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Challenge the Guidelines

Consensus statement on the management of dyslipidemia in Indian subjects: A different perspective

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In the last 35 years we have witnessed an impressive 76%–80% decline in coronary artery disease (CAD) mortality rates in the United States (US), Finland and other countries.[1,2] This dramatic decline in CAD mortality rates is all the more impressive as the rates of obesity and diabetes markedly increased during this period.[3] The decline is largely due to control of 3 major established risk factors—smoking, high blood pressure, and elevated cholesterol.[1,3] Data review confirms that control of cholesterol was the eminent factor in reducing risk compared to all others; and notably, advances in invasive treatments (stents and coronary bypass surgery) contributed the least.[1,3] The escalating epidemic of CAD in India is due to absent or poor control of the same 3 risk factors, superimposed on a genetic predisposition to CAD.[4] Indians have a 2-fold risk of CAD and a 3-fold risk of diabetes compared to their western counterparts when adjusted for various risk factors.[4] Indians also develop CAD at a younger age.[5,6] These factors underscore the need for interventions at a lower threshold and at a younger age for Indians than their Western counterparts.[7,8]

We commend Sarat Chandra and colleagues for their initiative and effort in publishing the Consensus Statement on the Management of Dyslipidemia in Indian Subjects (CSMDIS).[9] This document fills a deep void and has many strengths that include an informative discussion on the burden of cardiovascular disease (CVD) in India, appropriate strategies for lifestyle intervention, and an excellent elucidation of lipid-lowering-treatment (LLT) thresholds for intervention and targets. However, we take exception to the risk prediction and stratification in primary prevention (Section 3) as this would stifle statin therapy for millions of Indians who are at risk and perpetuate the undertreatment of dyslipidemia.[10,11]

Treatment decisions are largely driven by pharmacoeconomics (cost-benefit ratio) in the United Kingdom (UK) where the health care cost is borne by the government, whereas risk-benefit ratio drives it in the US.[12,13] As Indian patients pay for their medical expenses one would expect India to be aligned with the US paradigm. Yet the CSMDIS set 20% CVD risk within 10 years as the high-risk threshold to qualify for LLT compared to 10% in the UK and 7.5% in the US.[12,13] Despite access to the same scientific data, recommendations for statin therapy from India are disparate and restrictive. The use of statins presently is very low in India, <5% in secondary

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prevention (compared to 71% in the US) and it is very likely that it is even lower in primary prevention.[10,11,14]

We appreciate the opportunity to present a different perspective to address the escalating epidemic of CAD in India [6,15] in a 6 question format followed by evidence-based answers on the first 5 questions and our considered opinions on the last one.

1. What is the best measure of atherogenic cholesterol and what is it's optimal level?

High-density lipoprotein cholesterol (HDLC) is anti-atherogenic and the remainder of cholesterol (total cholesterol minus HDLC) is atherogenic and termed non-high density lipoprotein cholesterol (NHDLC).[16] NHDLC includes all Apo B containing lipoproteins—low-density lipoprotein cholesterol (LDLC), very LDLC (VLDLC), intermediate density lipoprotein cholesterol (IDLC), lipoprotein (a) and remnant cholesterol. NHDLC is both a necessary and sufficient risk factor for atherosclerosis—the underlying pathophysiological process in CVD.[17] Necessary risk factor, because atherosclerosis does not develop in the absence of some elevation in NHDLC. Sufficient risk factor, because atherosclerosis develops when NHDLC concentration is markedly elevated, even in children as young as 6 years of age, without other risk factors.[17]

NHDLC, appropriately emphasized in CSMDIS, is being increasingly recognized as a better predictor of CVD risk than LDLC, and has the practical advantage of not requiring a fasting measurement.[16] For any given level of total cholesterol, Indians tend to have greater elevation in NHDLC by virtue of high triglycerides and low HDLC common in this population.[18,19]

The optimal NHDLC is defined as <130 mg/dL which corresponds to a LDLC <100 mg/dL and total cholesterol <150 mg/dL[16]. Evidence gathered in the past decade also supports a NHDLC of goal of <130 mg/dL for Indians with low, medium and high risks (Table 1).[16,20–25] In people with very high risk (established CVD, diabetes, and lifetime risk ≥45%) the NHDLC goal is < 100 mg/dL.[16,26] More stringent goals (NHDLC <75 mg/dL and LDLC< 50 mg/dL) have emanated from 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and other studies.[12,23–26]

The best measure of atherogenic cholesterol is NHDLC and the optimal level is < 130 mg/dL for Indians.

2. How effective and safe is statin therapy?

Statins offer the most effective treatment to lower NHDLC by lowering both LDLC and triglycerides >50% (1:1 ratio).[18,27] More than 200 million people worldwide have taken statins since it was first introduced in 1987 and 170,000 were studied in well-designed randomized clinical trials; its excellent safety record surpass all other lipid-lowering medications.[12,27–30]

A recent discovery is that statin is the most effective medication to lower CVD risk.[12,27–30] Hence its use is not limited to patients with dyslipidemia or CAD but extends to all patients with elevated CVD risk.[12,27–30] Because of the impressive effect of statin medications in reducing CVD risk, a paradigm shift in statin therapy has occurred in that it's use is no longer restricted to those with high LDLC or NHDLC.[12,27–30] The broader use of statins in CVD risk reduction is analogous to the use of ACE inhibitors for cardiac and renal protection in the absence of hypertension.[18] The absolute CVD benefits of statin therapy are proportional to the intensity of therapy, the age of initiation of such therapy and the baseline risk of the individual (but not necessarily the baseline cholesterol level).[18] Most importantly, the benefit of statin therapy in primary prevention far outweighs the risk even in people with 5% CVD risk within 10 years.[29]

A meta-analysis of statin trials has demonstrated that every 80 mg/dL decrease in LDLC safely reduces the 5-year incidence of major CVD events by 42% and total mortality by 24%.[31] In primary prevention in every one million very high-risk persons (60% risk of CVD within 10 years), high-intensity statin therapy (that lowers LDLC by 98 mg/dL) prevents 9200 deaths and 28,400 CVD events.[29] Most importantly among those with <10% CVD risk within 10 years, high-intensity statin therapy can prevent 600 deaths and 1200 to 2400 CVD events.[29]

Many physicians and patients underestimate the absolute benefits and overestimate the absolute risks of statin therapy.[18] The absolute number of CVD events prevented (as discussed above) are 100 times greater than the absolute number of adverse events produced—an average excess of 3 deaths, 20 rhabdomyolysis, 100 myopathy, and 100 hemorrhagic stroke, per one million persons-years of statin therapy.[12,18] Contrary to a popular misconception, statins do not cause dementia and may actually decrease its risk by 29%[32]. The increased CVD risk resulting from statin-related new-onset diabetes is 60 times smaller than CVD prevented from statin therapy.[12] The excess risk of diabetes is 0.1% per year for low to moderate intensity and 0.3% per year for high intensity statin therapy. The risk of diabetes is also limited to those who are obese, sedentary and already on the path to diabetes.[12,18] The evidence suggests that statin therapy might shorten the time to diabetes by a few weeks or months but not years.[18] Statins may affect diabetes risk in the complex interplay between lipids, glycemia, LDL receptor function and obesity.[33] The safety and efficacy of statins is much greater than other forms of LLT.[12,18]

Statin therapy is effective and safe; the benefits far outweigh safety concerns.

3. What is the minimum age to measure lipid levels in Indians?

The range of recommendations available must be viewed in the context of the populations studied whether based on cost-benefit or risk-benefit analysis, and in conjunction with advances in scientific information on the topic. European guidelines recommend measuring lipid levels at age 40, whereas the 2013 AHA/ACC guidelines recommend lipid measurements at 20 years of age.[12] The National Institute of Health (NIH) of US sponsored major report "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents" (202 pages and 841 references),