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Benefits & risks of statin therapy for primary prevention of cardiovascular disease in Asian Indians – A population with the highest risk of premature coronary artery disease & diabetes

Enas A. Enas, Arun Kuruvila, Pravien Khanna, C.S. Pitchumoni* & Viswanathan Mohan**

*Coronary Artery Disease in Asian Indians (CADI) Research Foundation, Lisle, IL, USA, *St. Peters Univeristy Hospital- Drexel University College of Medicine, New Brunswick, NJ, USA & **Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialities Centre, Chennai, India*

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Several reviews and meta-analyses have demonstrated the incontrovertible benefits of statin therapy in patients with cardiovascular disease (CVD). But the role for statins in primary prevention remained unclear. The updated 2013 Cochrane review has put to rest all lingering doubts about the overwhelming benefits of long-term statin therapy in primary prevention by conclusively demonstrating highly significant reductions in all-cause mortality, major adverse cardiovascular events (MACE) and the need for coronary artery revascularization procedures (CARPs). More importantly, these benefits of statin therapy are similar at all levels of CVD risk, including subjects at low (<1% per year) risk of a MACE. In addition to preventing myocardial infarction (MI), stroke, and death, primary prevention with statins is also highly effective in delaying and avoiding expensive CARPs such as angioplasties, stents, and bypass surgeries. There is no evidence of any serious harm or threat to life caused by statin therapy, though several adverse effects that affect the quality of life, especially diabetes mellitus (DM) have been reported. Asian Indians have the highest risk of premature coronary artery disease (CAD) and diabetes. When compared with Whites, Asian Indians have double the risk of CAD and triple the risk of DM, when adjusted for traditional risk factors for these diseases. Available evidence supports the use of statin therapy for primary prevention in Asian Indians at a younger age and with lower targets for low-density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein (non-HDL-C), than those currently recommended for Americans and Europeans. Early and aggressive statin therapy offers the greatest potential for reducing the continuing epidemic of CAD among Indians.

Key words Asian Indians - coronary artery disease - diabetes - myopathy - primary prevention - statin therapy

Introduction

Numerous large double blind randomized clinical trials (RCTs) with statins demonstrate significant benefit on cardiovascular disease (CVD) outcomes without any notable increase in non-CVD mortality[1,2]. Statins have become the first-line therapy for reducing the risk of CVD mortality and morbidity as well as the need for coronary artery revascularization procedures (CARP) in people who have suboptimal lipid profile, with or without other risk factors[2,3]. Statins inhibit the enzyme 3-hydroxy 3-methyglutaryl coenzyme A reductase (HMG-CoA reductase), which catalyzes the rate limiting step in cholesterol biosynthesis. The dose and potency of the statin used and individual responsiveness determine the magnitude of low density lipoprotein cholesterol (LDL-C) reduction and CVD benefit[2]. However, there is increasing concern about the reported increased risk of diabetes mellitus (DM) as well as muscle, liver, and kidney toxicity associated with statin therapy. The objective of this review is to examine the profound differences in magnitude of benefits and risks of statin therapy in primary prevention of CVD and the rationale for its expansive use at a younger age, especially in Asian Indians.

Global burden of CVD

Cardiovascular disease (CVD) is the number one cause of mortality, accounting for 30 per cent of all deaths worldwide. Annually, it causes 17 million deaths, including 7.6 million due to myocardial infarction (MI) and 5.7 million due to stroke with a cost of $863 billion[1]. Over 80 per cent of CVD deaths occur in low-and middle-income countries[1]. In developing countries, it causes twice as many deaths as HIV, malaria, and tuberculosis combined[2,4,5]. CVD is also a major contributor to morbidity, reduced economic activity and accounts for a large share of health service resources. India has a disproportionately higher burden of CAD than most developing countries. According to the official government projections, India will have 2.9 million CAD deaths in 2015, of which 1.16 million (40%) will be in people <45 yr of age[5]. In comparison, CAD claims only 400,000 lives annually in the United States with only one per cent of these deaths in Whites and 4 per cent among Blacks occurring in people <45 yr of age[6,7].

Central role of total, LDL, and non-HDL cholesterol in atherosclerotic CVD

Atherosclerosis accounts for the vast majority of CVD and elevated serum cholesterol is the foremost risk factor for both[8]. The average cholesterol level within a population is the most important determinant of the CVD risk of the population. The differences in average cholesterol levels between populations are determined largely by differences in diet[9]. Populations with higher dietary intake of saturated fat and lower intake of polyunsaturated fat (lower ratio of polyunsaturated to saturated fatty acids) have higher cholesterol levels[10]. Since the relation between blood cholesterol level and CVD risk is continuous, there is no definite threshold to initiate treatment[11]. If a threshold for "high cholesterol" is set at over 147 mg/dl, it would account for 4.4 million deaths and 40.4 million disability-adjusted life years (DALYs) worldwide[12].

Among the various components of total cholesterol, HDL is generally believed to be cardioprotective, whereas low and very low density lipoprotein (LDL, VLDL) and lipoprotein(a) [LP(a)] are highly atherogenic[13]. Elevated LDL-C plays a pivotal role in the development and progression of atheromatous plaque and its rupture causes most fatal and nonfatal MIs[14]. LDL-C level in human umbilical cord blood is low (25-30 mg/dl) and lower than the HDL-C level[15]. LDL-C is both a necessary and sufficient risk factor for atherosclerosis; necessary because atherosclerosis cannot be produced in experimental animals without some elevation in LDL-C and sufficient because advanced atherosclerosis with MI occurs in children with very high levels of LDL-C even in the absence of any other risk factors[16]. Moderate lifelong reduction in LDL-C level (<70 mg/dl) as seen in people with hypobetalipoproteinaemia is associated with substantial reductions in risk of CVD and MACE, even in the presence of highly prevalent non-lipid risk factors (smoking, hypertension, *etc.*)[17-19].

Studies show that VLDL-C or remnant cholesterol is as much if not more atherogenic than LDL-C[20-22]. The combined risk from LDL-C and VLDL-C is best assessed by calculating non–HDL-C, which contains all the apo B containing atherogenic lipoproteins[23]. It is estimated by simply subtracting HDL-C from the total cholesterol and can be done even from non-fasting blood. High Non–HDL-C level has been shown to be a strong predictor of severity of coronary atherosclerosis and MACE, particularly in patients who have elevations in triglycerides[24]. Non-HDL-C target is 30 mg/dl higher than LDL-C target[23].

Target goals for LDL-C non-HDL-C and Apo B

Numerous outcome trials of intensive statin therapy using atorvastatin 80 mg and rosuvastatin 40 mg have

corroborated a causal role for LDL-C in atherogenesis and the safety and the benefits of lowering LDL-C to very low levels[13]. The optimum LDL-C level is currently standardized at 40 mg/dl[25]. Grundy *et al*[25] have demonstrated a log-linear relationship between increased serum LDL-C levels and increased relative risk for CAD. The data plotted this way suggest that for every 1 mg/dl change in LDL-C, the relative CAD risk changes by 1 per cent[25]. Thus, an individual with an LDL-C of 70 mg/dl has a 30 per cent higher risk than one with an LDL-C of 40 mg/dl[25]. Regression studies have demonstrated that coronary plaques continue to accumulate when LDL-C is >60 mg/dl and substantial regression requires LDL-C closer to the optimum levels[26].

Non–HDL-C is highly correlated with Apo B; hence, non–HDL-C is an acceptable surrogate marker for Apo B in clinical practice, especially for monitoring the response to statin therapy[23]. The optimum level of non-HDL-C level is 70 mg/dl. The non-HDL target is <100 mg/dl in very high risk patients with an LDL-C target of <70 mg/dl; the non-HDL-C target is <130 mg/dl in high-risk people whose LDL-C target is <100 mg/dl. It is worth highlighting that patients with LDL-C <100 mg/dl, but with non-HDL-C >130 mg/dl have a 34 per cent increased risk of CVD underscoring the clinical importance of non-HDL-C[27]. A 40 mg/dl decrease in non-HDL-C achieved with statin therapy confers a 35-40 per cent reduction in CAD risk (1:1 relationship between per cent non-HDL-C lowering and CAD risk reduction)[22,24,28]. Non HDL-C can be used as the poor man's test for apo B with non-HDL-C <100 mg/dl corresponding to Apo B <80 mg/dl. Apo B target is <90 mg/dl in high risk patients and <80 mg/dl in very high risk patients[29-32].

Life-saving benefits of statin therapy in primary prevention of CAD

Cardiovascular disease is multi-factorial in its causation and lifestyle changes are the first line of any treatment strategy. Lowering LDL-C and non-HDL-C are important target for pharmacotherapy and statins are the first-choice agents for both[32]. Statins are also effective in halting the progression and even reversing coronary atherosclerosis, either alone or in combination with niacin[26,33].

High doses of atorvastatin and rosuvastatin lowers LDL-C and non-HDL-C by 50 per cent or more (Table I)[34]. Evidence from clinical trials has demonstrated that statin therapy can reduce the risk of death, CVD events and the need for CARPs by 25-60 per cent, depending on the magnitude of LDL-C lowering achieved[13]. The 2012 Cholesterol Treatment Trials'(CTT) Collaboration demonstrated a consistent 21 per cent relative risk reduction in MACE with statins per 1 mmol/l (39 mg/dl) reduction in LDL-C, regardless of the baseline risk[35]. Although individuals without previous vascular disease are at lower absolute risk, more than two-thirds of MACE occur among them[36]. The CTT Collaboration has also published analyses focusing on the comparison between high and low doses of statins. It demonstrated that intensive lowering of LDL-C provides substantial additional CVD event reduction without any corresponding increase in non-vascular mortality[2]. Benefits of statins are seen across a broad spectrum of patients – men and women, young and old, and in people with and without diabetes or prior diagnosis of CVD[13].

Several primary prevention trials (MEGA, WOSCOPS, ASCOT, and AFCAPS, JUPITER, *etc*.) have demonstrated a reduction in CVD outcome with statin therapy in people with LDL-C ranging from 108-190 mg/dl[13]. The JUPITER Trial involving 17,802 low-risk adults without CAD was terminated prematurely (in 19 months) due to a 44 per cent reduction in the primary end point[37]. Further analysis demonstrated a 65 per cent reduction in the primary end point among those who achieved LDL-C <50 mg/dl - a level considered unachievable and dangerous until that study[38].

The Cochrane review[32] updated the previous reviews by including all statin trials published since

Table I. Per cent reduction in lipid parameters with increasing statin doses

	LDL-C (mg/dl)	Non-HDL-C (mg/dl)	Apo B* (mg/dl)	Triglycerides (mg/dl)
Rosuvastatin (mg/day)				
5	-39	-35	-30	-15
10	-44	-40	-35	-19
20	-50	-45	-39	-20
40	-55	-50	-43	-22
Atorvastatin (mg/day)				
10	-36	-33	-28	-16
20	-41	-38	-33	-19
40	-46	-43	-37	-21
80	-50	-47	-41	-35

*Measured in 24,340; other lipids measured in 32,258 patients
Source: Ref. 34, Adapted with permission

Table II. Meta-analysis of statin outcome trials in primary prevention

Category	Risk reduction (%)	*P* value
All-cause mortality	14	<0.00089
Fatal and non-fatal CVD	25	0.0001
Fatal CVD events	17	0.014
Reduction in non-fatal CVD events	23	0.022
Fatal and non-fatal CAD	27	0.00001
Fatal CAD	18	0.0016
Non-fatal CAD events	33	0.00001
Coronary revascularization	38	0.009
Fatal stroke	37	<0.48
Non-fatal stroke	31	0.000072
Hospitalization	26	0.36

Source: Ref. 32
CVD, cardiovascular disease; CAD, coronary artery disease

2007 and reconciled the findings with those published by CTT collaboration[35]. A total of 56,934 participants in18 randomized trials included in the analysis showed consistent reductions in LDL-C that was associated with a significant reduction in mortality rates, CVD events, and interventions as shown in Table II[32].

Similar benefits were seen in statin trials that were stopped prematurely and in those running their planned course. After in-depth review of the safety profile, the researchers concluded that the benefits of statins far outweigh any risks of serious adverse effects. Specifically no excess of cancers was found and all-cause mortality was lower in those on statins[32]. No excess of combined adverse events, liver enzyme elevation, renal dysfunction or arthritis was found. However, an increase in the risk of DM, myopathy, rhabdomyolysis, and haemorrhagic stroke in people treated with statins was noted particularly among those treated with higher rather than lower doses of statins[32].

Statin therapy and all-cause mortality

An earlier systematic review of five statin trials (N=30,817) found no evidence for increased rates of non-illness mortality (accidents, violence or suicide)[39]. The JUPITER trial had previously shown strong evidence of a reduction in total mortality[37]. Data on all-cause mortality were available for 13 trials involving 48,060 participants. During observation, 4.4 per cent died in the statin group compared with 5.1 per cent in the placebo group with a number needed to treat for five years of 96[32]. When the data were pooled, there was a 14 per cent reduction in all-cause mortality that favoured statin treatment. The number of deaths prevented with statin therapy varies from 200 to 9,200 per million person-years of treatment, depending upon the baseline risk and the degree of LDL-C reduction achieved (Table III)[35].

Statin therapy and CAD events

Fourteen trials with 48,049 participants reported on combined fatal and non-fatal CAD events. The event rates were 4.6 per cent in the placebo group and 3.4 per cent in the statin group resulting in a 5-yr NNT (number needed to treat) of 56 and relative risk reduction of 27 per cent[32]. Statin therapy, on average, would reduce 11 MACE per 1,000 patients treated over 5 yr per 39 mg/dl reduction in LDL-C (2,200 per million person-years)[35]. However, the number of CVD events prevented with statin therapy varies from 1,200 to 28,400 per million person- years of treatment, depending upon baseline risk and the degree of LDL-C reduction achieved (Table III)[35].

Statin therapy and stroke

Lipid abnormalities, especially elevated LDL-C are strong predictor and statin therapy is associated with significant reduction in first and recurrent stroke. International guidelines advise almost universal use of statins for secondary prevention. Statin therapy upon hospital discharge after a stroke not only lowers the recurrence of stroke but also decreases CAD events and improves survival[40-42]. Conversely, statin withdrawal in the hospital, even for a brief period, is associated with worsened survival[43]. Any possible excess of haemorrhagic stroke is greatly outweighed by the protective effect against ischaemic stroke and CAD events. A 31 per cent reduction in fatal and 37 per cent reduction in non-fatal stroke was observed in the recent Cochrane review[32].

Statins and coronary artery revascularization procedures (CARPs)

Seven trials with 42,403 participants reported the need for CARPs and showed a 38 per cent reduction in the need for such procedures in the statin group[32]. The enormous costs of stents (₹200,000 to 500,000), especially in relation to the average annual income

Table III. Absolute reduction in major adverse cardiovascular events and deaths per one million person-years of statin therapy in primary prevention, according to baseline risk status and degree of LDL-C reduction

LDL reduction				
Annual risk (%)	39 mg/dl (1 mmo/l)	58 mg/dl (1.5 mmo/l)	78 mg/dl (2 mmol/l)	98 mg/dl (2.5 mmo/l)
Reduction in CVD events				
<1	1,200	1,600	2,000	2,400
>1 to <2	3,000	4,200	5,400	6,200
>2 to <4	6,200	9,000	11,400	13,600
>4 to <6	9,000	13,200	16,800	20,000
>6	12,200	18,600	23,800	28,400
Reduction in deaths				
<1	200	340	440	600
>1 to <2	800	1000	1,400	1,600
>2 to <4	1,600	2,200	2,800	3,400
>4 to <6	2,200	3,200	4,200	5,000
>6	4,000	6,000	7,600	9,200

Source: Ref. 35

(₹ 68,747 per year and 80 per cent living with <₹100/ day), makes CARP beyond the reach of most Indians. Besides, only <10,000 coronary bypass surgeries and <100,000 angioplasties are done annually in a population of >30 million CAD patients due to lack of facilities[44]. Statin therapy offers an effective alternative to these expensive procedures as well as to reduce CVD morbidity and mortality, especially in India, where the annual cost of statin therapy is approximately ₹ 2000 to 3000.

Statin therapy in low-risk people

A seminal finding in the updated Cochrane review[32] was the conclusive demonstration of significant benefit of statin therapy among the low-risk individuals who would not qualify for statin therapy by the European and Australian guidelines (which have set an annual risk >2 per cent as the threshold risk for statin therapy)[45]. There was 43 per cent risk reduction in low-risk (annual risk <1%) and 39 per cent risk reduction in intermediate risk individuals (annual risk 1-2%) giving NNT values of 167 and 67, respectively. Treatment of 1000 people for five years would prevent six MACE (1,200 per million) in those with annual risk <1 per cent increasing to 15 MACE (3,000 per million) in those with annual risk of 1 to 2 per cent[32]. The NNT is well within the range considered worthwhile for other primary prevention strategies such as hypertension treatment[32]. The potential adverse effects of statins among people at low risk of CVD were a concern in earlier trials[46,47]. The meta-analyses conducted by the CTT Collaboration showed no excess risk of cancers, or non-vascular mortality[35]. The totality of evidence now suggests that the benefits of treatment in low-risk subjects far outweighs any possible hazards[32].

Statin therapy in women

Women are generally considered to be at low risk, especially before 65 yr of age. Yet, women had equal and similar benefits as men in primary prevention[32]. A meta-analysis of 15 statin trials showed a MACE reduction of 19 per cent in women compared to 24 per cent among men. The CVD outcome was primarily driven by reductions in unstable angina and need for CARPs[48]. In addition to reducing MACE, statin use also reduces the risk of atrial fibrillation, gall stones and need for cholecystectomy in women[49,50].

Statins therapy in people with elevated lipoprotein (a)

Lp(a), the most dangerous genetic variant of LDL-C, is believed to be the second causal factor of atherosclerotic CVD. Lp(a) alters the balance between intrinsic thrombotic and thrombolytic milieu more than any other risk factor. The risk of CVD in patients with elevated Lp(a) is markedly increased (12-14 fold) when LDL-C is also increased. Lowering LDL-C to target or

preferably to near-optimal level with statins offers an opportunity to reduce the excess risk while effective therapy for lowering Lp(a) is being developed[51].

Statin therapy for elevated triglycerides

Elevated triglyceride (TG) levels (usually accompanied by low HDL-C levels, except in patients with high alcohol consumption) are often due to obesity, insulin resistance, high glycaemic load, and physical inactivity[8]. Lifestyle modification and/or withdrawal of the offending agent may be the most appropriate risk reduction strategy. Pharmacologic therapy, however, is recommended when the TG serum levels remain >500 mg/dl, to prevent pancreatitis[23,52].

Many physicians and medical practitioners are unaware of the TG lowering properties of statins; potent statins can lower TG to the same extent as it lowers LDL-C levels (1:1 ratio)[53]. Intensive statin therapy with atorvastatin 80 mg/day lowers LDL-C by 60 per cent, non-HDL-C by 53 per cent, and TG by 37 per cent, in patients with normal TG levels[54]. But in patients with elevated TG, atorvastatin 80 mg can decrease TG by 52 per cent (instead of 37%), VLDL-C by 62 per cent, and non-HDL-C by 52 per cent[54]. In addition, statin therapy produces very favourable changes in LDL and HDL particle size[55]. Most Asian Indians have combined dyslipidaemia (TG <500 mg/dl and non-HDL >130 mg/dl) and respond well to high dose atorvastatin or rosuvastatin with a 50 per cent reduction in LDL-C, non-HDL-C, and TG levels[13].

While the combination of ezetimibe or fenofibrate with moderate dose-statins appears to be reasonably safe, outcome data are scant for statin-fibrate combination therapy[13]. The results of the ACCORD Trial provide some assurance of benefits with statin-fibrate combination therapy in men with DM and high TG levels, although potential harm was reported in women and non Whites[56]. Bile-acid sequestering agents are contraindicated in patients with high triglycerides.

Statin therapy in patients with chronic kidney disease (CKD)

The rates of CVD events and mortality progressively increase as the kidney function deteriorates[57]. Dialysis patients have up to 40-fold higher all-cause mortality and 15-fold higher CVD mortality than the general population[58]. A meta-analysis of statin therapy in 48,429 patients with CKD (6,690 major CVD events and 6,653 deaths) showed a 23 per cent reduction in major CVD events, 18 per cent reduction in CAD events, and 9 per cent reduction in CAD or all-cause deaths[57]. Subgroup analysis demonstrated that the relative CVD risk reduction with statin therapy decreased in parallel with the decrease in glomerular filtration rate (GFR), including those receiving dialysis (CKD stage 2-3:31%; CKD stage 4: 22%; CKD stage 5 non-dialysis:18%; CKD stage 5 dialysis: 7%). However, the absolute risk reductions were comparable (stage 2-3:NNT-24; stage 4: NNT-36; stage 5: NNT-46). There was no significant increase in adverse events or the development of renal failure[57]. In addition to dyslipidaemia, additional risk factors specific to CKD include: calcium and phosphorus dysregulation, anaemia, increased oxidative stress, and high levels of homocysteine and Lp(a)[57]. Thus, some of the excess CVD observed in people with advanced CKD may not be atherosclerotic in nature, and therefore, not amenable to be reduced with statins[57]. These data support the use of statins in all stages of CKD including dialysis patients[57].

Statin therapy and metabolic syndrome

Metabolic syndrome (MS) in youth that persists into adulthood is associated with a 3-fold risk of subclinical atherosclerosis and a 12-fold risk of DM[59]. In the INTERHEART study[60], patients with MS had 3-4 fold risk of first MI with greater risk noted in women. A post-hoc analysis of the TNT trial showed that patients with MS had a 44 per cent higher risk of CVD events, compared to those without MS. Those randomized to intensive statin therapy had a 29 per cent lower risk of MACE compared to standard therapy[61]. Although patients with MS have a higher risk of developing DM, statin therapy provides the greatest risk reduction in people with DM[62,63].

Statin therapy in people with diabetes

Type 2 DM is associated with a 2 to 4-fold higher risk of CVD incidence and mortality compared to people without DM[65,66]. CVD accounts for 80 per cent of death and disability among patients with DM. Framingham Risk Score (FRS) and European SCORE prediction tools do not include DM. However, the SCORE and other data indicate that DM confers much greater risk than suggested by FRS with a relative risk of 5 in women and 3 in men[45,67]. Two of the three patients with multi-vessel disease or acute coronary syndrome (ACS) have known DM, undiagnosed DM or prediabetes[68]. In a study of Asian Indians with ACS (mean age 55 yr) 37 per cent had DM and 46 per cent had prediabetes with only 17 per cent having normal glucose tolerance[69]. Asian Indians have the highest

rates of DM-3 times higher than Whites, after adjusting for obesity and other risk factors for DM[70].

The CAD risk from DM is substantially greater among Asian Indians than in Whites. In an ongoing prospective study in the UK, nearly half of all CAD deaths among South Asians occurred in individuals with DM at baseline compared to only 13 per cent among Europeans[71]. Compared with those with no diabetes, DM increased CAD mortality nearly 3-fold among South Asians but only 1.5-fold among Europeans. Results of several studies show a 3 to 4-fold higher CAD mortality among South Asians with DM than Whites with DM (after adjustment for gender, age, educational level, smoking, hypertension, alcohol intake, and obesity)[72-74]. Thus, South Asians are markedly sensitive to the impact of DM on CAD risk. This increased risk of CAD among South Asians with DM is in sharp contrast to the 32 to 44 per cent lower risk observed among Blacks, Hispanics and other Asians[75,76].

Hyperglycaemia is a weaker risk factor for CAD than high hypercholesterolaemia or high blood pressure. A meta-analysis of DM patients showed that a 1-percentage point increase in glycosylated haemoglobin level confers an 18 per cent risk of CVD[77]. The magnitude of the benefit from intensive glycaemic control is substantially lower than that reported with tight control of blood pressure and LDL-C[78].

Randomized statin trials show that an 80 mg/dl reduction in LDL-C results in a decrease of CAD by 42 per cent, and stroke by 20 per cent[2]. Similarly, a 10 mm Hg decrease in systolic blood pressure results in 22 per cent reduction in CAD events and 41 per cent reduction in stroke[79-81]. In the CARDS Trial, atorvastatin 10 mg/day for four years in patients with DM reduced MACE by 36 per cent, CARP by 31 per cent, stroke by 48 per cent, and all-cause death by 27 per cent[64]. A meta-analysis involving 18,686 people with DM showed that statins would prevent 8,400 MACE per million person-years of therapy[82]. Statin therapy is now recommended for all diabetics >40 yr of age regardless of the baseline lipid levels[13]. The documented benefits of statin therapy is arguably more compelling than aspirin in primary prevention of CVD in patients with DM[83]. A systematic review of trials evaluating the benefit of aspirin therapy for primary prevention of CVD in 11,618 patients with diabetes showed no significant reduction in MACE[84,85].

Legacy effect of statins

Long-term follow up of statin trials has shown that the absolute reductions in MACE increase while the statin treatment is continued[2] and that these benefits persist for at least five years after the treatment has stopped, with no evidence of any adverse effects emerging with extended follow up[86-88]. The findings further suggest that the long-term persistent benefits are large enough to outweigh the small increase in the risk of DM and haemorrhagic stroke.

Benefits of lifelong reduction in LDL-C

The Mendelian randomization studies[89,90] indicate that optimum LDL-C may be even lower than the 40mg/dl, currently set as optimal based on statin trials[91], and the benefits of lifelong low LDL-C (as a result of genetic polymorphisms) is 3 times greater than those indicated by statin trials which typically last only for 5-6 years[37,92,93]. For example, in one land mark study, three per cent of the population had a nonsense mutation of *PCSK9* gene. Whites with this mutation had a 15 per cent reduction in LDL-C but 47 per cent reduction in CAD. Blacks with this mutation had even greater impact -28 per cent reduction in LDL-C and 88 per cent reduction in CAD[89]. A lifelong 39 mg/dl decrease in LDL-C from a *PCSK9* mutation has been shown to reduce CVD risk by 55 per cent[90]. Conversely, a lifelong 34 mg/dl increase in LDL-C doubles the risk of CAD. Other studies have also shown that a *PCSK9* mutation is associated with a 60 per cent lower risk of premature MI[94]. Together, these studies indicate that a lifelong 1 mg/dl decrease in LDL-C confers 1.5 to 2 per cent reduction in CVD - far greater than the 0.5 per cent reduction observed in randomized clinical trials in middle aged people[90]. These data underscore the rationale for maintaining low LDL-C throughout life, including childhood and adolescence.

Pleiotropic benefits of statins beyond LDL-C reduction

In addition to improving lipid profile, statins have several beneficial biological, off-target or pleiotropic effects that contribute to their overall clinical benefit. These include reducing platelet aggregation and thrombus formation, improving fibrinolytic profile and lowering inflammation and C-reactive protein (CRP)[95-97]. In a meta-analysis involving a total of 863,805 patients, statin therapy significantly reduced the risk of venous thromboembolism by 19 per cent,

whereas fibrate therapy significantly increased the risk by 58 per cent[98].

Statin therapy was significantly associated with a decreased propensity for atrial and ventricular arrhythmia and venous thromboembolism[99,100]. A systematic review of randomized controlled trials with statins showed 77 per cent reduction in atrial fibrillation in secondary prevention and a 40 per cent reduction in new onset atrial fibrillation[101]. Statin therapy decreases risk of venous thromboembolism in a variety of patients including cancer[102]. Fibrate therapy was associated with increased risk of gallstones (39%) and cholecystectomy[103]. In sharp contrast, statin therapy decreases the risk of gallstones and cholecystectomy (36%), possibly by decreasing hepatic cholesterol biosynthesis and decreasing cholesterol concentration in bile[104]. These additional benefits are not currently included as clinical endpoints in outcome trials and may further increase the cost-effectiveness of statins. Further, clinical trials may have underestimated the benefit of statin by excluding second and third MACE which account for about 20 per cent of all MACE. A summary of the benefits of statin therapy in primary prevention is given in Table IV[13,32,90].

Statin therapy - the foundation of preventive cardiology

The large body of knowledge gained over the past 50 years in the field of CVD suggests that more than 90 per cent of the CVD events and interventions, (at least before age 65), is due to failure of primary and primordial prevention, which could have prevented the development and growth of cholesterol plaque in the first place[105]. Regression studies indicate that plaques continue to accumulate when the LDL-C levels are >60 mg/dl and primary prevention trials indicate that 65 per cent event reduction can be achieved when LDL-C is lowered to <50 mg/dl[26,38]. Yet, unlike American guidelines, the various European guidelines limit statin therapy to those with annual risk >2 per cent (based primarily on what the society can afford)[45,106,107].

The evidence of overwhelming benefits has led expert committees to promote the use of statins on a global scale[106,108,109]. Prescriptions and sale of statins have risen rapidly in the UK where the expenditure on statin increased from £20 million in 1993 to more than £500 million by 2006[106].

Drastic reductions in prices of many potent satins arising from the generic availability have made them cost-effective even among individuals at annual CVD risk <1 per cent in Europe and additional cost saving in the US[107,110]. The recent Cochrane review[32] clearly demonstrating the safety and effectiveness of statins in patients with annual CVD risk <2 per cent suggests that these guidelines might need to be reconsidered.

Statin therapy in children and young adults

Lowering LDL-C by 39 mg/dl with statins for five years in middle age-adults lowers the CVD risk by 20 per cent. A greater benefit is seen when statin therapy is initiated at a younger age. For example, a 39 mg/dl decrease in total cholesterol was associated with about

Table IV. Summary of the remarkable benefits and safety of statin therapy in primary prevention

1.	Lifelong avoidance of elevated cholesterol levels prevents the development of atherosclerosis, the underlying cause of most CVD. Statin therapy can alter the natural history of vascular disease ─ a feature shared by no other category of medications.
2.	Intense LDL-C lowering yields superior benefits (than moderate lowering), including regression of atherosclerosis if non-HDL-C is maintained <100 mg/dl.
3.	The absolute CVD risk reduction is related to the patient's' baseline absolute risk and the magnitude of LDL-C and non-HDL-C reduction but not the initial LDL-C levels.
4.	A 100 mg/dL reduction in LDL-C and/or non-HDL-C confers a 50% reduction in CVD after five years of treatment. In primary prevention, such a reduction of LDL-C is estimated to prevent 2,400 to 28,400 CVD per million person-years of treatment, (but produces only 20 non-fatal and 2 fatal rhabdomyolysis).
5.	Among diabetic patients, statin therapy would prevent 8,400 major adverse cardiovascular events per million person-years.
6.	Newer genetic studies indicate that a lifelong 39 mg/dl decrease in LDL-C confers a 55% reduction in CVD - almost 3 times greater than the 21% reduction observed in randomized clinical trials in middle-aged patients and usually lasting only for five years.
7.	Lowering LDL-C early in life is substantially more effective in reducing CAD risk than the current practice of lowering LDL-C later in life when subclinical atherosclerosis (silent heart disease) is probably already present.
8.	It is time for a paradigm shift in the LDL-C dictum " lower the better to "earlier and lower the better"

Source: Refs 13, 32, 35, 90

56 per cent lower CAD mortality at ages 40-49, in both sexes. But the risk reduction fell to 34 per cent at ages 50-69, and to 17 per cent at ages 70-89 yr, underscoring the need for lowering cholesterol levels at a younger age[81,111]. The data highlight the need and necessity of starting statin therapy earlier than the current practice.

Children with very high cholesterol levels develop atherosclerosis which progresses rapidly in young adulthood[112]. Elevated LDL-C and blood pressure in adolescence have been demonstrated to be predictive of coronary artery calcification (a marker of silent CAD) 3 decades later[113]. Mutations of genes that affect the LDL-receptor function or its ligand apo B, usually result in elevated LDL-C >400 mg/dl. Such individuals develop premature atherosclerotic CVD before 20 yr of age and death before 30 yr of age[114-116]. In fact, it was the investigation of a young brother and sister, ages 6 and 8 with advanced atherosclerosis and history of heart attacks that led to the discovery of LDL receptors and statin medications[16,117]. Increased cholesterol levels may affect the aortic valve and aortic regurgitation may be the earliest sign of accelerated atherosclerosis in children[114].

The objective of statin therapy in children is to prevent the development and progression of the plaque and delay the development of CVD (rather than preventing an MI at this young age)[13]. Statin therapy has been shown to induce a significant regression of carotid atherosclerosis with no adverse effects on growth, sexual maturation, hormone levels, liver or muscle[112,114]. Children with dyslipidaemia should be treated with aggressive lifestyle modification from age two and medication from age 10 onwards (8 years if LDL-C is very high) if the lipid targets are not met with lifestyle modifications alone[118]. This is based on historic evidence of heightened risk of CAD in people with elevated LDL-C. Long-term outcome studies with statins are unlikely to be performed in children.

The threshold of pharmacological intervention with statin in children is an LDL-C ≥190 mg/dl in the absence of any other risk factors, or >160 mg/dl in the presence of a positive family history of premature CVD or two other risk factors[118]. Children with diabetes and LDL-C ≥130 mg/dl should be considered for drug therapy[118]. The minimal LDL goal is <130 mg/dl and ideal goal is <110 mg/dl. The threshold of intervention for LDL-C is 30 mg/dl lower for Indians than for Americans and Europeans[119].

In summary, lowering LDL-C early in life is more effective in reducing CAD risk than the current practice of lowering LDL-C later in life when subclinical atherosclerosis (silent heart disease) is probably already present. A public health strategy that focuses on prolonged sustained reductions in LDL-C beginning early in life could potentially reduce the global burden of CAD[118].

Rationale for early and intensive statin therapy for Asian Indians

A large verbal autopsy study of 48,000 urban and 32,000 rural adults (35-69 yr) in India has shown CVD death rates of 685 per 100,000 in men and 428 per 100,000 in women[120]. These rates are substantially higher than in the US, where the CVD mortality was 245 per 100,000 (men and women combined in 2008)[121]. The study also found that CVD accounted for 41 per cent of mortality in urban males and 37 per cent of mortality in urban females as well as 25 per cent of mortality in rural males and 22 per cent of mortality in rural females[120]. The CVD mortality ratios in urban India were similar to those reported for Indian Americans from the State of California (39% males and 32% for females)[122]. Prospective studies have shown that the incidence of and mortality from CAD among Asian Indians are at least 2-fold higher than Whites even when adjusted for major risk factors (smoking, blood pressure, cholesterol, insulin resistance, MS, DM, and socio-economic status)[71,123,124]. The increased risk of CAD is primarily due to Asian Indian dyslipidaemia which is characterized by the following[125-128]: *(i)* High levels of lipoprotein(a); *(ii)* High levels of Apo B and non-HDL-C; *(iii)* High levels of triglycerides; *(iv)* Borderline high levels of LDL-C; *(v)* Low levels of Apo A1and HDL-C; and *(vi)* High ratios of TC/HDL-C, TG/HDL-C, and apo B/apo A1.

In the INTERHEART study, Indians had the lowest HDL-C (32 mg/dl in men and 36 mg/dl in women) and the highest TC/HDL ratio and apo B/apo AI ratio - the two lipid measures with the highest predictive value for CAD risk and severity[129]. In fact, apo B/apo AI ratio had the highest population- attributable risk for MI (65%)[130]. At a given level of cholesterol, Indians have a lower LDL-C level due to high levels of triglycerides which artificially lowers LDL-C[8]. At a given LDL-C level, Indians have higher risk of CVD because of high levels of Lp(a), low levels of HDL-C and possibly dysfunctional HDL-C particles[131]. South Asian newborns have higher levels of E-selectin and Lp(a),

which is in line with the hypothesis that endothelial dysfunction is present early in life[132,133].

Many Asian Indians are in double jeopardy from nature and nurture - nature being the genetically determined Lp(a) excess, and nurture through an unhealthy lifestyle associated with affluence, urbanization, and mechanization[131,134]. The adverse effects of the modifiable risk factors related to lifestyle such as dyslipidaemia, smoking, hypertension, atherogenic diet, physical inactivity, abdominal obesity and DM are markedly magnified in those with Lp(a) excess[135].

An analysis of LDL-C levels in a large cohort (n =136, 905) of patients hospitalized for CAD found a mean LDL-C of 105 mg/dl TG 161 and HDL 39 mg/dl at admission. However, more than half the group had LDL-C >100 mg/dl and 82 per cent had LDL-C >70 mg/dl[136]. The average LDL-C was 125 mg/dl among Indians with acute MI, which is higher than those of US patients[130], providing even further support for aggressive lowering of LDL-C before an acute MI[137].

LDL-C is the principal target for treatment and non-HDL-C is the secondary target[23]. Non-HDL-C goal is set at 30 mg/dl higher than the LDL-C goal[23]. Evidence-based treatment for dyslipidaemia in Indians has been hindered by the lack of direct evidence in this population, but lower stricter blood pressure treatment targets in Blacks, than in Whites provide important insights for matching the intensity of treatment with severity of risks among Indians. High blood pressure, is more common, more dangerous and yet, poorly controlled in Blacks. The impact of higher blood pressure levels on stroke is three times higher for Blacks than for Whites. For example, for the same 10 mm Hg increase in systolic blood pressure, Blacks have 24 per cent increase in stroke risk, but only 8 per cent in Whites[138]. The updated consensus on the management of blood pressure in Blacks issued by the International society of hypertension recommends lower targets for Blacks than in Whites in recognition of this markedly elevated CVD risk from hypertension. Blood pressure goal is <135/85 mm Hg for low-risk Blacks without target organ damage and <130/80 mm Hg for high-risk Blacks with target organ damage[139].

An analogous situation exists for the treatment of high cholesterol levels in Indians. At any given level of cholesterol, Indians have markedly increased risk of CAD. The impact of high cholesterol on CAD risk in Indians is much higher than that of high blood pressure on stroke in Blacks. Aarabi and Jackson[124] have estimated that a cholesterol value of 108 mg/dl has to be added for Indians to compensate for the underestimation of CAD risk calculated by the Framingham Risk Score. For example, the CAD risk of an Indian with a cholesterol level of 192 mg/dl is similar to that of a European with a cholesterol level of 300 mg/dl[124].

Because of the increased risk of CVD in Asian Indians, LDL-C and non-HDL-C targets are set at 30 mg/dl lower than that recommended by NCEP[23,119]. Accordingly, the LDL-C goal is <70 mg/dl and non-HDL-C <100 mg/dl for very high risk Indians [such as those with CVD, DM, MS, CKD or elevated levels of LP(a)]. The LDL-C goal is <100 mg/dl and non-HDL-C <130 mg/dl for Indians without these risk factors (Table V)[23,119]. Broader acceptance of this lower LDL-C and non-HDL-C targets and its implementation could reduce the CVD burden in the Indian population by 50 per cent in the next 25 years[13]. Moreover, these lipid targets more closely approximate the recent recommendations of the European Society of Cardiology[45]. For high-risk patients, the goals are TC <175 mg/dl and LDL-C <100 mg/dl with an option of <85 mg/dl if feasible; and TC <190 mg/dl and LDL-C <115 mg/dl for all Europeans (who are not at high risk).

Indians have a high prevalence of CAD and its risk factors with a high risk for first and recurrent MACE with the following prevalence: CAD 12 per cent; DM 16-20 per cent; CKD 10-15 per cent; and high Lp(a) 35-40 per cent[135,140]. The prevalence of MS is 35-45 per cent in urban India with approximately half this rate in rural areas[62,63]. Thus, 60-80 per cent of Indians belong to the very high risk category with a non-HDL-C target of <100 mg/dl[134]. Besides, Indians have highest prevalence of elevated homocysteine (77%), and second highest prevalence of elevated Lp(a)(40%)[141-144]. The CVD risk is maekrdly increased when both Lp(a) and homocysteine levels are elevated[51,145].

Intensive statin therapy is safe, well tolerated, and effective in decreasing LDL-C in South-Asians[13]. Intensive statin therapy with potent statins and at high doses is often required in patients who require a ≥50 per cent reduction in LDL-C[13]. Besides, most Indians with baseline LDL-C >160 mg/dl with a LDL-C target of <100 or baseline LDL >130 with a target of <70 mg/dl will require rosuvastatin 20-40 mg or atorvastatin 40-80 mg[13]. The percentage of patients who achieve the Indian targets at different doses of atorvastatin and rosuvastatin is given in Table VI[13,34].

Table V. Recommendations of the Indo-US Health Summit with lower treatment target for selected risk factors

People with CAD, CKD, diabetes, metabolic syndrome, or elevated lipoprotein(a) (very high risk)	Indo-US Health Summit	NCEP
Non-HDL cholesterol* (mg/dl)	<100	<130
LDL-C (mg/dl)	<70	<100
Lipoprotein(a) (mg/dl)	<20	<30
Triglycerides* (mg/dl)	<500	<500
People without CAD, CKD, diabetes, metabolic syndrome, or elevated lipoprotein(a)		
Non-HDL cholesterol (mg/dl)	<130	<160
LDL-C (mg/dl)	<100	<130
Lipoprotein(a)) (mg/dl)	<20	<30
Triglyceride (requiring pharmacologic therapy)* (mg/dl)	<500	<500
Overweight	BMI 23-24.9 kg/m^2	25-29.9 kg/m^2
Obesity	BMI >25 kg/m^2	BMI >30 kg/m^2
Abdominal obesity measured as waist circumference (cm)	Men >90 Women >80	Men >102 Women >88

*Non-HDL-C is the target in patients with TG <500 mg/dl according to the NCEP
NCEP, National Cholesterol Education Program
Source: Ref. 23, 119

A higher starting dose of statin results in rapid achievement of the LDL-C goals with minimal titration[146]. Intensive lipid-lowering with atorvastatin 80 mg or rosuvastatin 40 mg in patients with CAD provides significant clinical benefit beyond that afforded by treatment with lower doses.

Treatment with a low dose of pravastatin reduced the risk of CAD in Japan by as much the same degree as higher doses have shown in Europe and the USA[147]. This does not appear to be the case among Indians[8,13]. The available data indicate that the efficacy and safety of statins among South Asians are no different from Whites, except for anecdotal information of increased myalgia[8].

Adverse effects of statin therapy

Although there is no evidence of any increased risk of cancer or non-CVD deaths, several known or potential hazards need to be considered when estimating the net effects of statin therapy in people at lowest risk such as in primary prevention[32]. The avoidance of life-threatening or potentially disabling events in apparently healthy low-risk individuals is acceptable, provided that they are not accompanied by any definite hazard that is of comparable severity. The recent Cochrane review has conclusively demonstrated the absence of such a hazard[32]. This is in sharp contrast to the use of aspirin in primary prevention, where the risk outweighs the benefit in many cases. The adverse effects of statins include DM, haemorrhagic stroke, nephrotoxicity, hepatotoxicity, myopathy, rhabdomyolysis, and drug interactions. Unlike statin-induced LDL-C lowering, statin safety is not a class effect, because statins vary in their excretion and metabolism by other drugs.

Statin therapy and new onset diabetes (NOD)

Recent meta-analyses have suggested that statin therapy might be associated with a 9 per cent increase in the risk of NOD compared to placebo[148-150]. In terms of absolute risk, 255 people treated for four years with statin therapy would result in one case of NOD (or 980 NOD per million person-years of statin therapy)[148-150]. Intensive therapy is associated with a 12 per cent additional increase in NOD[148-150]. Moreover, the statin-associated risk of NOD appears to be a dose-dependent class effect.

Statin-related NOD is associated with four risk factors of MS – fasting blood glucose >100 mg/dl, fasting triglycerides >150 mg/dl, hypertension and obesity[151]. Moreover, these factors are also predictors of NOD in the general population (not on statin therapy)[152-154]. Post-hoc analysis of TNT and IDEAL (secondary prevention studies comparing intensive statin therapy versus standard statin therapy)[155-157] has shown that NOD is limited to those with 2-4 of these risk factors. Compared with low-dose statin, atorvastatin 80 mg reduced the number of CVD events both in patients at low and high risk for NOD[157]. Among those at high-

Table VI. Percentage of patients achieving the LDL-C goals with various doses of atorvastatin and rosuvastatin

Statin (dose in mg)	LDL-C goal <70 mg/dl			LDL-C goal <100 mg/dl		
	Baseline LDL-C in mg/dl					
	<130	130-160	>160	<130	130-160	>160
Atorvastatin (10)	28	9	2	71	62	29
Rosuvastatin (10)	47	33	11	82	76	57
Atorvastatin (20)	65	33	11	82	76	57
Rosuvastatin (20)	81	57	21	95	90	65
Atorvastatin (40)	73	45	10	94	91	57
Rosuvastatin (40)	84	68	32	97	95	74
Atorvastatin (80)	76	52	18	97	86	71

Source: Adapted with permission from Ref. 34

risk of NOD, atorvastatin 80 mg increased NOD by 24 per cent but was more than offset by greater CVD risk reduction. For example, among the 6,231 patients at high risk for NOD, treatment with atorvastatin 80 mg/day compared with a lower statin dose was associated with 80 more cases of NOD but 94 fewer major CVD events[157]. Moreover, many patients with CVD will die from another CVD event long before they develop complications from DM[157].

Approximately 50-65 per cent of patients in these secondary prevention trials were at low risk of NOD with 0-1 risk factors[157]. No increased risk of NOD was seen in these low-risk patients who received atorvastatin 80 mg/day. The absence of increased risk of NOD with intensive statin therapy (atorvastatin 80 mg/day), while providing greater CVD event reduction, is a welcome reassurance for physicians treating patients at low risk for DM[157]. In the 1,501 TNT trial patients with established DM at baseline, those randomized to atorvastatin 80 mg/day experienced 25 per cent reduction in CVD events (14 vs 18%) compared to those randomized to atorvastatin 10 mg/day[158].

New onset diabetes (NOD) in primary prevention: The risk of NOD should be viewed against the background of long established CVD benefits of statin therapy in patients with DM. In the CTT meta-analysis of 18,686 patients with DM in 14 randomized statin trials, a 39 mg/dl (1-mmol/l) reduction in LDL-C was associated with a 21 per cent reduction in MACE – a relative risk reduction nearly identical to that reported in all patients on statin therapy[2].

A detailed analysis of the risk of NOD and benefits of CVD event reduction among the 17,603 men and women without previous CVD or DM in the JUPITER trial has been reported[159]. The subjects were randomly assigned to rosuvastatin 20 mg or placebo and followed for up to five years for the primary endpoint (cardiovascular death, MI, stroke, admission to hospital for unstable angina, CARP) and the protocol-prespecified secondary endpoints (venous thromboembolism, all-cause mortality, and incident physician-reported diabetes)[159]. The participants were stratified on the basis of having zero or ≥1 major risk factors for NOD: MS, fasting glucose ≥100 mg/dl, body-mass index ≥30 kg/m^2, or glycated haemoglobin (A_1c) ≥6 per cent[159]. Trial participants with ≥1 NOD risk factors (n=11,508) indeed had a 28 per cent higher risk of NOD than were those with no risk factor (n=6095). In individuals with ≥ 1 risk factors, statin therapy was associated with a 39 per cent reduction in the primary endpoint as well as a 36 per cent reduction in venous thromboembolism, and 17 per cent reduction in total mortality. For the 11,508 people with NOD risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of DM diagnosed. For trial participants with no NOD risk factors, statin therapy was associated with a 52 per cent reduction in the primary endpoint, a 53 per cent reduction in venous thromboembolism, and a 22 per cent reduction in total mortality with no increase in DM. For these 6095 individuals, a total of 86 MACE or deaths were avoided with no diagnosis of NOD[159].

A further analysis of the 486 participants who developed DM during follow-up (270 on rosuvastatin vs 216 on placebo) statin therapy was associated with 37 per cent CVD risk reduction – nearly similar to the 44 per cent risk reduction for the trial as a whole.

By comparison with placebo, statins accelerated the average time to diagnosis of DM by five wk on rosuvastatin vs. 90 wk on placebo[159].

In the updated recent Cochrane review[32] among the 12,205 participants on statins therapy 342 (2.8%) developed diabetes compared with 290 out of 12,202 (2.4%) participants on placebo, with a relative risk of developing diabetes of 1.18 (95% CI 1.01 to 1.39)[32]. However, this higher risk of statin-related NOD was driven primarily by JUPITER trial which used rosuvastain 20 mg/day[159]. Although JUPITER trial showed higher risk of NOD, the CVD benefit was also high, resulting in premature termination of the trial.

The mechanism by which statins increase the risk of NOD has been the subject of speculation. Atorvastatin and rosuvastatin have been reported to increase insulin resistance. Nonetheless, the mechanism may only be operative in patients with multiple risk factors for DM[159].

Balance of risk of NOD and benefit on CVD and mortality: A population-based study of nearly a million subjects from Taiwan, has also confirmed higher risk of NOD but and even higher CVD risk reduction with statin therapy. During a median follow up of 7.2 yr, NOD developed in 2.4 per cent of patients on statin therapy compared to 2.1 per cent not receiving statin therapy. This 14 per cent increase in NOD was more than offset by 18 per cent reduction in MACE and 39 per cent reduction in in-hospital mortality resulting in a highly favourable benefit risk ratio (Table VII)[160]. In terms of absolute numbers, statin therapy prevented one fatal event for every 202 subjects and led to one case of NOD for every 301 patients. However, the overall NOD incidence was high (21 per 1000 person-years) – four times higher than in the meta-analysis of studies conducted mostly in Whites[148]. The 14 per cent risk of NOD from statin therapy, however, was much smaller compared to 53 per cent NOD risk from diuretics and 40 per cent NOD risk from beta-blockers in the same study[161]. Many other studies have also shown much higher risk of NOD from diuretics (20-45%) and beta-blockers (20-36%) than from statins[162,163]. Thus, the magnitude of risk of NOD with statins appears to be about half than that of diuretics and beta-blockers widely used in the management of hypertension and CVD.

A Canadian study involving 143,630 Whites, 9529 South Asians, and 14,084 Chinese with newly diagnosed DM has also confirmed substantial reduction in mortality among those who were prescribed statins. Compared with no prescribing, statin prescribing was associated with mortality reduction of 31 per cent among South Asians, 40 per cent among Chinese and 35 per cent among Whites[164].

A review of the literature indicates that the CVD benefits of statin therapy far outweighs the risks for statin-related DM and other risks[165]. A patient with CAD who develops DM faces several new challenges such as blood glucose monitoring requirements, increased dietary restrictions, and usually additional drug therapy. Besides, there are long-term threats of the macrovascular and microvascular complications of diabetes. However, the impact of NOD is relatively minor compared with the CVD events (fatal and nonfatal MI, fatal and nonfatal stroke, and death). Considering the balance between NOD and CVD event prevention, it is worth noting that the microvascular and macrovascular complications of diabetes are

Table VII. In-hospital mortality risk ratio according to diabetes status and prior statin use in real world, from a National Health Insurance Data

Outcome	Number	Risk ratio for in-hospital mortality*		
		Overall	High risk group**	Secondary prevention
Nondiabetic individuals without prior statin use	29,332	1	1	1
Nondiabetic individuals with prior statin	7,025	0.58	0.62	0.62
Diabetic patients without prior statin use	4,316	1.91	1.69	1.68
Diabetic patients with prior statin use	1,387	1.54	1.31	1.28

*Adjusted for age, sex, hypertension, coronary artery disease, stroke, and haemodialysis
** ≥I risk factors other than hypertension
Source: Adapted with permission from Ref. 160

relatively uncommon during the first decade after diagnosis[166] .

In summary, NOD with statin therapy is confined to those with risk factors for DM and the CVD benefits far outweigh risk of NOD[32,35,159]. Even if statin- related NOD was associated with an immediate doubling in CVD risk, the expected effect would be approximately 40 fewer events avoided per million person-years[167]. This figure is 50 times smaller than the absolute benefit observed with statin therapy in such individuals (2,200 fewer MACE per million person-years per 39 mg/dl reduction in LDL-C)[35].

Haemorrhagic stroke

International guidelines recommend statins in secondary prevention of stroke and advise objective assessment of CVD risk to determine the appropriateness of statins for primary prevention of stroke. Post-hoc analysis of SPARCL trial[168] (4731 stroke survivors randomized to treatment with atorvastatin 80 mg/day or placebo, regardless of cholesterol level) has shown that those who achieved a >50 per cent LDL-C reduction had double the reduction in ischemic stroke compared to the overall cohort (33 vs. 16%) without any statistically significant increase in haemorrhagic stroke. More importantly, there was a 37 per cent reduction in MACE compared to those who had no change in LDL-C (possibly due to not taking the statin)[168]. Caution is advised in patients with a history of intracerebral haemorrhage[169]. Totality of data indicates that statins therapy may increase the risk of haemorrhagic stroke with an annual excess risk of 0.5 per 1000 people treated over five years (100 per million person-years) per 39 mg/dl LDL-C reduction[35]. The risk may be even higher in Asian populations, who have higher rates of stroke and higher proportion of haemorrhagic strokes than Whites[170]. This does not apply to Asian Indians who have very high risk of CAD and lower risk of stroke[9].

Cognitive impairment and peripheral neuropathy

There are sporadic reports of cognitive impairment, primarily from observational data, but not from randomized trials. The data indicate that statin therapy has either a neutral or beneficial effect on cognition. Statin use and type were not associated with cognitive impairment after adjusting for known variables that affect cognition in a large cross-sectional analysis of 24 595 participants (7191 statin users and 17,404 nonusers age ≥45 yr), from a population-based national cohort study[171]. There is some speculation that statins that are hydrophilic (*i.e.* pravastatin and rosuvastatin) may be less likely to contribute to cognitive impairment (due to limited penetration across the blood-brain barrier). If statin-associated cognitive impairment is suspected, a trial discontinuation can reveal a temporal relationship. Switching from a lipophilic (*e.g.* simvastatin) to a hydrophilic statin (*e.g.* rosuvastatin) may resolve cognitive impairment. Given that the vascular benefits outweigh any potential risk of cognitive impairment associated with statin use, the current evidence does not support changing practice with respect to statin use[172]. A modest association between peripheral neuropathy and statin use has also been reported[173,174]. Evidence from four cohort studies and case reports suggests that the risk is small. Statin treatment is associated with increased self-reporting of reduced energy and fatigue on exertion but does not affect self-reported quality of life, mood, hostility, psychological well being, or anger expression[175,176].

Liver toxicity and confounding by fatty liver

Moderate asymptomatic hepatic transaminase elevations (<3 times upper limit of normal or ULN) are common among patients taking statins, but serious liver damage is extremely rare. Asymptomatic transaminase elevations are also seen with all non-statin lipid-lowering therapies and believed to be the result of lowering LDL-C *per se*. Such elevations often resolve with continued statin treatment[177-181]. The incidence of significantly elevated liver transaminases (AST/ALT) (>3x ULN) levels is <1 per cent with moderate doses of statins. A pooled analysis of 18,696 patients treated with atorvastatin 80 mg/day showed an incidence of only 1.4 per cent which was much lower than the 5.3 per cent incidence in patients treated with fixed dose fenofibrate therapy[182-184]. There is no reason to suspect the incidence of minor transaminase elevations would be different among Indians.

Nearly 50 per cent of dyslipidaemia patients have coexisting non alcoholic fatty liver disease (NAFLD) – a condition well known for fluctuating transaminase levels[185,186]. Physicians should not withhold statin therapy from patients whose transaminase elevations have no clinical relevance or are attributable to known stable chronic conditions. Statins can be used in such patients and may actually improve the enzyme levels and liver histology[187-191]. This is also true in patients with obesity and MS who often have elevated transaminases from hepatic steatosis.

The post-hoc analysis of the GREACE trial has demonstrated that statin therapy is not only safe but

also improves liver tests and reduces CVD morbidity in patients with mild-to-moderately abnormal liver enzymes that are potentially attributable to NAFLD[192]. Of the 437 patients with moderately abnormal liver function at baseline, (possibly associated with NAFLD), 227 were treated with a statin (mainly atorvastatin at a mean dose 24 mg per day) and 210 were not on statin therapy. Those who received statin had substantial improvement in liver enzymes whereas those who did not receive statin had further increase of liver enzyme levels. Among the patients with abnormal liver enzymes, CVD events occurred in 10 per cent of patients who received statin therapy and 30 per cent of those who did not receive statin. The 68 per cent CVD risk reduction with statin therapy was substantially higher than that observed in people with normal liver function. Further, only 1 per cent discontinued statin therapy because of liver-related adverse effects[192]. In any case, statin therapy should be discontinued in people with persistent transaminase elevation >3 x UNL.

Neither chronic liver disease nor compensated cirrhosis is a contraindication for statin therapy[187,193]. Statins have been successfully used in people with hepatitis B and C without adverse outcome. However, statin therapy should not be given to patients with progressively deteriorating liver function with decompensated cirrhosis, acute liver failure or active alcoholic liver disease. Statins should also be used with caution in people with excessive alcohol intake (>2 drinks/day for men and >1 drink/day for women). Heavy alcohol consumption and binge drinking (≥5 drinks in 24 h) increase the risk of hepatotoxicity. Alcohol abstinence or moderation can allow many patients to safely use statin medications.

No deaths due to liver failure have been reported to date despite the fact that more than a billion statin prescriptions have been filled worldwide during the past 26 years[194,195]. Serious liver damage or liver failure occurs at a rate of one per million person-years, which is similar to the incidence in the general population. The Food and Drug Administration (FDA) has finally acknowledged that liver damage with statins is rare and that routine transaminase tests are neither necessary nor effective in predicting or preventing severe hepatitis[196].

Kidney toxicity

Statins do not cause kidney injury. The only clinical setting in which statins may be associated with acute renal failure is rhabdomyolysis. One meta-analysis compared renal effects of atorvastatin and rosuvastatin in 29,147 patients over 23 trials[197]. A significant decrease in renal function was detected in placebo as compared to either rosuvastatin or atorvastatin. No significant difference in GFR was detected in five head-to-head studies comparing atorvastatin to rosuvastatin. Likewise, there was no difference in proteinuria except a slight increase noted with rosuvastatin at 40 mg/dose. Atorvastatin and rosuvastatin have similar reno-protective effects in patients at high CVD risk, with comparable rates of new-onset proteinuria, when commonly used doses are considered[197]. Another meta-analysis with six trials involving 24,278 participants showed that both atorvastatin and rosuvastatin improved GFR, and atorvastatin appeared to be more effective in reducing proteinuria[198]. There is no dose restriction for atorvastatin in people with low GFR but the dose of rosuvastatin should be reduced to 10 mg when GFR is <30 ml.

Muscle toxicity (myalgia, myopathy, and rhabdomyolysis)

Severe muscle toxicity from statin therapy is rare[199]. However, vague muscle pain, creatine kinase (CK) elevation or both are fairly common among middle-aged and older people, even in the absence of statin therapy. Fatigue with or without pain has also been reported with the use of statins[175,200,201].The definition of various muscle symptoms and toxicity is given in Table VIII[199]. In patients with myalgia, while receiving a statin, creatine kinase levels should be measured. Although most cases of the myalgia are not accompanied by elevated CK, asymptomatic CK elevation can occur without myalgia.

Myopathy: Myopathy is a general term for all potential muscle problems such as muscle pain or weakness and can occur with or without elevated CK[199]. Statin-related myopathy is usually symmetrical, involves large proximal muscle groups and resolves within two months of discontinuation of the medication[199]. It occurs in 5 per cent of the statin treated patients in clinical trials and 10 per cent of patients in clinical practice[199]. The risk of severe myopathy is very low with statin monotherapy and in primary prevention (excess incidence of about 0·5 per 1000 over 5 years or 100 per million person years)[199].

Myopathy is a class effect of statins and the leading cause of non-adherence to statins[202]. The risk of myopathy is not related to the LDL-lowering efficacy, but the dose or the blood concentrations of the

Table VIII. Definition of myopathy, rhabdomyolysis, and CK elevation

Condition	Definition
Myopathy	A general term for all potential muscle problems
Symptomatic myopathy	Refers to all complaints referable to skeletal muscle and include cramps, pain, or weakness
Asymptomatic myopathy	Refers to CK elevation without complaints referable to skeletal muscle
Mild CK elevation	CK<10 times ULN or <2000 units
Moderate CK elevation	CK >10 times but <50 times ULN or <10,000 units
Severe CK elevation	CK >50 times ULN or >10,000 units
Clinically important rhabdomyolysis	Refers to muscle symptoms with CK elevation >10,000 or change in renal function

CK, creatine kinase; ULN, upper limit of normal
Source: Ref. 199

statin[199]. However, atorvastatin is a notable exception and has similar low rates of myalgia at all doses (10 to 80 mg/day)[13,203]. The patient characteristics that increase the risk of myopathy include low body mass index, female gender, uncontrolled hypothyroidism, collagen vascular disease, hepatic or renal dysfunction, age >80 yr, HIV infection, polypharmacy, and the use of medications that interact with statins[204]. Consumption of Chinese herbs containing red yeast rice and large quantities of alcohol also increase the risk[205]. The risk of myopathy varies markedly among the high potency statins with atorvastatin having the least and simvastatin having the most risk[13]. The prevalence of myopathy was 0.02 per cent or 240 per million among the almost 250,000 patients randomized into trials comparing atorvastatin 80 mg daily with various standard regimens of statins or placebo[184].

Asymptomatic myopathy refers to CK elevation without any myalgia or weakness and is common among patients taking statins as well as placebo[199]. Mild CK elevations (> 2 to <10 x ULN) require careful monitoring. Clinically significant moderate or high CK elevation from statin monotherapy is rare. In a primary care practice, 1 per cent of patients taking statins was found to have significant elevation in both CK and transaminase levels but not attributable to statins upon careful evaluation[206]. African Americans have higher baseline CK levels. Other causes of CK elevation include: *(i)* hypothyroidism and hyperthyroidism; *(ii)* red rice yeast that contains lovastatin or use of large quantities of grape fruit juice that retards statin metabolism; *(iii)* muscle injury including intramuscular injection; and (iv) vigorous physical activity or seizure[199,207]. Most CK elevations are due to recent physical exertion which can increase the CK to >50,000[204]. The National Lipid Association (NLA) does not recommend baseline CK measurements before starting therapy, except for those who are at the high risk[207].

Rhabdomyolysis: This is a rare but severe form of myopathy related to statin therapy. Breakdown of skeletal muscle results in release of myoglobin into the circulation and can produce acute renal failure, if not detected and treated early[195]. According to the NLA definition, the diagnosis of rhabdomyolysis is to be considered when CK is >10x ULN (>2000 units) together with elevation in serum creatinine. Treatment includes aggressive iv hydration therapy and in rare cases renal replacement therapy[207]. Myalgia is usually present but not an essential requirement.

The incidence of rhabdomyolysis is negligible – 34 per million person-years with statins and 18 per million with placebo in clinical trials[195,208]. Thus, the excess risk of rhabdomyolysis is estimated to be 16-20 per million person-years of statin therapy. Since the case fatality is about 10 per cent, excess deaths attributed to statin-related rhabdomyolysis is only 2 per million person-years[1,195]. Potential contributors to statin-related rhabdomyolysis are the same as myopathy plus surgery and trauma[199].

The risk of rhabdomyolysis varies with different statins. It is four times more common with lovastatin, and simvastatin (metabolized by cytochrome 450 3A4 (P450 3A4) than fluvastatin and rosuvastatin (metabolized by cytochrome P450 2A9 (P450 2 A9) and pravastatin (not metabolized by P450 system)[199]. Rhabdomyolysis has been reported with hydrophilic statins such as pravastatin and rosuvastatin[199,209]. Pravastatin, simvastatin, and rosuvastatin, at

doses double that is currently marketed, have been documented to produce unacceptable rates of muscle toxicity[209-211]. This increased risk of myopathy prompted the FDA to deny approval of rosuvastatin 80 mg dose and the withdrawal the 80 mg dose of simvastatin. The FDA has also imposed dose restrictions for simvastatin when used in combination with many commonly used medications (Tables IX, X)[1,177,195,199,205,207,212,213]. Although partially metabolized by P450 3A4, atorvastatin 80 mg/day has the most favorable risk-benefit ratio for rhabdomyolysis with no higher risk at 80 mg/day compared to 10 mg/day dose[13,182].

If rhabdomyolysis is detected, statin treatment must be stopped immediately, followed by hospitalization and intravenous hydration. Approximately 90 per cent of patients recover fully and the usual mortality from rhabdomyolysis is 10 per cent. Full recovery usually occurs in a few weeks. If a particular interaction has been implicated, it may be appropriate to restart the statin without the interacting drug. Otherwise a lower dose or an alternative statin could be tried with careful monitoring[13].

Medications that increase statin toxicity through drug interactions

More than 80 per cent of statin-associated myopathy and rhabdomyolysis are attributable to concomitant use of P450 3A4 inhibitors or gemfibrozil[205]. Approximately 20 per cent of patients taking statin also receive a drug that had a warning against co-prescribing with statin[214]. In a study of 245 co-prescriptions of statins with P450 3A4 inhibitors, simvastatin was prescribed in 134 and atorvastatin in 111 patients. Diltiazem (86), verapamil (72), erythromycin (48) and clarithromycin (29) were the other most common co-prescribed medications. The risk of rhabdomyolysis is particularly high in those with genetic *SLCO1b1* variant[215].

Pharmacokinetic differences in statins are major determinants of drug interactions. Nearly 80 per cent of all drugs including statins require biotransformation to hydrophilic metabolites for renal excretion, with about 50 per cent of these drugs undergoing metabolism by the cytochrome P450 3A4 isoenzyme. Concomitant use of drugs that are inhibitors of P450 3A4 results

Table IX. Concomitant use of medications that may necessitate the use of statins with least drug interaction (rosuvastatin,* fluvastatin, pravastatin or pitavastatin)

Medication class	Interacting concomitant medications
Strong CYP3A4 inhibitors	Clarithromycin, telithromycin, ketoconazole, itraconazole, posaconazole, voriconazole, boceprevir, conivaptan, indinavir, telaprevir, lopinavir/ritonavir, nelfinavir, saquinavir, mibefradil, nefazadone
Moderate inhibitors	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil, and grapefruit juice (>950 ml)
Weak inhibitors	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, Ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir, ticagrelor, zileuton
CYP450 Inducers	Rifampin, midazolam,
Antiarrhythmic	Amiodarone and verapamil
Antidepressants	Nefazodone, paroxetine and venlafaxine, fluoxetine (Prozac)
Azole fungal agents	Ketoconazole (Nizoral), itraconazole (Sporanox), and miconazole (Monistat)
Calcium antagonists	Verapamil, diltiazem, felodipine
Cyclosporine	Increases the blood levels of statins 2-20-fold Inhibits CYP3A, P-glycoprotein and OATP1B1
HIV protease inhibitors	Atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir, and darunavir
Macrolide antibiotics	Clarithromycin, telithromycin erythromycin,
Fibrates	Gemfibrozil, fenofibrate, fenofibric acid
Miscellaneous	Ranolazine (Ranexa), conjugated estrogens; digoxin, warfarin Grape fruit juice (>1 quart or 950 ml)

*Dose restrictions in certain conditions are described in Table X
Source: Refs 1, 177, 195, 199, 205, 207, 212, 213, 217

Table X. Strategies to reduce muscle toxicity during lipid-optimizing therapy

1.	Warn the patient about the possibility of muscle toxicity and teach to recognize and report muscle symptoms such as diffuse muscle pain or weakness
2.	Have a pretreatment baseline CK level in high risk individuals
3.	Avoid co-prescribing of multiple medications not compatible with statins and reduce the dose of statins to prescribed limits.
4.	Simvastatin and lovastatin are contraindicated with itraconazole, ketoconazole, posaconazole, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir, atazanavir, nefazonone, danazole, cyclosporine, erythromycin, clarithromycin, telethromycin and gemfibrozil
5.	Limit the simvastatin dose to 10 mg when used with amiodarone, verapamil, and diltiazem and 20 mg/dl with amlodipine, lomitapide, ranolazine and large quantities of grape fruit juice (>950 ml).
6.	Rosuvastatin dose should be limited to 5 mg in people taking cyclosporine, and 10 mg in people taking lopinavir, ritonavir or atazanavir, and gemfibrozil and severe renal impairment (glomerular filtration rate <30 ml). Avoid gemfibrozil and carefully monitor INR on patients taking coumarin anticoagulants.
7.	No dose limitation for atorvastatin with niacin, amiodarone, verapamil, danazole, cyclosporine, warfarin, or glomerular filtration rate as low as <15 ml/min/1.73 $m^{2.}$
8.	Use statins that are least affected by P450 3A4 pathway (pravastatin, rosuvastatin, and pitavastatin), when another agent that inhibits P450 3A4 pathway has to be used concomitantly.
9.	Statins predominantly metabolized by 450 3A4 should be discontinued temporarily when erythromycin is used or instead substitute with azithromycin. Use statin alone for non-HDL-C goals when possible.
10.	While using fibrate-statin combination therapy, get base line CK and creatinine levels; avoid the highest dose of statins and use the lower dose of statin-fibrate comination therapy. Do not exceed the recommended maximum dose of gemfibrozil with statins; use fenofibrate when possible.

Source: Refs 13, 199, 214, 217-219

in increased concentrations of both drugs. The risk of myopathy and rhabdomyolysis is increased 7-fold when a statin is used concomitantly with a strong P450 3A4 inhibitor[216]. Some medications are strong and others are weak P450 3A4 inhibitors. Atorvastatin, simvastatin, lovastatin, and pitavastatin are relatively lipophilic (hydrophobic) compounds. Lipophilic statins are more susceptible to metabolism by the P450 3A4, except for pitavastatin, which undergoes limited metabolism via this pathway. Pravastatin and rosuvastatin are relatively hydrophilic and not significantly metabolized by P450 3A4 enzymes. Fluvastatin and rosuvastatin are metabolized primarily by P450 2C9[205,220].

Concomitant drug-induced inhibition of P450 3A4 isoenzymes can result in marked increase in blood levels of simvastatin (most lipophilic) and lovastatin but not pravastatin and rosuvastatin. Atorvastatin is only partially (20%) metabolized by P450 3A4 and, therefore, elevation of blood levels with strong P450 3A4 inhibitors is mild. Pravastatin, rosuvastatin, and pitavastatin are excreted mainly unchanged, and their plasma concentrations are not significantly increased by P4503A4 inhibitors[221]. Strong P450 3A4 inhibitors increase the blood levels of rosuvastatin and fluvastatin by less than 2-fold but up to 20-fold with simvastatin and lovastatin[217].

In patients requiring the concurrent use of statins and P4503A4 inhibitors, pravastatin, fluvastatin, and rosuvastatin carry the lowest risk of drug interactions and atorvastatin carries moderate risk. Simvastatin and lovastatin have the highest risk and should be avoided in patients taking concomitant CYP3A4 inhibitors[222,223]. For patients requiring long-term therapy with amiodarone, diltiazem, or verapamil, statins that are not metabolized by P4503A4 (rosuvastain, fluvastatin or pravastatin) are preferable. Although small doses of lovastatin and simvastatin can be used with moderately potent P4503A4 inhibitors (*e.g.* ranolazine, diltiazem and verapamil), rosuvastatin, fluvastatin, pravastatin, or pitavastatin (that are not metabolized by CYP 3A4) may be preferable for long-term use. Likewise, paroxetine and venlafaxine are preferable antidepressants for patients taking lovastatin and simvastatin. Rosuvastain is the most effective statin for dyslipidaemia associated with protease inhibitor therapy[199,224].

Grape fruit juice >200 ml when given with felodipine increases the blood levels of simvastatin but safe up to 1.2 liters with atorvastatin. Since the duration of effect of grapefruit juice can last 24 h, repeated consumption can result in increase statin blood levels[199]. Statins and

grape fruit juice ingestion should be separated by 2 h. Grape fruit juice inhibits intestinal but not hepatic 3A4 pathway but no report of myopathy has been published to date. Concomitant use of prescription and/or non-prescription medications including acetaminophen, herbal and alternative therapies that increases blood levels of statins should be evaluated in people with statin-related side effects[225-228].

Management of myopathy and rhabdomyolysis

Muscular symptoms usually improve with withdrawal of the statin and recur with rechallenge[177]. If symptoms are tolerable and CK <10 x ULN, statin can be continued at the same or reduced dose and symptoms may be used as a guide to stop or continue therapy[207]. But statin should be discontinued if the symptoms are intolerable, regardless of CK, until the patient is asymptomatic[199]. Strategies for managing myalgia include: *(i)* a therapeutic trial of coenzyme Q10, 200-1200 mg/day; *(ii)* evaluation and correction of vitamin D deficiency if detected; and *(iii)* switching to atorvastatin which has less myalgia and myopathy (if applicable)[199]. Recurrent symptoms with multiple statins (despite concurrent and adequate doses of coenzyme Q10 and vitamin D supplements) require non-statin lipid therapy.

Vitamin D insufficiency

Vitamin D insufficiency appears to be a novel mechanism of statin-induced myalgia and two-thirds of patients who have myalgia while on statin therapy have low vitamin D levels[229]. Vitamin D deficiency (<30 ng/ml) is a highly prevalent condition, affecting approximately 30 to 50 per cent of the general population in the US[230]. Anecdotal evidence indicates that most Indians have very low levels. Low 25-hydroxyvitamin D levels are associated with CVD risk factors and adverse outcomes. Vitamin D deficiency activates the renin-angiotensin-aldosterone system leading to hypertension, left ventricular hypertrophy, insulin resistance, diabetes, and increased cardiovascular risk. Vitamin D supplementation is simple, safe, and inexpensive and often results in reduction in myalgia. Those with severe myalgia require a higher vitamin D level of 50-60 ng/ml. Those with severe vitamin deficiency and myalgia require 50,000 units per week or 8000 units per day for 8-12 wk followed by a lower maintenance dose[231,232]. Obese patients may also require higher doses of Vitamin D supplementation.

Coenzyme Q10: Coenzyme Q10 (CoQ10) functions as an electron carrier in the mitochondrial electron transport chain. It is carried in LDL-C and serves as an antioxidant, protecting the cell from free radical induced oxidation. HMG-CoA reductase inhibition blocks the production of farnestyl pyrophosphate (FPP) which is an intermediary for the production of CoQ10 (the predominant form of ubiquinone in man)[199]. Statin therapy lowers CoQ10 blood levels, (partly because CoQ10 is transported in the LDL-C particle)[233-236]. The resulting impairment of mitochondrial function may be exacerbated by exercise[237]. Serum and intramuscular CoQ10 levels are not correlated[238]. Myalgia, fatigue, dyspnoea, memory loss, and peripheral neuropathy often respond to CoQ10 supplements but may need doses of 400 to 1200 mg/day early in treatment[239,240]. CoQ10 supplementation offers an alternative to stopping treatment with these life saving medications[237,241]. There are no known risks to this supplement. Indians have lower levels of CoQ10 levels and higher incidence of myalgia while taking statins[8,235,237].

Stain therapy and cancer

A meta-analysis of individual participant data from 27 randomized trials and 175,000 patients provides reassuring evidence that reducing LDL-C with statin therapy does not increase the risk of developing a new cancer or deaths from cancer. Specifically, there is no indication of any excess of particular types of cancer with prolonged or more intensive lowering of LDL-C, even among older people[242]. If low LDL-C concentration is a cause of cancer then one might expect to see a trend towards larger rate ratios among those with lower LDL-C before treatment. In fact, there were fewer cancers among participants with lower baseline LDL-C who were allocated statin or more intensive regimens[242]. For example, lowering LDL-C from 75 to 50 mg/dl was associated with a non-significant 8 per cent reduction in cancer incidence[242]. The data provide considerable reassurance about the safety of using intensive statin regimens to lower LDL-C levels substantially in patients who remain at high risk of major vascular events[242].

Low cholesterol and high health risk – a case of reverse causality

Observational studies but not randomized clinical trials have shown an association between low cholesterol levels and increased risk of mortality from cancer, respiratory disease, liver disease and accidental/violent death[32]. This is mostly, or entirely, due to the fact that people with low cholesterol levels include a disproportionate number whose cholesterol has been reduced by illness - early cancer, respiratory

disease, gastrointestinal disease and alcoholism, among others[243,244]. Besides, there was no evidence that lowering of LDL-C increased the risk of non-vascular death or of cancer, even when LDL-C was reduced to 50 mg/dl[242]. Thus, it appears that both low cholesterol and increased non CVD mortality are due to preexisting disease (reverse causality) and not vice versa[10].

Balance of benefits and risks of statin therapy in primary prevention

Despite a doubling of obesity and diabetes, CAD mortality in the United States has declined by 70 per cent in the last 35-40 yr[245,246]. This decline is attributed to effective control of blood pressure and cholesterol along with reduction in smoking[247]. The benefits of lowering LDL-C and non-HDL-C are substantially greater in reducing CAD events than lowering blood pressure, which is more effective in preventing stroke rather than CAD. Statins are the most effective agents in lowering LDL-C and non-HDL-C by 50 per cent or 100 mg/dl or more[32,34]. Statins are also effective in halting the progression and even reversing coronary atherosclerosis, either alone or in combination with niacin[26,33]. The benefits of statin therapy is overwhelming whereas life threatening complication are extremely rare (Table XI)[13,32,35,199,205]. The benefit to risk ratio is much higher for statins than for fibrates or aspirin.

Balance of benefits and risks of aspirin versus statin therapy in primary prevention

Aspirin has overwhelming benefit in secondary prevention with an absolute 1.5 per cent risk reduction in MACE which outweighs risk of major bleeding. However, evidence from the collaborative meta-analysis of individual participant data from randomized trials involving 660,000 person-years of follow-up and 3,554 serious MACE, has cast a serious doubt about the use of aspirin in primary prevention[248]. Both the relative and absolute benefits of aspirin are significantly lower than that of statins in primary prevention. For example, in the JUPITER trial[37], people receiving rosuvastatin 20 mg/day had 44 per cent relative risk reduction in MACE which was 4-fold higher than the 12 per cent relative reduction reported in the meta-analysis of aspirin in primary prevention[37]. More importantly, the absolute risk reduction with rosuvastain was 0.59 per 100 person years, which is 8 times higher than with aspirin (0.07 per 100 person years) in primary prevention[248].

In primary prevention of CVD, aspirin use, like alcohol consumption, is a double-edged sword. While physicians and public are well aware of the potential benefits, the risk of serious bleeding with aspirin has received less attention. These serious risks include major gastrointestinal bleeding (even in the absence of other agents that increase the risk) and haemorrhagic stroke. The risk of major bleeding is 1.2 per cent for women and 2.4 per cent for men 60-69 yr of age. The risk increases with increasing age of the patient and increasing dose of aspirin[249,250]. The risk is nearly double when aspirin is given concomitantly with clopidogrel and 3 times when warfarin is also added. Such triple therapy is common in patients with coronary stent and atrial fibrillation and can be avoided in the first place by starting statin early[13].

A million person-years of treatment with aspirin would prevent 10,000 MACE in secondary prevention but only 1,300 MACE in primary pevention[248,251]. But aspirin therapy will also produce 14,800 bleeding complications including 2,300 major bleeding (requiring hospitalization and transfusion) and 100 haemorrhagic strokes. Accordingly, for every MACE prevented with statin therapy, 10 bleeding will be produced including two major bleedings[251]. Paradoxically, the benefits of aspirin in people who are already on a statin would be even smaller[251]. Statin therapy has been shown to reduce MACE by 44 per cent in the JUPITER trial[37]. Accordingly, the use of a statin before aspirin would reduce the number of MACE prevented to from 1300 to 728 per million, but the bleeding rates would remain the same. This would result in an even worse risk-benefit-ratio with aspirin, producing three major bleeding and 20 total bleeding for every MACE prevented.

Several meta-analyses of randomized controlled trials in patients with DM also failed to confirm a clear benefit of aspirin therapy in the primary prevention of major CVD events. This has led to the withdrawal of the previous recommendations for universal administration of aspirin in patients with DM[84,252]. It appears that statin therapy is 100 times safer than low dose aspirin (for life threatening complications)[249,250]. The accumulated evidence shows that statins should supplant aspirin as the first drug of choice in primary prevention of CVD with aspirin reserved for highly select individuals among whom the benefits clearly outweigh the risk.

Balance of benefits and risks of fibrates therapy

Unlike statins, most fibrate trials were conducted in patients with CVD, DM, and/or high triglycerides.

Table XI. Summary of the balance of benefits and risk of statin therapy in primary prevention

1. The benefits of lowering LDL-C are substantially greater in reducing CAD events than from lowering blood pressure, which is more effective in preventing stroke rather than CAD. Statins therapy can also halt the progression and even reverse coronary atherosclerosis.
2. Statins are the most effective medications in lowering LDL-C and higher doses of potent statins can lower LDL-C and non-HDL-C by >50% (>100 mg/dl). In primary prevention, such a reduction in LDL-C is estimated to prevent 2,400 to 28,400 CVD events and 200 to 9,200 deaths per million person-years of treatment, but produces only 20 non-fatal and 2 fatal rhabdomyolysis.
3. Whereas the benefit of statin therapy is related to the absolute reduction in LDL-C, the serious side effects are not related to the degree of LDL-C reduction.
4. Unlike statin-induced LDL-C lowering, statin safety is not a class effect. The statin toxicity is driven by the blood concentrations of the drug, which in turn may be related to the dose of the specific statin used, drug interactions and/or genetic susceptibility.
5. Myalgia is common with statin therapy and responds well to Vitamin D and Coenzyme Q10 therapy in most cases.
6. More than 80% of statin associated myopathy and rhabdomyolysis is attributable to concomitant use of fibrates or drug interactions, especially those involving P450 3A4 inhibitors. The risk of myopathy is increased 6-fold in patients receiving a statin concomitantly with a potent P450 inhibitors that markedly elevate the blood levels of statins.
7. Compared with statin monotherapy the risk of rhabdomyolysis is six times higher with statin-fibrate combination therapy and 47 times higher among elderly diabetics receiving such combination therapy.
8. There is no convincing evidence that elevated liver enzymes are associated with liver damage. Low cholesterol does not produce cancer, lung disease or liver disease but these conditions do produce low cholesterol (reverse causality).
9. The risk of diabetes (DM) is real (9-18%) but limited to those with risk factors for DM. The risk is only about half that of diuretics (20-45%) and beta-blockers (20-36%). The CVD risk reduction is much larger with statins even among those who develop new onset diabetes (980 per million person-years).
10. The increased CVD risk (40 MACE per million person-years) resulting from statin-related new onset diabetes is 50 times smaller than CVD prevented from statin therapy (2,200 per million person-years for every 39 mg/dl decrease in LDL-C). The absolute CVD benefits from intensive statin therapy is likely to be much higher in Indians than in other populations because of the malignant nature of CAD.

Source: Refs 13, 32, 199, 205

None of the clinical trials showed clear benefit of reducing CVD risk from lowering triglycerides *per se*, although some benefit was noted in subgroups with high triglycerides and low HDL-C[52,56,253]. Currently the main indication for fibrates is for patients with high triglycerides of >500 mg/dl to prevent pancreatitis and not MI[23]. When the triglycerides levels are between 150 and 499 mg/dl, statin is the first line agent to achieve the primary target (LDL-C goal). When the LDL-C level is at goal but triglycerides levels are between 150 and 499 mg/dl, a fibrate is often used in combination with a statin to achieve the secondary target of non-HDL-C (but not necessarily to lower triglycerides)[52]. Fibrates lower triglycerides by as much as 50 per cent, but the reduction in non-HDL-C is only 20 per cent with monotherapy. Although combination of fibrate therapy with moderate dose statins such as 20 mg/day of rosuvastatin or 40 mg of atorvastatin can produce 42 per cent reduction in non-HDL-C and 37 per cent reduction in apo B, these values are lower than those achieved with high dose statin therapy alone. (47% reduction in non-HDL-C and 42 per cent reduction in apo B)[52].

The risk of rhabdomyolysis with fibrate monotherapy was 6 times higher than the risk with statin monotherapy[208,254]. In a study of 252,460 patients treated with lipid-lowering agents, 24 cases of hospitalized rhabdomyolysis occurred during treatment[255]. Average incidence per million person-years for monotherapy was 44 for statins, 282 for fibrate and 598 for statin fibrate combination therapy. Per person-year of therapy, the number needed to produce one case of rhabdomyolysis was 22,727 for statin monotherapy compared to 484 for older patients with DM who were treated with statin-fibrate combination. However, no such harm was reported in the ACCORD Trial despite net harm was noted in women and non Whites[56]. It is worth highlighting that the incidence of significant elevation in transaminases elevation in transaminases (AST/ALT) is 5 per cent with fenofibrate – 3 times higher than all statins at the highest doses[183]. Other adverse effects of fibrates include cholelithiasis and increase in creatinine level[56].

Barriers to statin use in clinical practice

Therapy directed at controlling both high blood pressure and high cholesterol can reduce the first or

second CVD event by 80 per cent[256]. However, many patients stop taking medications that are intended to be taken lifelong or take it less than described (non adherence) reducing the potential benefits[257].

Many patients fail to achieve the LDL-C and non-HDL-C treatment goals because of a combination of suboptimal prescription rates, failure to titrate statin dose and or premature cessation of therapy. Non-adherence to medications is common and as high as 50 per cent in primary prevention and 34 per cent in secondary prevention. This results in 260,000 avoidable CVD deaths and countless CVD events annually in the US[257]. Use of higher doses of potent statins such as atorvastatin or rosuvastain results in the greatest number of patients achieving therapeutic goals for all atherogenic lipoproteins [except for Lp(a)][34,51]. The lack of any insurance coverage for prescription medications resulting in patient paying the entire costs is another major barrier in India.

Conclusions and recommendations

Previous arguments that statins do not reduce total mortality and that the benefits are limited to high risk individuals (with an annual risk of >2%) are no longer valid. The critical review of evidence clearly demonstrates that statin therapy provides significant overall benefit in primary prevention[32,258]. In primary prevention, statin therapy prevents between 1200 and 28,400 CVD events and between 200 and 9,200 deaths depending on the degree of LDL-C reduction and the patients risk status. The benefits of statin therapy far outweigh any possible serious adverse effects, even in people at very low risk of CVD events[32,35]. The risk of NOD is limited to those with known risk factors for DM and the magnitude of the risk is only about half that of diuretics and beta-lockers. The CVD risk reduction is 50 times larger with statins even among those who develop NOD. The excess risk of rhabdomyolysis with statins is 20 and fatal rhabdomyolysis is 2 per million person-years. There is no correlation between magnitude of LDL-C lowering and serious muscle or liver toxicity. This is in sharp contrast to the use of aspirin in primary prevention, where the net harm outweighs the benefit in many people, especially if they are already on a statin. Thus, statins should supplant aspirin as the drug of choice in primary prevention of CVD with aspirin reserved for highly select individuals among whom the benefits clearly outweigh the risk. Lowering LDL-C early in life is substantially more effective in reducing CAD risk than the current practice of lowering LDL-C later in life when subclinical atherosclerosis (silent heart disease) is probably already present. A public health strategy that focuses on prolonged sustained reductions in LDL-C beginning early in life could potentially reduce the global burden of CAD, especially in India. It is time to expand the widely accepted LDL-C dictum from "the lower the better" to "lower and earlier the better".

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Reprint requests: Dr Enas A. Enas, Coronary Artery Disease in Asian Indians (CADI) Research Foundation, Lisle, IL USA
e-mail: cadiusa.org@gmail.com