Intensive Statin Therapy for Indians: Part-I Benefits.

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***Abstract**: The underlying disorder in the vast majority of cases of cardiovascular disease (CVD) is atherosclerosis, for which low-density lipoprotein cholesterol (LDL-C) is recognized as the first and foremost risk factor. HMG-CoA reductase inhibitors, popularly called statins, are highly effective and remarkably safe in reducing LDL-C and non-HDL-C levels. Evidence from clinical trials have demonstrated that statin therapy can reduce the risk of myocardial infarction (MI), stroke, death, and the need for coronary artery revascularization procedures (CARPs) by 25-50%, depending on the magnitude of LDL-C lowering achieved. Benefits are seen in men and women, young and old, and in people with and without diabetes or prior diagnosis of CVD. Clinical trials comparing standard statin therapy to intensive statin therapy have clearly demonstrated greater benefits in CVD risk reduction (including halting the progression and even reversing coronary atherosclerosis) without any corresponding increase in risk. Numerous outcome trials of intensive statin therapy using atorvastatin 80 mg/d have demonstrated the safety and the benefits of lowering LDL-C to very low levels. This led the USNCEP Guideline Committee to standardize 40 mg/dL as the optimum LDL-C level, above which the CVD risk begins to rise. Recent studies have shown intensive statin therapy can also lower CVD events even in low-risk individuals with LDL-C <110 mg/dL. Because of the heightened risk of CVD in Asian Indians, the LDL-C target is set at 30 mg/dL lower than that recommended by NCEP. Accordingly, the LDL-C goal is <70 mg/dL for Indians who have CVD, diabetes, metabolic syndrome, or chronic kidney disease. Intensive statin therapy is often required in these populations as well as others who require a ≥50% reduction in LDL-C. Broader acceptance of this lower LDL-C targets and its implementation could reduce the CVD burden in the Indian population by 50% in the next 25 years. Clinical trial data support an extremely favorable benefit–to–risk ratio of intensive statin therapy with some but not all statins. Atorvastatin 80 mg/d is 100 times safer than aspirin 81 mg/d and 10 times safer than diabetic medications. Intensive statin therapy is more effective and safe compared to intensive control of blood sugar or blood pressure in patients with diabetes.*

INTRODUCTION

This article reviews the role of statins in general and intensive statin therapy, in particular for the prevention and control of cardiovasculardisease (CVD), thus reducing the need for expensive hospitalizations and coronary artery revascularization procedures (CARPs) and improving the overall quality of life. Part II discuses the safety issues and strategies for predicting and preventing serious adverse effects with intensive statin therapy. Asian Indians have the highest rates of premature CVD and therefore requires early intensive intervention for all modifiable risk factors. The results of a meta-analysis of 10 prospective studies and 28 randomized controlled trials, based on half a million men and women and 18,000 coronary events in 1994 by Law et al showed that a 25 mg/dL decrease in total cholesterol (TC) decreases the risk of coronary artery disease (CAD) by 54% at age 40, falling to 20% at age 70[1]. The results of a recent large meta-analysis by Lewington in 2007[2], have reinforced the crucial role of TC, lipoproteins and their ratios in the development of atherosclerosis and its devastating sequel such as myocardial infarction (MI), stroke and sudden deaths. The analysis included 61 prospective observational studies, consisting of almost 900,000 adults without previous CVD and with baseline measurements of TC recorded. During the 12 million person-years of follow-up, there were >55,000 vascular deaths (34,000 CAD, 12,000 strokes and 10,000 other). A 40 mg/dL lower TC level was associated with about 56% lower CAD mortality at ages 40-49, in both sexes. This study also showed that the risk fell to 34% at ages 50-69, and to 17% at ages 70-89 years. Both these meta-analysis underscore the need for lowering cholesterol levels at a younger age[2].

Total cholesterol consists of both atherogenic and antiatherogenic lipoproteins. The atherogenic lipoproteins include low-density lipoprotein cholesterol (LDL-C), very low density lipoprotein (VLDL-C), and lipoprotein(a) [LP(a)] and each of these particles carries one particle of apolipoprotein B (apo B). High density lipoprotein (HDL-C) is the predominant antiatherogenic lipoprotein and carries one particle of the highly cardioprotective apoliprotein A1 that protects against plaque formation and promotes plaque regression. A 1% increase in HDL-C confers a 2% decrease in CVD risk and a 1 mg/dL decrease confers a 4% decrease in CVD risk[3]. Moreover, the risk of CAD for a given TC varies 2-3-fold depending on the amount and proportions of atherogenic and antiatherogenic lipoproteins.

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***Table 1**: Abbreviations and Acronyms*

ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACS	Acute Coronary Syndrome
ARBITER 6	ARBITER 6: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 - HDL And LDL Treatment Strategies in atherosclerosis (HALTS)
ARIC	Atherosclerosis Risk In Communities Study
ADA	American Diabetic Association
AHA	American Heart Association
AIM-HIGH	Atherothrombosis Intervention In Metabolic Syndrome With Low HDL/High Triglyceride and Impact On Global Health outcomes
Apo B	Apolipoprotein B
ALT	Alanine aminotransaminase (previously SGPT)
AST	Aspartate aminotransaminase (previously SGOT)
BIP	Bezafibrate Infarction Prevention Study
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CARP	Coronary Artery Revascularization Procedures such as angioplasty, stent and bypass surgery
CK	Creatine Kinase
CKD	Chronic kidney disease
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CRP	C- reactive protein
CVD	Cardiovascular Disease
EGFR	Estimated Glomerular Filtration Rate
FHS	Framingham Heart Study; FRS =Framingham risk score
HALTS	HDL and LDL Treatment Strategies in Atherosclerosis
LOT	Lipid optimizing therapy
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
MACE	Major Adverse Cardiovascular Events including cardiac death, heart attacks, and strokes
LOT	Lipid – Optimizing Therapy
NCEP	National Cholesterol Education Program
LDL-C	Low- Density Lipoprotein Cholesterol
HDL-C	High-Density Lipoprotein Cholesterol
IMPROVE-IT	The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
IRIS trial	Comparison of rosuvastatin versus atorvastatin in South-Asian patients at risk of coronary heart disease
MI	Myocardial Infarction
NAFLD	Non Alcoholic Fatty Liver Disease
NLA	National Lipid Association
NCEP	National Cholesterol Education Program
Non-HDL-C	Non-HDL Cholesterol
NSTTEMI	Non-ST Elevation Myocardial Infarction (formerly subendocardial MI)
PCI	Percutaneous Coronary Intervention
RCT	Randomized Clinical Trial
SCORE	Systematic COronary Risk Evaluation
STEMI	ST Elevation Myocardial Infarction
TC	Total Cholesterol
TG	Triglycerides
VA-HIT	Veteran Administration HDL Intervention Trial
VLDL-C	Very Low-Density Lipoprotein Cholesterol
WHO	World Health Organization

CRUCIAL ROLE OF LDL-C, NON-HDL-C, AND APOLIPOPROTEIN B.

Elevated LDL-C plays a pivotal role in the development and progression of the atheromatous plaque and its rupture, which causes most of the acute manifestations of CAD[4]. Atherosclerosis cannot be produced in experimental animals without some elevation in LDL-C. LDL-C level in human umbilical cord blood is low (25-30 mg/dL) and lower than the HDL-C level[5]. Moderate lifelong reduction in the plasma level of LDL-C is associated with a substantial reduction in the incidence of major adverse cardiovascular events (MACE) such as cardiac death, MI and stroke even in the presence of highly prevalent non-lipid related CVD risk factors. Individuals with hypobetalipoproteinemia (LDL-C<70mg/dL) have reduced levels of haemostatic risk factors and have reduced risk of atherosclerosis[6-8]. In the ARIC study, 3% of the population had a mutation of PCSK9 gene. This mutation was associated in blacks with a 28% reduction in LDL-C and 88% reduction in CAD and in whites a 15% reduction in LDL-C and a 47% reduction in the risk of CAD[9]. Other studies have also shown that a PCSK9 mutation is associated with a 60% lower risk of premature MI[10]. Together, these studies indicate that a lifelong 1% reduction in LDL-C confers a 3% reduction in CVD % far greater the 1% reduction observed in randomized clinical trials that usually lasts only 5 years. Conversely, children with LDL-C >400 mg/dL can develop advanced CAD before 10 years of age[11]. In fact it was the study 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[12].

Evidence from controlled clinical trials for lowering LDL-C has corroborated a causal role for LDL-C in atherogenesis. The optimum LDL-C level is currently standardized at 40 mg/dL. Grundy etal[13] have demonstrated a log-linear relationship between increased serum LDL-C levels and increased relative risk for CAD. The data plotted in this way suggest that for every 1 mg/dL change in LDL-C, the relative risk changes by 1%. Thus, an individual with an LDL-C of 70 mg/dL has a 30% higher risk than one with an LDL-C of 40 mg/dL.

LDL-C is the principal target for treatment and non-HDL-C is the secondary target. Non–HDL-C goal is set at 30 mg/dL higher than the LDL-C goal[14]. Recent studies show that VLDL-C is as much or more atherogenic than LDL-C[15-17]. The combined risk from LDL-C and VLDL-C is best assessed by calculating non-HDL-C, which is obtained by simply subtracting HDL-C from the TC. Non–HDL-C has been shown to be a strong predictor of severity of coronary atherosclerosis and CVD events particularly in patents who have elevations in both TC and triglycerides (TG)[18]. In patients with LDL-C <100 mg/dL, those with non-HDL-C >130 have an 84% increased risk of CVD[19]. As expected, the relationship with CVD was stronger for non-HDL-C than for LDL-C in the meta-analysis by Lewington[2]. However, the TC/HDL-C was the strongest predictor of CAD mortality 40% more informative than non-HDL-C and more than twice as informative as TC[2]. Furthermore, the CAD risk was higher at a TC/HDL ratio of 7, than that for a non-HDL-C of 240 mg/dL (or TC 280 mg/dL) at every age group. In patients with LDL-C <100 mg/dL, those with TC/HDL ratio >5 have a more than double the risk compared those with TC/HDL ratio <5[19].

Non–HDL-C is highly correlated with ApoB; hence, non–HDL-C is an acceptable surrogate marker for Apo B in clinical practice for the initial testing and then for monitoring the response to therapy. A 40 mg/dL lower non-HDL-C achieved with lipid-optimizing therapy confers a 35-40% reduction in CAD risk (1:1 relationship between percent non-HDL-C lowering and CAD risk reduction)[17,18,20]. The apo B target is <90 mg/dL in high risk patients and <80 mg/dL in very high risk patients[21-23] .

LIFESAVING BENEFITS OF STATINS

In 1994, the first randomized statin trial (4S) demonstrated that lowering LDL-C reduced total mortality[24]. The 4S was followed by numerous additional successful RCTs, with a variety of statins and a variety of patient populations. These studies clearly established LDL-C reduction as the most effective intervention to reduce the CVD risk (**Table 2**). Statin therapy not only reduces LDL-C, but also confers lifesaving benefits by reducing coronary events, stroke, cardiac deaths and all-cause deaths,

without increasing non-coronary mortality. As a result, reduction in LDL-C with statin therapy has become the mainstay of primary and secondary prevention of CAD. The benefits have been demonstrated in men, women, elderly, children and those with diabetes, metabolic syndrome and hypertension, low HDL-C, low LDL-C, high Lp(a) and high C-reactive protein (CRP). As the only agents that favorably affect its natural history, statins have transformed the management of patients with vascular disease with significant reduction in the incidence and mortality from MI. The hospital mortality is 8-10% for ST-elevation myocardial infraction (STEMI) and 5% for Non ST-elevation myocardial infraction (NSTEMI) in the US, the latter accounting for 85% of all MI[25-27]. The number of patents hospitalized for an MI decreased by 15% and stroke by 14% from 1997 to 2007.

Table 2: *Placebo-Controlled Standard Statin Therapy Trials*

Trial	*# of patients*	*Treatment*	*Lipid Change*	*Reduction in MACE*
4S[24, 28, 29]	4,444	Simvastatin 20-40 mg/d for 60 months	TC 210-320 mg/dL	30%↓ for all-cause death and 42%↓ for coronary death
LIPID[30]	9,014	Pravastatin 40 mg/d for 73 months	TC 150-271 mg/dL	26% ↓in MACE
CARE[31]	4,151	Pravastatin 40 mg/d for 60 months	LDL-C139 mg/dL	24% ↓ in MACE*
WOSCOPS[32]	6,595	Pravastatin 40 mg/d for 60 months	TC 272 mg/dL	26%↓ LDL-C 31%↓in MACE
PROSPER[33]	5,804	Pravastatin 40 mg/d for 36 months	TC160-360 mg/dL	34% ↓in LDL-C 15% ↓in MACE
HPS[34]	20,536	Simvastatin 40 mg/d for 60 months	LDL-C ↓ 40 mg/dL	24% ↓in MACE
AFCAPs/Tex CAPS [35]	6,605	Pravastatin 40 mg/d for 62 months	LDL-C 150 mg/dL	37% ↓in MACE
ASCOT-LA[36]	10,305	Atorvastatin 10 mg/d for 39 months	TC<250 mg/dL	50 mg/dL ↓in LDL-C 36%↓in MACE
CARDS[37]	2,838	Atorvastatin 10 mg/d for 45 months	LDL-C 120 mg/dL	43mg/dL ↓in LDL-C 37% ↓in MACE
MEGA[38]	7,832	10-20 mg/d pravastatin for 51 months	LDL-C 156 to 128 mg/dL	18%↓ MACE

4S	(1994) Scandinavian Simvastatin Survival Study
WOSCOPS	(1995) West Of Scotland COronary Prevention Study
CARE	(1996) Cholesterol And Recurrent Events
AFCAPs/Tex CAPS	(1998) Air Force/Texas Coronary Atherosclerosis Prevention Study
LIPID	(1998) Long-Term Intervention with Pravastatin in Ischemic Disease
PROSPER	(2002) Pravastatin in elderly individuals at risk of vascular disease
HPS	(2002) Heart Protection Study
ASCOT-LA	(2003) Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm
CARDS	(2004) Collaborative Atorvastatin Diabetes Study (CARDS)
MEGA	(2006) Primary prevention of cardiovascular disease with Pravastatin in Japan

CARP = coronary artery revascularization procedures such as angioplasty, stent and bypass surgery
MACE = Major adverse cardiovascular events including death, heart attacks, and strokes and CARP

Now the elderly (>65 years of age) accounts for 83% of deaths from CAD and the vast majority of MI (58% for men and 79% for women)[39]. In several large randomized controlled clinical trials involving >100,000 patients, statins have consistently reduced the risk of CVD events across a broad spectrum of patients at risk[40]. In 3 large trials of patients with stable CAD, statins reduced not only MACE but also total mortality[24, 34, 41]. In addition, meta-analysis of statin trials have shown reduction in all-cause mortality[42].

Patients in almost every category that has been studied have benefited substantially from statin therapy. Such outcome data are scant with other lipid-lowering agents. The benefits accrue in men and women, hypertensives and normotensives, diabetics and nondiabetics, and particularly in smokers. The biologic effects are mediated by lipid and non-lipid related (pleiotropic) effects. These include: 1) rapid improvement in endothelial function; 2) attenuation of vascular inflammation; 3) stabilization of plaques; 4) decreased prothrombotic tendencies; 5) influencing myocardial protection and remodeling; and 6) LDL-C lowering[43,44]. The statin trials evidence is consistent with a one-to-one relationship between LDL-C lowering and CAD and stroke reduction over five years of treatment[45]. Although the CRP-lowering effect of statins has received renewed attention in recent years, in clinical practice, most of the anti-inflammatory effect of LDL-lowering therapies is related to the magnitude of change in LDL-C. The potential non-LDL effects of statins on inflammation are much smaller in magnitude[46]. In clinical trials the benefits of statin continues for at least 10 years[47].

The reduction in MACE depends on the degree and extent of LDL-C reduction. There was a significant positive relationship between reduction in LDL-C and reduction in MACE in a meta-analysis of 25 statin trials published in 2009% comprising 155,613 subjects, 6321 vascular deaths, 23,791 major vascular events, 11,357 major coronary events and 4,717 strokes[48]. For every 50 mg/dL reduction in LDL-C the reduction in MACE was as follows:

- 22% reduction in vascular mortality
- 28% reduction in major vascular events
- 32% reduction in major coronary events
- 20% reduction in stroke
- 35% reduction in CVD risk[49]

Reduction in TC levels with diet and statins have played a crucial role in the decline of CAD mortality observed over the past 40 years in the US[50]. In the Coronary Drug Project (1960s), 26% of the patients had died and another 16% had a recurrent MI after 6 years of follow-up, in the control group[51]. On the other hand, both mortality and recurrent MI rates were 6% in the control group in the TNT Study (2005)[52]. In addition, the severity of MI has decreased dramatically with STEMI, currently accounting for only 15% of all MI in the US. However, STEMI is more common than non-STEMI in India[53].

STATIN POTENCY

The CVD outcome is directly proportional to the extent of lipid lowering, which in turn is dependent on the potency of the statin and the dose used. There are currently six commercially available statin medications on the US market. Three of these % lovastatin, simvastatin and pravastatin are available in generic formulations (and are thus less expensive). Of the commercially available statins, rosuvastatin, atorvastatin and simvastatin have the highest potency. While atorvastatin has the most clinical event data for CVD prevention, the JUPITER Trial has filled this void for rosuvastatin. The LDL-C lowering efficacy of rosuvastain and atorvastatin in Europeans and Americans are given in **Table 3** and Asian Indians in **Table 4**[55]. In general, doubling the dose of a statin results in approximately 5-6% greater reduction in LDL-C and non-HDL-C[54].

Rosuvastatin presents significant advantages in goal achievement and lipid lowering over other statins at commonly prescribed doses. In one study, rosuvastatin 10 mg/d achieved LDL-C goal of <70 mg/dL in 45% compared with 38% of those who received simvastatin 40 mg/d[56]. In general, 10 mg/d of rosuvastatin

treatment results in more patients reaching the LDL-C goal compared with 10 mg/d of atorvastatin and 40 mg/d of simvastatin, potentially reducing the need for titration visits[57]. However, the goal achievement depends upon the base line LDL-C as well as the LDL-C goal. For example, in patients with baseline LDL-C >160 mg/dL, the achievement of LDL-C goal with rosuvastain 10mg/d is 57% when the LDL target is <100 mg/dL but only 11% when the LDL-C target is <70 mg/dL (**Table 5**). Pitavastatin is more potent and will be available in the US in the near future.

Table 3: *Percent Reduction in Lipid Parameters with Increasing Statin Doses*[54] .

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

**Measured in 24,340; other lipids measured in 32,258 patients*

Table 4: *The Efficacy and Adverse Effects of Atorvastatin and Rosuvastatin in Asian Indians in IRIS* [55]

Statin and dose	*Non-HDL-C mg/dL*	*LDL-C mg/dL*	*LDL-C <100 mg/dL*	*LDL-C <70 mg/dL*	*Adverse Effects****
Atorvastatin 10 mg/d (n=185)	-36%	-40%	70%	18%	1.1%
Rosuvastatin 10 mg/d (n=189)	-40%**	-45%*	76%	42%	3.2%
Atorvastatin 20 mg/d (n=184)	-42%	-47%	81%	42%	2.7%
Rosuvastatin 20 mg/d (n=182)	-44%	-50%	88%	56%	4.5%

** p = 0.002 ; **p = 0.012; *** adverse effects leading to discontinuation*

Table 5: *Percentage of Patients Achieving the LDL-C Goals.*[54]

	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
Rosuvastatin						
5 mg/d	NA	0%	3%	NA	67%	38%
10 mg/d	47%	33%	11%	82%	76%	57%
20 mg/d	81%	57%	21%	95%	90%	65%
40 mg/d	84%	68%	32%	97%	95%	74%
Atorvastatin						
10 mg/d	28%	9%	2%	71%	62%	29%
20 mg/d	65%	26%	4%	91%	84%	45%
40 mg/d	73%	45%	10%	97%	91%	57%
80 mg/d	76%	52%	18%	94%	86%	71%

TIME TO BENEFIT FROM STATINS

Although clinical trials are not designed to demonstrate when the benefit of treatment begins, they have given some insights into the onset of benefits from statins. Intensive statin therapy early after ACS leads to a reduction in clinical events within 30 days, consistent with greater early pleiotropic effects. According to the meta-analysis by Law, the reductions in incidence of MACE were 7% in the first two years, 22% within 2 to 5 years, and 25% after five years for a 24 mg/dL decrease in LDL-C. The full effect of the reduction in risk is achieved by five years[1].

STATIN THERAPY AND SECONDARY PREVENTION

Men and women derive substantial benefit from statin therapy in secondary prevention, with the SPARCL Trial demonstrating a 40% reduction in MACE and 50% reduction in CARPs[58]. Although the relative risk reduction with statin therapy is similar in both primary and secondary prevention, the absolute risk reduction is greater in secondary prevention. The overall reduction is about 20% for a 40 mg/dL LDL-C reduction. This translates into 48 fewer participants having MACE per 1000 among those with pre-existing CAD at baseline, compared with 25 per 1000 among participants with no such history. A UK study of patients treated by general practitioners showed that statin therapy following an MI reduced death rates by >60% compared to statin non-users (41 per 1000 person-years vs. 127 per 1000 person- years)[59]. Thus, the community effectiveness of statins was similar to the efficacy of statins in th clinical trials.

STATIN THERAPY AND PRIMARY PREVENTION

A meta-analysis of 10 primary prevention trials that comprised a total of 70,388 people, of whom 23,681 (34%) were women and 16,078 (23%) had diabetes mellitus was reported in 2009. This analysis showed a 12% reduction in all-cause mortality, 30% reduction in MACE, and 19% reduction in stroke. No evidence of an increased risk of cancer was observed[60]. The benefits were even higher in the large JUPITER Trial, which achieved 50% reduction in LDL-C to <50 mg/dL in 50% of the patients[61].

STATIN THERAPY AND MYOCARDIAL INFARCTION (MI)

In a meta-analysis of 65,000 patients treated with statins or placebo, the risk of MI was reduced by 23 % among patients treated with statins[62]. Other studies have shown a 28% reduction in recurrent MI and a 44% reduction in first MI (JUPITER)[61, 63].

STATIN THERAPY AND CORONARY ARTERY REVASCULARIZATION PROCEDURES

A substantial 25-40% reduction in the need for first and repeat CARP was observed with intensive statin therapy with atorvastatin in several trials[64-67]. The reduction in the need for CARP was 40% in SPARCL Trial and 46% in JUPITER Trial. Atorvastatin 80 mg/d administered at least 1-7 days before elective PCI reduced the incidence of periprocedural MI by 40% and MACE by 50% in 30 days, in both statin naïve and statin-treated patients[68-70]. A systematic review of the safety and efficacy of statin therapy before and after CABG has demonstrated that statins improve the outcomes of patients undergoing CABG. The benefits outweigh the risks associated with statin use, both

in the preoperative and postoperative period. Essentially all CABG patients are candidates for life-long statin therapy that should be started before surgery, in the absence of contraindications[71].

STATIN THERAPY AND STROKE

Despite the inconsistent or weak association between TC levels and stroke, lowering of TC concentrations with statins reduces the risk of stroke in a broad range of populations including patients with non-cardioembolic stroke or transient ischemic attack[72]. Statin therapy is the most important advance in stroke prevention since the introduction of aspirin and antihypertensive treatments[42]. Among diabetic patients in the CARDS Trial (**Table 2**), atorvastatin 10 mg/d reduced stroke by 48%[37]. In a meta-analysis of randomised trials of statins (in combination with other preventive strategies) comprising 165,792 individuals, there was evidence that each 40 mg/dL decrease in LDL-C resulted in a 21% reduction in non-cardioembolic stroke. In the SPARCL Trial (**Table 2**), atorvastatin 80 mg/d reduced the risk of stroke by 16% in the overall cohort in the intention-to-treat analysis[73]. The risk of ischemic stroke was reduced by 31% among those who achieved a >50% reduction in LDL-C with no increase in hemorrhagic stroke[74]. The impact of lowering TG and increasing HDL-C in stroke prevention is not as robust as lowering of LDL-C[72].

STATIN AND PERIPHERAL VASCULAR DISEASE (PVD)

In the HPS (**Table 2**), allocation to 40 mg/d simvastatin daily reduced the rate of MACE by about 25%, and that of PVD events by 16%, with large absolute benefits seen in participants with PVD. Because of their high vascular risk, statin therapy should be considered routinely for all patients with PVD[75]. In sharp contrast, aspirin has not shown any benefit in patents with PVD[76].

STATIN THERAPY AND CHRONIC KIDNEY DISEASE (CKD)

Over 10% of the US population has some form of CKD and this figure is likely to be higher in India where the control of blood pressure and diabetes is poor. Although some patients with CKD will ultimately develop renal failure, most patients with CKD will die of CVD before dialysis becomes necessary. Statins are the cornerstone of therapy for dyslipidemia in most patients with CKD. However, differences in their pharmacokinetic properties give some statins a safety advantage in patients with advanced CKD. Atorvastatin has <2% renal excretion and does not need dose adjustments for GFR <30 ml/minute, but the rosuvastain dose should be reduced to 5-10 mg/d when GFR is <60 ml[77]. Fibrates are renally metabolized and CKD patients require both adjustments in dose and very careful monitoring when used as monotherapy or comination therapy with statins due to the increased risk of rhabdomyolysis.

STATIN THERAPY AND DIABETES

Type 2 diabetes is associated with a 2 to 4-fold higher risk of CVD incidence and mortality[37]. Two out of three patients with multi-vessel disease or ACS have known diabetes, undiagnosed diabetes or prediabetes[78]. CVD remains the leading cause of death and disability among patients with diabetes**.** Both FRS and SCORE prediction models do not include diabetes, which is particularly common among Asian Indians. The SCORE and other data indicates that diabetes confer a greater risk than suggested by FHS with a relative risk of 5 in women and 3 in men[79,80]. In a study of Asian Indians with ACS (mean age 55) 24% had diabetes and 46% had prediabetes with only 16% having normal glucose tolerance[81].

The CAD risk from diabetes 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 diabetes at baseline compared to only 13% among Europeans[82]. Compared with nondiabetics, diabetes 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 mortally rates among South Asians with diabetes than whites with diabetes (after adjustment for gender, age, educational level, smoking, hypertension, alcohol intake, and obesity)[83-85]. These data suggest that South Asians are markedly sensitive to the impact of diabetes on CAD risk. This heightened risk of CAD among South Asians with diabetes is in sharp contrast to the 32-44% lower risk observed among blacks, Hispanics and other Asians[86,87]. Thus, there is a marked difference in the impact of diabetes on CAD mortality among people of different ethnic origin. Some studies have shown Asian Indian diabetics achieve poor control of risk factors[88].

Hyperglycemia is a weaker risk factor than high cholesterol or high blood pressure for CAD. A meta-analysis of diabetic patients showed that a 1-percentage point increase in glycosylated hemoglobin level confers an 18% risk of CVD[89]. Moreover, intensive control of blood sugar has been difficult to achieve without significant hypoglycemia and the CVD benefits have been less than spectacular. A 2009 meta-analysis of the effect of intensive control of glucose on CVD outcomes in patients with diabetes mellitus involved 5 trials. There were 1,497 MIs, 2,318 CAD 1,127 of strokes, and 2,892 of all-cause mortality, during approximately 163,000 person-years of follow-up. The difference in hemoglobin AIC was only 0.9% between participants given intensive treatment and standard glycemic treatment. Intensive glycemic control resulted in a 17% reduction in MI and 15% reduction in CAD events, but no significant effect on stroke or all-cause mortality. The magnitude of the benefit from intensive glycemic control was substantially lower than that reported with tight control of blood pressure and intensive lowering of LDL-

C[90]. Epidemiological and interventional studies show that a 50 mg/dL decrease in LDL-C results in 32% reduction in MACE and 20% reduction in stroke whereas s a 10 mm Hg decrease in systolic blood pressure results in 22% reduction in MACE and 41% reduction stroke[2,48,91]. Statins and newer hypertensive agents provide simple regimens with minimal side effects. Conversely, intensive glucose lowering requires drugs that might have to be injected several times a day that can produce severe side effects. The need for monitoring, with finger stick samples for blood sugar several times a day, have a significant effect on quality of life and the medical cost may be beyond the reach of most patients.

In sharp contrast to the limited benefits of intensive glucose-lowering therapy, several studies in diabetic patents have clearly demonstrated substantial reduction in MACE with statin therapy. In the CARDS Trial, atorvastatin 10 mg/d for 4 years in patients with diabetes reduced MACE by 36%, CARP by 31%, and stroke by 48% and all-cause death by 27%[37]. A 2008 meta-analysis involving 18,686 people with diabetes (in 14 randomized trials of statins) has further corroborated the benefits of statins in patients with diabetes[92]. According to this analysis, after 5 years of statin therapy, 42 fewer people with diabetes had MACE per 1000 allocated statin therapy. This correspond to a rate of 8,400 MACE prevented per million person-years of statin therapy. Although there was some increase in diabetes in the JUPITER Trial, a meta-analysis of all statin trials showed no increased risk of diabetes[93].

Statin therapy is now recommended for all diabetics >40 years of age by the AHA and ADA, regardless of the baseline lipid levels. The clear benefits of statin therapy in patients with diabetes is in sharp contrast to the lack of benefit of aspirin in primary prevention of CVD in diabetic patients[94]. A systematic review of trials evaluating the benefit of aspirin therapy for primary prevention of CVD in 11,618 individuals with diabetes showed no significant reduction in MACE[95,96].

STATIN THERAPY AND METABOLIC SYNDROME

A post hoc analysis of the TNT Trial assessed whether intensive statin therapy results in greater CVD benefits for patients with both CAD and metabolic syndrome. The mean LDL-C was 99 mg/dL in those randomized to atorvastatin 10 mg/d and 73 mg/dL in those randomized to atorvastatin 80 mg/d. Irrespective of treatment assignment, at a median of 4.9 years, significantly more patients with metabolic syndrome (11.3%) had a MACE than those without metabolic syndrome (8.0%) % a 44% higher risk. MACE occurred in 367 patients (13%) receiving atorvastatin 10 mg/d, compared with 262 patients (9.5%) receiving atorvastatin 80 mg/d % 29% reduction in MACE. This large study has demonstrated that patients with CAD and metabolic syndrome derive incremental benefit from intensive therapy with high-dose atorvastatin therapy, irrespective of the presence of diabetes[97].

STATIN THERAPY IN WOMEN

A meta-analysis of 15 statin trials showed a MACE reduction of 19% in women compared to 24% among men. The CVD outcome was primarily driven by reductions in unstable angina and need for revascularization[98]. In addition to reducing MACE statin use also reduces the risk of atrial fibrillation, gall stones and need for cholecystectomy in women[99,100].

STATIN THERAPY IN ELDERLY

Statins continue to be underutilized in elderly (>65 years of age) patients based on the assumption that with fewer years ahead, there may be little benefit with such treatment. The PROSPER Trial randomized 5,804 men and women aged 70-82 years with pravastatin vs. placebo, which lowered LDL-C by 34% and reduced MACE by 15%[33].The SAGE Trial (**Table 6**) has demonstrated that elderly men and women age 65-85 not only tolerate intensive statin therapy with atorvastatin 80 mg/d, but also derive greater benefit with a 67% reduction in all-cause mortality[101]. A pooled analysis of statin trials in the elderly with CAD (19,569 subjects, ages 65-92 years; mean follow-up 4.9 years) showed a relative risk reduction in CAD mortality by 30%, MI 26%, CARP 30% and stroke 25%. In addition, there was a 22% relative risk reduction and a 3.1% absolute risk reduction (15.6% in the statin users and 18.7% for control) in all-cause mortality. The number needed to treat to prevent one death was 28. Thus, absolute benefit of statin therapy in the elderly appears to be significantly greater than that observed in younger populations[102].

Table 6: *Intensive Statin Therapy Trials*

Trials	*# of subjects*	*Treatment*	*Change in LDL-C*	*Reduction in MACE*
Atorvastatin Trials				
ALLIANC[65, 120]	2,442	80 mg/d vs. usual care for 53 months	147 to 95 mg/dL	17%↓ in MACE 27%↓ >65 years
AVERT[121, 122]	314	80 mg/d vs. placebo for 18 months	>115 mg/dL	36% ↓ in MACE
IDEAL[123]	8,888	80 mg/d vs. simvastatin 20 mg/d for 56 months	122 to 81 mg/dL	13% ↓in MACE
MIRACL[124]	3,086	80 mg/d vs. placebo for 4 months	124 to 72 mg/dL	26% ↓ in MACE
PROVE-IT [125]	4,162	80 mg/d vs. pravastatin 40 mg/d for 24 months	106 to 62 mg/dL	16% ↓in MACE
REVERSAL[118]	654	80 mg/d vs. pravastatin 40 mg/d for 18 months	150 to 79 mg/dL	Halted progression of atherosclerosis
SAGE[101]	893	80 mg/d vs. pravastatin 40 mg/d for 24 months	N/A	29%↓in MACE 67% ↓ in death
SPARCL[73, 74]	4,071	80 mg/d for 57 months	129 to 73 mg/dL	20% ↓ in MACE 16 to 31% ↓ in stroke
TNT[62]	10,001	80 mg/d vs. 10 mg/d for 53 months	<130 to 77 mg/dL	22% ↓ in MACE
Rosuvastatin Trials				
ASTEROID[115, 116]	507	40 mg/d for 24 months	130 to 61 mg/dL	Regression of atherosclerosis
JUPITER	17,802	20 mg/d for 21 months	108 to 55 mg/dL	50% ↓ in LDL-C 44% ↓ in MACE
METEOR[117]	984	40 mg/d for 24 months	154 to 78 mg/dL	↓ progression of CIMT
Simvastatin Trials				
A-Z trial [126]	4497	Simasatin 80 mg/d vs. 20 mg/d	122 to 77 mg/dL 122 to 63 mg/dL	No ↓in MACE 25% ↓ in CV death
SEARCH	12,064	Simvastatin 80 mg/d vs. 20 mg/d	14%↓ LDL-C	6%↓in MACE

AVERT[121, 122]	(2000) Atorvastatin versus Revascularization Treatment
MIRACL[124]	(2001) Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
ALLIANC[65, 120]	(2004) Aggressive Lipid-Lowering Initiation Abates New Cardiac Events
PROVE-IT[125]	(2004) Pravastatin or Atorvastatin Evaluation and Infection Therapy
REVERSAL[118]	(2004) Reversal of Atherosclerosis with Aggressive Lipid Lowering
IDEAL	(2005) Incremental Decrease in Endpoints through Aggressive Lipid Lowering
SPARCL[73, 74]	(2006) Stroke Prevention by Aggressive Reduction in Cholesterol Level
ASTEROID[115, 116]	(2006) A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden
SAGE[101]	(2007) Study Assessing Goals in the Elderly
METEOR[117]	(2007)Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin
JUPITER [61]	(2008) Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
SEARCH	(ongoing) Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
TNT	Treat to New Target

MACE=major adverse cardiovascular events; CIMT=Carotid Intimal medial Thickness

STATIN THERAPY IN CHILDREN

The objective of statin therapy in children is to prevent the development and progression of the plaque (rather than preventing an MI at this young age) and delay the development of CVD. Children with very high TC levels develop atherosclerosis and progress rapidly in early teenage years[103]. 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[11,103]. Increased TC level may affect the aortic valve; aortic regurgitation may be the earliest sign of accelerated atherosclerosis in children[11].

The 2007 AHA Guidelines for management of dyslipidemia recommend intensive dietary management of children with focus on reducing the saturated fat and cholesterol intake[104]. The AHA recommends drug therapy in children >10 years of age, whereas the American Academy of Pediatrics now recommends drug therapy for dyslipidemia for children >8 years of age (including girls before menarche)[105]. The threshold of intervention 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 2 other risk factors. 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 Americans and Europeans as discussed below[106].

INTENSIVE STATIN THERAPY VERSUS STANDARD STATIN THERAPY

Increasing evidence suggests that intensive risk factor management beyond that currently proposed by guidelines has a beneficial impact on patients at risk of CVD. The COURAGE Trial which achieved substantially lower targets for all modifiable risk factors has substantiated the rationale for tempering the enthusiasm to perform PCI immediately upon detection of an obstructive lesion that are amenable to such procedure[107].

There is growing evidence that indicates that it is not the absolute value of the LDL-C after reduction, but the proportion of reduction from initial pre-treatment values that is significant, particularly in high-risk patients with high LDL-C levels[13, 34]. The 2009 Canadian Guidelines recommend 50% reduction in LDL-C as an achievable goal for many patients as an alternative to fixed target[108]. The UK guidelines for lipids suggests a fixed dose statin without a target[109].

Earlier statin trials using pravastatin 40 mg/d, lovastatin 20-40 mg/d, and simvastatin 20-40 mg/d established the benefits of lowering LDL-C in reducing MACE, cardiac deaths and total deaths by 25-35% in a broad range of patients. Earlier studies were done in patients with very high LDL-C and few patients achieved LDL-C <125 mg/dL. These studies led to the erroneous conclusion that lowering LDL-C to <125 mg/dL may be sufficient and that further lowering LDL-C is unwarranted and may be even harmful[31]. These misconceptions were further reinforced when clinical trials using simvastatin 80 mg/d not only failed to produce any beneficial CVD outcome but also produced unacceptable rates of myopathy and rhabdomyolysis. The US FDA approval of atorvastatin 80 mg/d and rosuvastatin 40 mg/d led to numerous randomized clinical trials that demonstrated the safety and ability of these statins to lower LDL-C to previously unimaginable very low levels. **Table 6** shows the clinical trials of intensive statin therapy that provided the supporting evidence. These trials led to NCEP lowering of the LDL-C targets to the current <70 mg/dL for high risk patients and the sea change of standardizing 40 mg/dL as the optimum LDL-C level. A wealth of evidence from these studies now points to the inevitable conclusion *"lower is better as far as LDL-C is concerned, provided that this can be achieved safely"*[110]. Intensive lipid lowering with high-dose statin therapy provided a significant benefit over standard-dose therapy for reducing MACE in several large clinical trials (**Table 6**)[111]. The benefit was seen in patients with both chronic CAD and ACS. The results of a meta-analysis of a total of 27,548 patients were enrolled in 4 large trials yielded a significant 16% reduction in CAD deaths or MI ($p < 0.00001$).

INTENSIVE STATIN THERAPY AND REGRESSION OF ATHEROSCLEROSIS

Slowest progression of atherosclerosis occurs in people with the lowest levels of both LDL-C and blood pressure[112]. But LDL-C is a stronger promoter of plaque progression than blood pressure[112]. The results of 11 secondary prevention trials on the effect of lipid-lowering therapy on coronary atherosclerosis have found that the percentage reduction in LDL-C levels correlates more closely with angiographic outcome (regression) than absolute LDL-C levels and is more significant in stabilizing the atherosclerotic plaque for prevention of CAD events[113, 114]. These observations support recommendations for intensive statin therapy for high-risk patients with established CAD[115]. Intensive therapy with rosuvastatin 40 mg/d and atorvastatin 80 mg/d have been shown to halt the progression of atherosclerosis in ASTEROID, METEOR and REVERSAL studies, but not in patients receiving moderate statin therapy with pravastatin 40 mg/d[115-118]. A post-hoc analysis combined raw data from 4 prospective randomized trials in which 1,455 patients with angiographic CAD underwent serial intravascular ultrasonography while receiving statin treatment. This demonstrated that a decrease in LDL-C and increase in HDL-C contributed significantly to the regression of atherosclerosis. Substantial atheroma regression (≥ 5% reduction in atheroma volume) was observed in patients with levels of LDL-C <88 mg/dL during treatment and percentage increases of HDL-C >8%[119]. The SANDS Trial has shown that reducing non-HDL-C to <100 mg/dL and systolic blood pressure to <110 mm Hg was necessary to produce regression of atherosclerosis[127]. Other studies have shown that patients with LDL-C >70 mg/dL and normal systolic

blood pressure did not reduce progression of coronary atherosclerosis[112].

INTENSIVE STATIN THERAPY IN ACS

Each year 1.5 million Americans suffer ACS[39]. The ACC/AHA Guidelines recommend early initiation of statin treatment in 1-4 days with the aim of achieving LDL-C <100 mg/dL and intensive statin therapy with the aim of LDL-C <70 mg/dL initiated within 10 days of ACS[128,129]. This level 1A recommendation is based upon 2 clinical trials: MIRACL and PROVE-IT (**Table 6**). In the MIRACL Trial, 3,086 patients with unstable angina or non- STEMI were randomized within 4 days of the event to atorvastatin 80 mg/d or to placebo and followed for 16 weeks. The primary composite end point occurred in 14.8% of atorvastatin patients and 17.4% of placebo patients % a 16% relative risk reduction with no difference between those <65 years and >65 years[124]. But the absolute event rates were approximately 2 to 3-fold higher in older than in younger patients. The safety profile of atorvastatin 80 mg/d was similar between the 2 age groups[130].

In the PROVE-IT trial, 4,162 patients hospitalized with ACS within the preceding 10 days were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d and were followed for a mean of 24 months (**Table 5**). The primary event rate was 22.4% in the atorvastatin group and 26.3% in the pravastatin group, (a 16% relative risk reduction, p = 0.005)[125]. A strong trend toward a reduction in total mortality was seen in the atorvastatin group (2.2% vs. 3.2%, p = 0.07). The differences between the treatment groups were already statistically significant at 30 days and remained so throughout the follow-up period. Pravastatin 40 mg/d had significantly reduced the primary end points in four previous large randomized clinical trials; this dose is equivalent to 40 mg/d lovastatin, 20 mg/d simvastatin or 10 mg/d atorvastatin. Comprehensive treatment programs in ACS patients that include initiation of statins before hospital discharge have been shown to improve outcomes such as recurrent MI and total mortality at 1 year[131].

In the PROVE IT-TIMI 22, those who achieved LDL-C <40 mg/dL had a 39% reduction in MACE compared to those who achieved an LDL-C of <80-100 mg/dL, irrespective of the statin randomization[132]. The benefit of intensive therapy was greatest in those with baseline LDL-C >132 mg/dL % a 37% reduction in MACE compared to 16% reduction in MACE in the overall cohort. Atorvastatin 80 mg/d was associated with improved outcomes provided the baseline LDL-C was >66 mg/dL[133]. The benefit of early initiation of statin therapy during ACS accrues over time so that a survival advantage is seen by 4-24 months.[134, 135]. Early intensive statin therapy reduces death and MACE after 4 months of treatment in ACS[136]. A meta-analysis of statin trials shows that in patients with recent ACS, intensive statin therapy reduced all-cause mortality by 25% (from 4.6% to 3.5% over 2.0 years)[137]. Starting the patients on intensive statin therapy during hospitalization for CAD have shown to increase the LDL-C goal attainment 10-fold %from 6% to 58%[131].

INTENSIVE STATIN THERAPY IN CHRONIC CAD

Statins have become the first-line agents in lipid therapy. The achievement of LDL-C targets often requires intensive statin therapy using high doses of potent statins like atorvastatin 80 mg/d or rosuvastain 40 mg/d. More aggressive LDL-C lowering with higher doses of more potent satins compared with lower doses of less potent statins has been shown to provide incremental benefits in patients with stable CAD[40, 52, 123]. In the TNT Trial, 10,002 patients with chronic CAD were randomized to a standard dose of atorvastatin 10 mg/d or a high dose of atorvastatin 80 mg/d. Intensive statin therapy compared to standard therapy provided the following clinical benefits[52]:

- 12% reduction in angina
- 12% reduction in myocardial infarction
- 25% reduction in stroke
- 28% reduction in revascularization procedures
- 26% reduction in hospitalization for heart failure

Only 8% of those who achieved the most reduction in LDL-C (<54 mg/dL) had MACE, compared to 12% among those who had the least reduction in LDL-C (>122 mg/dL) irrespective of the dose of the atorvastatin dose received[52]. Overall, intensive statin therapy was associated with a 16% reduction in MACE in a meta-analysis of statin trials in patients with chronic CAD[137]. Beneficial results from several clinical trials of high-versus moderate-dose statin therapy (**Table5**) support the recommendation to achieve a LDL-C <70 mg/dL in high-risk patients. As such, aggressive target goals for LDL-C levels have been established by Guideline Committees. Accumulating data from several recent randomized studies of more aggressive LDL-C reduction to <70 mg/dL in the high risk patients favor acceptance of such a new lower target for LDL-C using more intensive statin therapy. Such a strategy would affect the treatment of patients with CAD, metabolic syndrome, diabetes mellitus, cerebrovascular disease and chronic kidney disease[138]. Non-HDL-C is the secondary target of therapy for CAD prevention with the target set at 30 mg/dL higher than LDL-C. Most lipid-modifying drugs used as monotherapy, especially statins have an approximately 1:1 relationship between percent non-HDL-C lowering and CAD risk reduction[20].

INTENSIVE STATIN THERAPY IN PRIMARY PREVENTION

Most of the clinical trials demonstrating favorable outcome with intensive statin therapy were done in patients with CAD or stoke and used 80 mg/d of atorvastatin. Four primary prevention trials (MEGA, WOSCOPS, ASCOT, and AFCAPS) have demonstrated the reduction in CVD outcome with standard statin therapy in people with LDL-C in the range of 131-190 mg/

dL. The JUPITER Trial has now demonstrated the safety and benefits of intensive statin therapy in 17,802 low-risk adults without CAD, diabetes, or high LDL-C. The prevalence of risk factors was low and few. The study was terminated 2 years ahead of schedule due to overwhelming benefit. The baseline LDL-C was 108 mg/dL, considered well below the treatment threshold and rosuvastatin 20 mg/d resulted in the following biochemical and clinical outcome[61]:

- 50% reduction in LDL-C to 55 mg/dL
- 50% having LDL-C <55 mg/dL
- 25% having LDL-C <44 mg/d
- 23% having LDL-C <40 mg/dL
- 44% reduction in primary end point (P<0.0001)
- 44% reduction in MI (P=0.0002)
- 48% reduction in stroke (p=0.002)
- 46% for arterial revascularization (P<0.0001)
- 41% reduction in hospitalization for unstable angina (P<0.09)
- 47% reduction in stroke, MI or CVD death (P<0.00001)
- 20% reduction in death from any cause (P=0.02)
- 43% reduction in total venous thromboembolism (p=0.007).

The number needed to treat (NNT) prevent one MACE was 95 over 2 years, and 18 over 5 years which is a rate of 11,111 MACE prevented per million person years of therapy with rosuvastatin 20 mg/d. The relative risk reduction with rosuvastain was 4-fold higher than the 12% reduction reported for aspirin in primary prevention[61]. More importantly, the absolute risk reduction with rosuvastatin was 0.59 per 100 person years, which is 8 times higher than the absolute risk reduction with aspirin (0.07 per 100 person years) in primary prevention[139]. Those randomized to rosuvastatin did not have a significant increase in myopathy or cancer.[61] This was also true of the nearly 3000 patients who had an LDL-C of <40 mg/dL[61].

INTENSIVE STATIN THERAPY AND VERY LOW LDL-C (<40 MG/DL)

Intensive statin therapy has now become the standard of care for patients with CAD. The safety and effectiveness of statin usage for patients with extremely low LDL-C levels were recently evaluated. The study done in a tertiary care medical center, comprised of 6,107 patients with LDL-C <60 mg/dL; the mean age was 65 years, 43% had prior CAD, and 47% had diabetes mellitus. Statins were prescribed in 2,564 patients (60%) after the low LDL value was observed. During a mean follow-up of 2 years, there were 510 deaths; statin therapy was associated with 35% lower morality overall and 49% lower morality among those with very low LDL-C levels (<40 mg/dL, n=623). Statin use was not associated with an increase in malignancy, transaminase elevation, or rhabdomyolysis. This study has shown that statin therapy in the setting of a very low LDL-C level appears to be safe and associated with improved survival[140].

STATIN THERAPY AND RECURRENT EVENTS

Atherosclerosis is a lifelong pan-vascular disease and patients continue to face recurrent MACE after the initial one, which are usually ignored in statistical analysis in clinical trials. In the IDEAL Trial, there were 2,546 first MACE and 1,749 recurrent MACE, thus increasing the total MACE during the study duration to 4,295 among the 8,888 patients. Intensive statin therapy resulted in a 24-28% reduction in total MACE compared to 17% reduction in first MACE. A similar observation was made in PROVE IT Trial. These post-hoc analyses suggest that the totality of the benefit of intensive statin therapy in reducing CVD burden may be at least 50% greater than previously recognized, with one MACE prevented for every 10-15 patients receiving such treatment. Together, these analyses provide further support to the "lower is better" concept for the management of LDL-C in high-risk patients[141, 142].

DYSLIPIDEMIA AMONG ASIAN INDIANS

Prospective studies have shown that the incidence of CAD and mortality from CAD among Asian Indians are at least 2-fold higher than whites even when fully adjusted for smoking, blood pressure, cholesterol, insulin resistance, metabolic syndrome, diabetes and socioeconomic status[82, 143]. This heightened risk of CAD is due primarily to Asian Indian dyslipidemia that is characterized by: high serum levels of apo B; TG ; Lp(a); borderline high levels of LDL-C; and low levels of apolipoprotein A1 (apo A1) and HDL-C[144]. Asian Indians have high ratios of TC/HDL-C, TG/HDL-C, and apo B/apo A1[145-147]. These ratios are highly correlated with severity of CAD, as well as acute MI among Asian Indians[145, 148]. At a given level of TC, Indians have a lower LDL-C due to high triglycerides that artificially lowers LDL-C. At a given LDL-C level, Indians have higher risk because of high levels of lipoprotein(a), low levels of HDL-C and possibly dysfunctional HDL-C particles[144, 149-151].

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. The adverse effects of the modifiable risk factors related to lifestyle such as dyslipidemia, smoking, hypertension, atherogenic diet, physical inactivity, abdominal obesity and diabetes are markedly magnified in those with Lp(a) excess. This synergy between nature and nurture best explains the excess burden of CAD among Asian Indians.

INTENSIVE STATIN THERAPY FOR INDIANS

Evidence-based treatment for dyslipidemia in India has been hindered by the lack of direct evidence in this population. The results of the IRIS Study % the largest study of statins in Indians % demonstrated that evidence of efficacy with statins derived from Western populations cannot be extrapolated to the Indian

population. In Western populations the reduction in LDL-C is 41% with atorvastatin 20 mg/d and 50% with rosuvastain 20 mg/d **(Table 3)**. In a comparative study of 740 South Asians, the reduction in LDL-C was 47% with atorvastatin 20 mg/d (greater than in Western populations) and 50% with rosuvastatin 20 mg/d (similar to the Western populations). The difference in LDL-C reduction was small and statistically not significant between rosuvastatin 20 mg/d and atorvastatin 20 mg/d[55](**Table 4).** The achievement of LDL-C goal of <100 mg/dL was similar but achievement of LDL-C goal <70 mg/dL was higher with rosuvastatin 20 mg/d. The discontinuation rate for serious side effects was higher for rosuvastain 20 mg/d[55]. Thus, intensive statin therapy is safe, well tolerated, and effective in decreasing LDL-C in South-Asians. Nonetheless, this study also showed that nearly 50% of very high-risk Indians whose LDL-C target is <70 mg/dL (CAD, stroke, diabetes, metabolic syndrome or CKD) will require higher doses of these statins. According to the current estimates, the prevalence of CAD is 12%, diabetes 16%, and metabolic syndrome 35-45% in urban India. The rural rates of these conditions are approximately half that of the urban rates[106, 152].

The average LDL-C was 125 mg/dL among Indians with acute MI and 115 mg/dL among controls supporting even more intensive statin therapy[153]. These values are higher than those of US patients. 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% had LDL-C >70 mg/dL[154]. These findings provide even further support for aggressive lowering of LDL-C before an acute MI.

Among CVD risk factors for Asian Indians, abnormal lipids as assessed by apo B/apo AI ratio had the highest population attributable risk for CAD (65%) in the INTERHEART Study[153]. 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 2 lipid measures with the highest predictive value for CAD risk. Thus, LDL-C underestimates the CAD and underscores the need for lower targets that are closer to the optimum. The Indo-US Health Summit has recommended lower targets for Indians (30 mg/dL lower LDL-C than that recommended by NCEP for Americans):

- LDL-C <100 mg/dL, non-HDL-C <130 mg/dL and TC<160 mg/dL for most Indians
- LDL-C <70 mg/dL and non-HDL-C <100 mg/dL for Indians with CVD, diabetes, metabolic syndrome, CKD, high Lp(a) or homocysteine level.

These lipid targets more closely approximate the 2007 recommendations of the European Society of Cardiology[79]. The recommended goals are TC <190 mg/dL and LDL-C <115 mg/dL for all Europeans (who are not at high risk). For high-risk persons, the goals are TC <175 mg/dL, LDL-C <100 mg/dL with an option of <85 mg/dL if feasible.

Selecting a higher starting dose of atorvastatin (20 and 40 mg/d) in those requiring intensive statin therapy to achieve the LDL-C target has been shown to achieve the LDL-C goals rapidly and with minimal titration[155]. This may be particularly true in India where testing lipid profile is expensive. Intensive lipid-lowering therapy with 80 mg/d of atorvastatin in patients with stable CAD provides significant clinical benefit beyond that afforded by treatment with 10 mg/d of atorvastatin **(Table 3).**

The incidence of elevated AST/ALT >3x ULN levels was only 1.4% in a pooled analysis of 18,696 patents treated with atorvastatin 80 mg/d compared to 5.3% in patients treated with fixed dose fenofibrate therapy[52,156]. There is no reason to suspect this to be different among Indians[40, 156]. Treatment with a low dose of pravastatin reduced the risk of CAD in Japan by much the same amount as higher doses have shown in Europe and the USA[38]. This does not appear to be the case among Indians.[150] The available data indicate that the safety of statins among South Asians are no different from whites, except for anecdotal information of increased myalgia[150].

INTENSIVE STAIN THERAPY IN HYPERTRIGLYCERIDEMIA

High TG levels (usually accompanied by low HDL-C levels, except in patients with high alcohol consumption or women who are on hormone replacement therapy) are markers of obesity, insulin resistance, high glycemic load, and physical inactivity. Lifestyle modification and/or withdrawal of the offending agent may be the most appropriate risk reduction strategy. The TG lowering properties of statins have been ignored by many physicians; potent statins can lower TG to the same extent as it lower LDL-C levels (1:1 ratio)[157]. Intensive statin therapy with atorvastatin 80 mg/d lowers LDL-C by 60%, non-HDL-C by 53%, and TG by 37%, when the TG levels are not elevated[158]. But in patients with elevated TG there is greater reduction in TG (52%) and VLDL-C (62%), similar reduction in non-HDL-C (52%), but less reduction in LDL-C (41%)[158]. In addition, statin therapy produces very favorable changes in HDL-2 , IDL, LDL particle size, small dense LDL-C, and VLDL-C[159].

INTENSIVE STAIN THERAPY VERSUS MODERATE STATIN-FIBRATE COMBINATION THERAPY

High-dose statin therapy or combination therapy will be required for the large majority of very high-risk patients to achieve the optimal LDL-C goal of <70 mg/dL. While the combination of ezetimibe, bile-acid sequestering agents, and fenofibrate with moderate dose-statins appears to be reasonably safe, outcome data are scant for statin-fibrate combination therapy. The results of the ACCORD Trial provide some assurance of benefits with statin-fibrate combination therapy in diabetic patients in men

with high triglyceride levels, although potential harm was reported in non-whites and women[160].

MODERATE STATIN-NIACIN COMBINATION THERAPY

Combination therapy using atorvastatin 40 mg/d and prescription niacin 2 g/d has shown improvements in all lipoproteins including decrease in LDL-C by 56%, non-HDL-C by 55%, TC/HDL ratio by 50%, lipoprotein(a) by 14% and increase in HDL-2 by 93%.[161] Rosuvastain 20 mg/d and Niacin 1g/d also produced similar results. The HALTS Trial evaluated the effects of adding Niacin 2 g/d or ezetemibe 10 mg/d in patients with CAD or CAD-risk equivalents, who were treated with statins and achieved an LDL-C of <85 mg/dL. Niacin produced both regression of atherosclerosis and reduction in MACE, whereas no such benefit was observed with ezetemibe (despite a greater reduction in LDL-C). The Niacin increased HDL-C by 18% to 50 mg/dL whereas ezetemibe decreased LDL-C by 19% to 66 mg/dL[162]. In another trial of statin-treated patients with low LDL-C (85 mg/dL) with low HDL-C (39 mg/dL), Niacin 2 g/d compared with placebo, has been shown to significantly reduce carotid atherosclerosis within 12 months[163]. The AIM-HIGH Trial and HPS Thrive Trials are expected to provide conclusive evidence for or against statin-niacin combination therapy in the near future.

COST AND COST-EFFECTIVENESS OF STATINS

The price of lovastatin 40 mg/d and pravastatin 40 mg/d in the US has decreased dramatically after they became generic. The Wal-Mart stores now sell a 3 month supply of these medications for just $10 each with an annual cost of $40, compared to approximately $1,500 for atorvastatin 80 mg/d or rosuvastatin 40 mg/d. A recent meta-analysis evaluated the cost-effectiveness of high-dose statins versus simvastatin 40 mg/d in individuals with ACS[164]. The meta-analysis demonstrated a clear dose-response relationship in terms of reductions in LDL-C, with rosuvastatin 40 mg/d achieving the greatest percentage reduction (56%) from baseline, followed by atorvastatin 80 mg/d (52%), simvastatin 80 mg/d (45%) and simvastatin 40 mg/d (37%)[164]. Using a threshold of £20,000 per quality-adjusted life-year (QALY) and assuming that the benefits and adherence rates observed in the clinical trials are generalizable to a clinical setting, then simvastatin 80 mg/d, atorvastatin 80 mg/d and rosuvastatin 40 mg/d would be considered cost-effective, compared with simvastatin 40 mg/d in individuals with ACS. The analysis showed that rosuvastatin 40 mg/d or atorvastatin 80 mg/d are the optimal treatment for individuals with a recent history of ACS. If the cost of atorvastatin decreases in line with that observed for simvastatin when the patent ends in 2011, atorvastatin 80 mg/d will be the most cost-effective treatment for all thresholds[164]. The atorvastatin-based regimens produced cost savings when the anticipated impact of the generic availability of atorvastatin was modeled[165].

Statin therapy was significantly associated with a decreased propensity for atrial and ventricular arrhythmia[166,167]. A systematic review of controlled trials with statins showed 77% reduction in atrial fibrillation in secondary prevention and a 40% reduction in new onset atrial fibrillation[168]. Statin decreases risk of venous thromboembolism in a variety of patients including cancer[169]. A meta-analysis involving a total of 863,805 patients showed that statin therapy significantly reduced the risk of venous thromboembolism by 19%, whereas fibrate therapy significantly increased the risk by 58%[170]. Fibrate therapy was associated with increased risk of gallstones (39%) and cholecystectomy[171]. 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[172]. These additional benefits are not currently included as clinical endpoints in outcome trials and may further increase the cost effectiveness of statins.

SAFETY OF HIGH DOSE STATINS IN CLINICAL PRACTICE

Clinical trial evidence supports the use of intensive statin therapy for patients with CAD, stroke, diabetes, metabolic syndrome and other high-risk individuals[97]. High doses of potent statins have shown the greatest clinical benefit, but concerns persist regarding the efficacy and safety of achieving very low levels of LDL-C. Overall, low rates of serious musculoskeletal (<0.6%) and hepatic (<1.3%) toxicity have been observed with high-dose statin therapy[173]. A million person-years of statin therapy would produce only 3 fatal and 30 non-fatal rhabdomyolysis and no higher risk of liver failure. An analysis of 18,696 patients randomized to atorvastatin 80 mg/d in clinical trials, (usually for 4-5 years), only 4 developed CK >10x UNL (240 per million person years). No rhabdomyolysis or fatality was reported from muscle or liver toxicity. AST/ALT >3x ULN was 1.4% in this pooled analysis among patients treated atorvastatin 80 mg/d[40]. For comparison, fenofibrate therapy is associated with a 5.3% elevation in transaminases. There is no correlation between extent of LDL-C lowering and serious muscle or liver toxicity with atorvastatin.

The safety issues of intensive LDL-C lowering with statins in comparison with aspirin and diabetic medications are given in **Table 7**. A 2009 collaborative meta-analysis of individual participant data from randomised trials of aspirin has questioned the role of aspirin in primary prevention. According to this analysis by the true believers of aspirin, among those taking statins, one major bleeding is produced for every MACE prevented with low-dose aspirin therapy, in primary prevention[139]. This is partly because statins reduce the risk by 50% without any serious risk and as a result, the benefits from aspirin are reduced

by a corresponding 50% while the risk from aspirin remains 100%. It appears that atorvastatin 80 mg/d is 100 times safer than 81 mg/d of aspirin, as well as most diabetic medications [174, 175] Simvastatin 80 mg/d is indeed associated with an unacceptably high risk of myopathy and rhabdomyolysis and therefore the dose of simvastatin should be limited 40 mg/d in monotherapy and to 20 mg/d in many conditions associated with myotoxicity[126]. The extensive data on issues related to safety, toxicity and drug interactions with fibrates and cytochrome p450 inhibitors will be reviewed in **Part II.**

Table 7: *Clinical Outcomes per 1 Million Person-years of Treatment*

Study	*Treatment Modality*	*Outcome per million*
Statin therapy benefits		
Meta-analysis[180]	↓ in MACE for a 40 mg/dL↓ in LDL-C with statins in 1º prevention	5,000
Meta-analysis[180]	↓ in MACE for a 80 mg/dL ↓ in LDL-C with statins in 1º prevention	10,000
Meta-analysis[180]	↓ in MACE for a 40 mg/dL ↓ in LDL-C with statins in 2º prevention	9,600
Meta-analysis[180]	↓ in MACE for a 80 mg/dL↓ in LDL-C with statins in 2º prevention	19,200
CARDS[37]	↓ in MACE in diabetic patients with atorvastatin 10 mg/d	9,250
JUPITER[61]	↓ in MACE with rosuvastatin 20 mg/d in low risk patients with LDL-C <110 mg/dL in 1º prevention	11,000
HPS[34]	↓ in MACE with simvastatin 40 mg/d in high risk patients	14,000-20,000
Meta-analysis[178, 179]	Reduction in all-cause deaths in 2º prevention	3,600
Statin therapy risks		
Systematic review[181]	Myopathy	110
Systematic review[181]	Rhabdomyolysis	30
Systematic review[181]	Fatal rhabdomyolysis	3
Systematic review[181]	Peripheral neuropathy	120
Systematic review[181]	Liver failure	1
Chan[182]	Liver failure or serious liver injury* from diabetic medications	100
Low- dose aspirin therapy benefits and risk		
Systematic review[139]	↓ in MACE in 2º prevention	10,000
Systematic review[139]	↓ in MACE in 1º prevention	700
Systematic review[139]	↓ in deaths in 1º prevention	100
Systematic review[139]	Extracranial (GI) bleed	300
Systematic review[139]	Hemorrhagic stroke	100
Risk from Bleeding from aspirin 75-100 mg/d and clopidogrel 75 mg/d		
ACTIVE[183]	Any bleeding	74,673
ACTIVE[183]	Minor bleeding	30,046
ACTIVE[183]	Major bleeding	18,484
ACTIVE[183]	GI bleeding	9,720
ACTIVE[183]	GI bleeding	8,616
ACTIVE[183]	EC bleeding	14,728
ACTIVE[183]	IC bleeding	3,977
ACTIVE[183]	Fatal major bleeding	3,093
*GI = Gastro-intestinal; EC= Extracranial; IC= Intracranial; * AST/ALT >10x upper limit of normal*		

BARRIERS TO LDL-C GOAL ACHIEVEMENT IN CLINICAL PRACTICE

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 early cessation of therapy. The use of higher doses of atorvastatin and rosuvastain results in the greatest number of patients achieving therapeutic goals for all atherogenic lipoproteins (except for Lp(a)[54].

OVERWHELMING BENEFITS AND THE MINIMAL RISKS WITH INTENSIVE STATIN THERAPY

Large outcome trials have clearly shown that statin treatments have a favorable benefit/risk profile in a wide range of patients at different levels of risk, (with the exception of patients with heart failure with high BNP and those with renal failure undergoing dialysis)[176]. Statins have the ability to lower the risk of MI, stroke and CARPs by 25-50% depending upon the magnitude of LDL-C reduction achieved[177]. Statin therapy reduces mortality and morbidity even in patients with pretreatment LDL-C levels as low as 60-100 mg/dL[61, 133, 140, 178] .

The overwhelming benefit of statin therapy in comparison to the minimal risk can be better understood when placed in the context of person-years of treatment. The mortality risk from fatal rhabdomyolysis is approximately 3 per million person-years, and the risk of nonfatal rhabdomyolysis is 30 per million person-years. The rates of acute liver failure and acute or chronic kidney disease are no different from those of the general population[179]. In contrast, the benefit of statin therapy is to avert several thousand deaths, heart attack, stroke, and CARPs per million person-years, in appropriately treated high-risk patients[179].

A meta-analysis of 19 placebo-controlled secondary prevention studies enrolling 69,511 patients showed that statin therapy (using various statins) reduced nonfatal MI by 25%, CAD mortality 23%, and all-cause mortality by 16%[61]. The absolute reduction in all-cause mortality was over 1.8% with a trial duration averaging 5 years. This is a rate of 3,600 per million person-years[178,179]. The composite end point of heart attack, stroke and cardiac death is 2-3 times higher than mortality reductions alone or 7,200-10,800 per million person-years [179]. Statin treatment with atorvastatin 10 mg/d was estimated to prevent at least 9,250 MACE per million person-years in diabetic patients based on the CARDS Trial[37]. In the HPS Study, 5 years of simvastatin treatment was estimated to prevent about 70-100 per 1000 people from suffering a MACE. This is a rate of 14,000 to 20,000 per million person-years[34]. The size of the benefit depends primarily on the individuals' overall CVD risk rather than on their blood lipid concentrations alone[34]. **(Table 7)** Clinical trials typically cost $4,000 per person per year and the mean duration of follow-up is 5 years. The reductions in incidence of MACE in the randomized trials (for ages 55-64 years) were 7% in the first two years, 22% from 2 to 5 years, and 25% after five years, for a reduction in LDL-C of 25 mg/dL[1]. Accordingly a 80 mg/dL reduction in LDL-C would confer a corresponding 80% risk reduction after 5 years, provided the therapy is continued indefinitely (a 1:1 relationship between LDL-C reduction in mg/dL and CVD risk reduction)[184] . Although the relative risk reduction is similar, the absolute risk reduction is greater in secondary prevention than in primary prevention and in people who achieve substantial LDL-C reduction. **(Table 7)** According to the meta-analysis by Baigent[180], an 80 mg/dL decrease in LDL-C (which would necessitate intensive statin therapy) would prevent 10,000 MACE in primary prevention and 19,200 MACE in secondary prevention. The remarkable benefits of intensive statin therapy are summarized in **Table 8.** The benefit is likely to be double among Asian Indians who have double the risk of CVD for any and all major modifiable risk factors[106].

Over the past 20 years, quantitative coronary angiography, carotid intimal medial thickness and intravascular ultrasound studies have demonstrated that statins alter the natural history of vascular disease % a feature shared by no other category of medications[185]. Aggressive lowering of LDL-C with intensive statin therapy can not only prevent the development of atherosclerosis but also halt the progression and induce regression of the noncalcified plaque. The COURAGE Trial has demonstrated that patients with chronic CAD who are receiving

optimal medical management with tight control of all risk factors do not derive any additional benefit from PCI[186]. For these patients even ACS patients who are stabilized, an initial conservative approach can be elected and PCI deferred until dictated by persistent or progressive symptoms, without an increased risk of MACE or detriment to quality of life[186].

Table 8: *Summary of the Remarkable Benefits of Intensive Statin Therapy*

1. 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; the absolute benefit is related to the patient's' baseline absolute risk and the degree of LDL-C lowering but not the initial LDL-C level.
3. Regression in non-calcified atherosclerotic plaque requires intensive therapy that will achieves a combined goal of a non-HDL-C <100 mg/dL and a systolic blood pressure <115 mm Hg.
4. The CVD risk reduction is directly proportional to the magnitude of LDL-C and non-HDL-C reduction.
5. A 50% reduction in LDL-C is a reasonable goal when specific LDL-C targets are not met despite intensive statin therapy (<70 mg/dL in patients with diabetes and CVD).
6. Intensive lowering of LDL-C by 50% (from 108 to 55 mg/dL) with rosuvastain 20 mg/d reduced the risk of MI, stroke, and CARPs by about 45% in primary prevention. This and other studies have demonstrated benefits and safety of lowering LDL-C <40 mg/dL.
7. An 80 mg/dL reduction in LDL-C and/or non-HDL-C confers a 60-80% reduction in CVD after 5 years of treatment (1:1 relationship).
8. An 80 mg/dL decrease in LDL-C level is estimated to prevent 10,000 MACE in primary prevention and 19,200 MACE in secondary prevention per million person-years of treatment. Among diabetic patients, statin therapy would prevent 8,400 MACE per million person-years of therapy.
9. In patents with high TG, potent statin at high doses can lower TG and non-HDL-C by >50% % the same magnitude as LDL-C reduction.
10. Statin therapy has extremely low rates of serious side effects % only 3 fatal and 30 non-fatal rhabdomyolysis cases per million person-years. The risk of liver failure is not increased with statin therapy.
11. The absolute CVD risk reduction is 10 times greater and serious side effects 100 times lower with statin therapy than for low dose aspirin in primary prevention.

CONCLUSION

The optimum LDL-C is currently set at 40 mg/dL. Since every 1 mg/dL increase in LDL-C confers a 1% higher risk for CVD, those with LDL-C 70 mg/dL have a 30% higher risk and those with LDL-C 100 mg/dL have a 60% higher risk compared to people with optimum LDL-C. The LDL-C target is <100 mg/dL for Asian Indians and <70 mg/dL for those who are at the highest risk % CVD, diabetes, metabolic syndrome, or chronic kidney disease. Intensive statin therapy with an LDL-C goal <70 mg/dL is advisable for Asian Indians with low HDL-C, high lipoprotein(a), high CRP, high homocysteine or other emerging risk factors. For Indians who already have evidence of a vascular disease, physicians should now aim to lower their LDL-C as low as possible. This does not mean all Asian Indians should go on the highest dose of statin; nonetheless one need not worry too much about the safety in using high enough dose to achieve the LDL-C and non-HDL-C goals. Widespread use of statin therapy to achieve the above goals has the potential to drastically reduce the burden of CAD in the Indian subcontinent. For patients with ACS, statin therapy should be started in-hospital and continued life-long. Statin therapy is the most important advancement in stroke prevention since the introduction of aspirin and antihypertensive treatments. For every one million person years of treatment, intensive statin therapy can prevent approximately 10,000 MACE compared to 700 for aspirin in primary prevention. The benefit is greater in secondary prevention with a reduction of MACE by 20,000 with statin compared to 10,000 with aspirin. Intensive statin therapy is poised to perform greater wonders for cardiovascular diseases in the 21st century than antibiotics did for infectious diseases and H2 antagonists did for peptic ulcer in the 20th century.

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