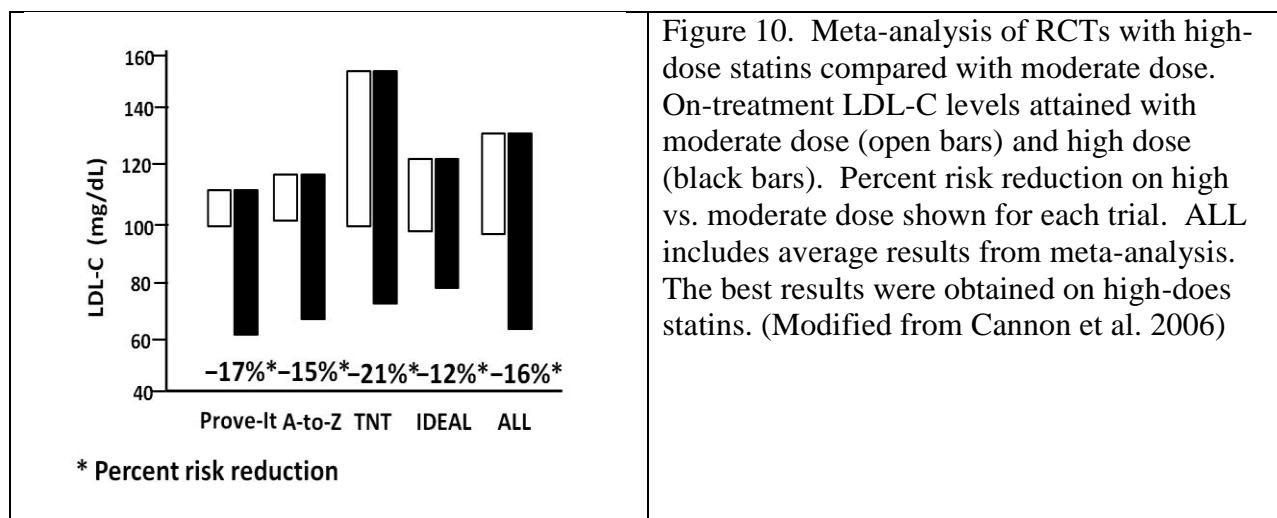


Figure 10. Meta-analysis of RCTs with high-dose statins compared with moderate dose. On-treatment LDL-C levels attained with moderate dose (open bars) and high dose (black bars). Percent risk reduction on high vs. moderate dose shown for each trial. ALL includes average results from meta-analysis. The best results were obtained on high-dose statins. (Modified from Cannon et al. 2006)

It is important to note that a portion of patients with acute coronary syndromes have baseline LDL-C levels below 100 mg/dL (2.6 mmol/L) (Sachdeva et al. 2009). The Heart Protection Study (2002) showed that patients of this type benefit from starting statin therapy even though their LDL-C levels are already low. Another trial demonstrated that lowering LDL-C to very low levels significantly reduced stroke (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators 2006). In none of these trials was there evidence that very low LDL-C levels produced adverse events.

To summarize, evidence supporting a lower level for optimal LDL-C in secondary prevention comes from clinical trials in ASCVD patients: TNT, IDEAL, PROVE-IT, HPS and their subgroup analyses. These trials all are consistent with “the lower, the better” for LDL-C. Since patients with ASCVD carry high-risk for future events and death, prudence favors a more aggressive preventive strategy than a more conservative one. Cholesterol-lowering drugs are

generally safe; therefore greater danger comes from under treatment than over treatment. If a precise optimal LDL-C level cannot be identified, the decision will have to be made whether LDL lowering should be more intensive or less intensive.

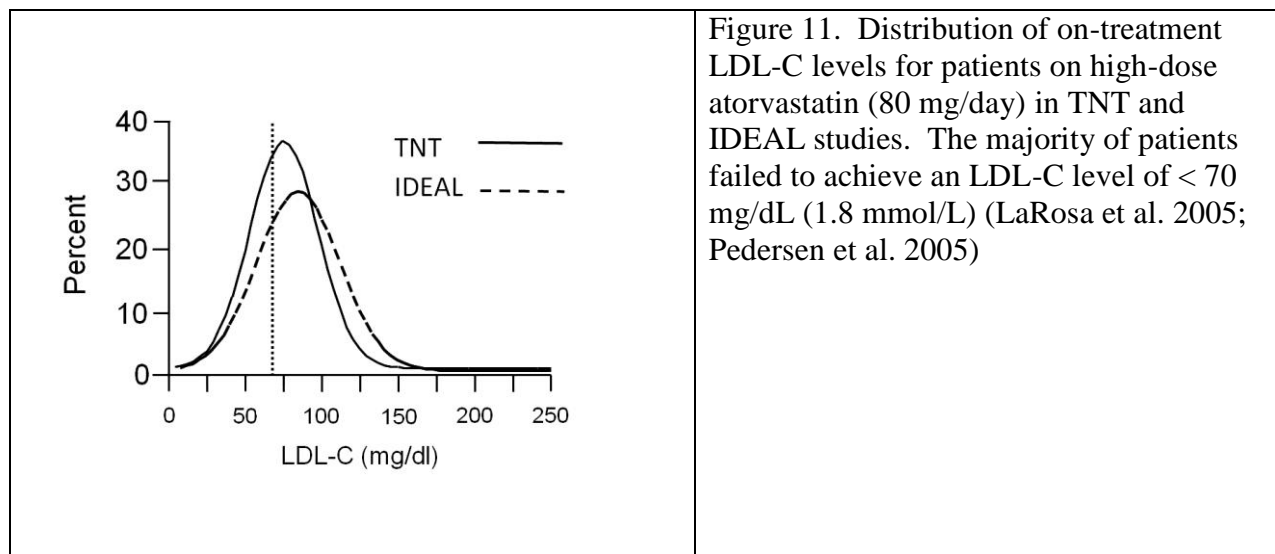
To determine whether other lipid targets might be superior to LDL-C for predicting ASCVD events in secondary prevention, investigators from TNT and IDEAL compared the relationships of on-treatment levels of LDL-C, non-HDL-C and apo B as well as ratios of total/HDL cholesterol, LDL/HDL cholesterol, and apolipoprotein B/A-I, with the occurrence of cardiovascular events in patients receiving statin therapy (Kastelein et al. 2008). In this study, on-treatment levels of non-HDL-C and apo B were more closely associated with cardiovascular outcomes than were levels of LDL-C. These data supported use of non-HDL-C or apo B targets of therapy in secondary prevention. A larger meta-analysis gave precedence to non-HDL-C over apo B as therapeutic targets in secondary prevention (Boekholdt et al. 2012).

IAS panel deliberations. The panel was aware that some investigators believe that patients with ASCVD should be treated with high-dose statins without regard to LDL-C concentrations (Ledford 2013). The argument in favor of such a recommendation is that RCTs have not identified an optimal LDL-C in secondary prevention. The panel did not agree with this line of reasoning. Instead, the panel found convincing evidence from RCTs and subgroups analysis of major RCTs for an optimal LDL-C in the range of 70 mg/dL (1.8 mmol/L) or lower. Future RCTs utilizing highly efficacious LDL-lowering drugs could uncover a still lower optimal range. In the meantime, an optimal LDL-C in the range of < 70 mg/dL seems acceptable. The panel further identified an optimal non-HDL-C as being < 100 mg/dL. The panel is aware that Ballantyne et al. (Ballantyne et al. 2013) reported that on treatment non-HDL-C levels of 90 mg/dL correspond to LDL-C levels of 70 mg/dL; but in large epidemiological studies, non-HDL-C concentrations generally are 30 mg/dL higher than LDL-C. Moreover, non-HDL-C has its greatest utility in patients with elevated triglyceride; in this population, the likelihood is that there will be a somewhat greater differential between LDL-C and non-HDL-C than observed by Ballantyne et al. (Ballantyne et al. 2013) for all patients. In the latter study, the differential between LDL-C and non-HDL-C in patients with hypertriglyceridemia averaged 24 mg/dL.

Recommendation. Optimal levels for LDL-C and non-HDL-C in secondary prevention are < 70 mg/dL (1.8 mmol/L) and < 100 mg/dL (2.6 mmol/L), respectively.

Cholesterol-lowering Drugs in Secondary Prevention

Background. There is abundant RCT evidence that statins are first-line therapy in secondary prevention. High-dose statins, which produced the greatest LDL lowering, gave the greatest risk reductions. Although RCT data support an optimal LDL-C for secondary prevention being < 70 mg/dL (1.8 mmol/L), these RCTs showed that the majority of patients receiving high-dose statins fail to reach this levels. An example is shown for the TNT and IDEAL trials in Figure 11. This figure shows the need for use of add-on drugs to achieve an optimal LDL-C level for secondary prevention.



Five classes of lipid-lowering drugs are available as potential add-on to statin therapy. These are bile acid resins, ezetimibe, nicotinic acid, fibrates (i.e. fenofibrate), and n-3 fatty acids. The only drug to be tested as add-on to maximal statin therapy in secondary prevention is niacin. In AIM-HIGH and HPS-2 THRIVE, adding niacin to maximal statin therapy failed to produce a further reduction in risk for ASCVD events. It might be noted however that combining statins with niacin produced a favorable effect on subclinical atherosclerosis; but clinical end-point trials have failed to document a reduction in clinical events. Although bile acids resins reduce CHD events in patients with very high LDL-C levels (Lipid Research Clinics Program 1984) they have not been tested as add-ons to maximal statin therapy. Ezetimibe is currently being testing as add-on to high dose statin in IMPROVE-IT (Cannon et al. 2008); however, the results of this trial have not been reported. Recently it was reported that the combination of statin + fenofibrate failed to reduce ASCVD risk more than statin alone in patients with diabetes (ACCORD Study Group et al. 2010); nonetheless, subgroup analysis of this trial suggested risk reduction in patients with hypertriglyceridemia and low HDL-C (Elam et al. 2011). Subgroup meta-analysis of other fibrate trials suggests that these drugs reduce risk for ASCVD events in patients with elevated triglycerides and reduced HDL-C (Lee et al. 2011). In a sizable secondary prevention trial, the addition of n-3 fatty acids to statin therapy (along with effective therapy of other risk factors) failed to produce an incremental reduction in ASCVD events (Kromhout et al. 2010). Moreover in the ORIGIN trial, daily supplementation with 1 g of n-3 fatty acids did not reduce the rate of cardiovascular events in patients at high risk for cardiovascular events (ORIGIN Trial Investigators 2012). On the other hand, the JELIS trial showed a beneficial effect of EPA add-on in secondary prevention (Yokoyama et al. 2007).

IAS panel deliberations. The IAS panel recognized a lack of evidence for incremental risk reduction from adding a second cholesterol-lowering drug to maximal statin therapy. Further, considering the curvilinear relationship between LDL-C and CHD risk, it is not known how much additional benefit can be obtained by lowering LDL-C to well below 70 mg/dL (1.8 mmol/L). The failure of combining niacin with high-dose statin to reduce ASCVD events in AIM-HIGH (AIM-HIGH investigators 2011) and HPS2-THRIVE is sobering. On the other hand, most panel members felt that if statin therapy alone does not achieve an LDL-C < 70 mg/dL (1.8 mmol/L), adding a second cholesterol-lowering drug is warranted. Two recent

clinical trials have cast doubt on the benefit of supplementation of the diet with n-3 fatty acids (Kromhout et al. 2010; ORIGIN Trial Investigators 2012).

Recommendations. When statin therapy fails to achieve an LDL-C goal of < 70 mg/dL (1.8 mmol/L) on maximal therapy, consideration should be given to use of either a bile acid resin or ezetimibe as an add-on drug to achieve this level. If non-HDL-C and triglycerides remain elevated when the LDL-C goal is achieved, consideration can be given to adding a fibrate, niacin, or high doses of n-3 fatty acids for triglyceride lowering. Any statin add-on therapy must be used with the recognition that risk-reduction efficacy has not been documented on combined-drug RCTs. Further, low doses of n-3 fatty acids seemingly do not reduce risk in routine secondary prevention.

Treatment of Non-lipid Risk Factors in Secondary Prevention

Since ASCVD is a multifactorial condition, preventive therapy must be directed to all of the risk factors. The most recent inclusive guideline for secondary prevention has been published by the American Heart Association/American College of Cardiology Foundation (Smith et al. 2011). These guidelines have been recently endorsed by the World Heart Federation. Recommendations for hemoglobin A1C have recently been modified by the American Diabetes Association and the European Association for Study of Diabetes (Inzucchi et al. 2012, 2012)

Smoking: The goal is complete cessation. No exposure to environmental tobacco smoke.

Blood pressure: Should be reduced to levels < 140/90 mm Hg.

Physical activity: At least 30 minutes, 7 days per week (minimum 5 days per week).

Weight management: Achieve a body mass index of 18.5 to 24.9 kg/m².

Type 2 diabetes mellitus: Achieve a hemoglobin A1C appropriate to a patient's clinical condition.

Antiplatelet agents/anticoagulants: Aspirin 75-162 mg daily is recommended in all patients with coronary artery disease unless contraindicated. For other antiplatelet/anticoagulant agents, see national guidelines.

Renin-angiotensin-aldosterone system blockers: See national guidelines

β-Blockers: See national guidelines

Influenza vaccination: Patients with cardiovascular disease should have an annual influenza vaccination.

Other considerations: Identify and treat mental depression; employ cardiac rehabilitation when appropriate.

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