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

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Dear Editor,

We read with interest the commentary by Enas A. Enas and colleagues[1] on the recently published Consensus Statement on Management of Dyslipidemia in Indian Subjects (CSMDIS)[2] and thank them for their insightful comments. It is heartening to see that the document has generated such interest and has drawn attention of such world-renowned leaders in the field of lipid management.

We are in agreement with many of the observations made by Enas A. Enas and colleagues about the current understanding of the role of statin therapy in reducing cardiovascular (CV) morbidity and mortality. As highlighted by them, there is unequivocal evidence to show that statins are currently the most powerful pharmacological agents available to reduce CV risk. More importantly, the beneficial effects of statins are observed in direct proportion to the baseline CV risk and occur regardless of the low-density lipoprotein cholesterol (LDLC) levels. Accordingly, most guidelines today recommend initiating statin therapy based on the estimated CV risk rather than the absolute LDLC levels. We also agree that there is now increasing data to suggest that lifetime CV risk may be a more appropriate metric, rather than the short-term (i.e. 10-years) CV risk, for guiding management decisions in primary prevention of CV disease, particularly in young individuals. However, we wish to emphasize that there is currently no validated risk assessment tool available for estimating short-term or lifetime CV risk in Indians. The risk assessment algorithm proposed by the International Atherosclerosis Society (IAS)[3] is simple to use but its use in Indians has practical limitations, as highlighted below. In addition, we also notice that the interpretation by Enas A. Enas et al. of the recommendations for initiating statin therapy is different from what has actually been proposed in the CSMDIS. We discuss below these issues in greater detail.

1. IAS algorithm for estimation of lifetime CV risk

The algorithm proposed by the IAS for estimating lifetime CV risk was first developed by Lloyd-Jones et al. based on the Framingham study data.[4] This algorithm considers only four risk factors – diabetes, smoking, systolic blood pressure (SBP), and total cholesterol (TC). Both diabetes and smoking are considered to be major risk factors, whereas SBP and TC are graded as minor, moderate, and major risk factors depending on the actual levels (SBP: minor – 120–139 mmHg, moderate – 140–159 mmHg, and major – >160 mmHg; TC: minor – 180–199 mg/dL, moderate – 200–239 mg/dL, and major – >240 mg/dL). Based on the number of minor, moderate, and major risk factors, lifetime CV risk can be estimated in any individual. For nonwhites, the IAS document also provides appropriate ethnic-specific calibration factors in order to derive more accurate risk estimates in different population groups. Thus, IAS risk algorithm is simple to use, does not require elaborate laboratory testing, and is well suited for clinic-based estimation of CV risk.

However, the use of this algorithm for risk estimation in Indian subjects has important practical limitations. According to the IAS algorithm, any male subject who has just one minor risk factor is considered to have 25% lifetime risk of CV events. Since the calibration factor for urban Indians is 1.8, this translates in to 45% risk of CV events, which is the threshold for defining high risk. Thus, every urban Indian man with even SBP marginally above 120 mmHg or TC above 180 mg/dL and no other CV risk factor at all will be designated as having high CV risk. To put this in perspective, let us consider an example of a 40-year old urban Indian man who is free from any CV disease. He is nondiabetic, nonsmoker, nonhypertensive, and does not have any family history of premature CV disease. His blood pressure is 122/80 mmHg and his TC is 170 mg/dL. Most readers will agree that this person seems to be in reasonably good state of health and only needs general advice about healthy lifestyle. However, the IAS risk algorithm will identify this individual as being at high risk, and therefore, a candidate for lifelong high-intensity statin therapy! Thus, it is evident that the IAS risk algorithm, in its present form, will identify almost every urban Indian man as being at 'high-risk,' which defeats the very purpose of using a risk estimation tool. Further, even if it was agreed that all such men were at high lifetime risk of having a vascular event, the appropriateness of using this risk estimate to recommend life-long, high-intensity statin therapy in all these individuals remains highly controversial.

Another challenge with the IAS risk algorithm is that it is based on the data derived from individuals above 50 years of age, and therefore, is ideally applicable to these individuals only. Using this algorithm in younger individuals can lead to unwarranted discrepancies since age is not included as one of the risk factors. For example, if we have another urban Indian male who is 55 years of age and has the same risk profile as the younger individual in the above illustration but has BP 118/80 mmHg, he will be considered to be at low risk of CV events as per the IAS risk algorithm. This again seems to be counterintuitive.

2. Definition of 'high-risk' and the threshold for initiating statin therapy

The concept of classifying patients into high-, intermediate- and low-risk based on 10-year risk estimates, and matching intensity of lipid-lowering treatment with the estimated CV risk was first propounded by the National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III).[5] The 'high-risk' was defined as >20% risk of hard coronary heart disease (CHD) events over the next 10 years. This risk level was believed to be similar to that anticipated in a patient who already had evidence of atherosclerotic vascular disease. Accordingly, 'high-risk' category was designated as 'coronary artery disease risk equivalent,' and treatment strategy similar to that used for secondary prevention was recommended for this group of patients.

Since then, numerous guidelines have adopted this approach but have used different cut-off values to define 'high-risk'. Although most definitions have hovered around the same threshold of >20%, the use of lower thresholds for initiating statin therapy (in primary prevention setting) by some of the recent guidelines seems to have caused confusion. In this context, it is important to note that the 'high CV risk' may not necessarily be same as 'risk high enough' to warrant statin therapy. Statins are known to reduce CV events even in patients who are at much lower level of CV risk. The thresholds proposed by these guidelines are only the levels beyond which there is clear benefit of statin therapy but do not attempt to redefine 'high CV risk'. In fact, if the term 'high-risk' is expected to convey 'CV disease risk equivalent' status, there is little justification for significantly lowering the threshold for defining 'high-risk'. This understanding is corroborated by the following observations:

- **National Lipid Association guidelines (October 2014)** clearly mention that using the pooled cohort equation, 'high-risk,' should be defined as 10-year risk >15%.[6]
- In primary prevention setting, the **NICE guidelines (July 2014)** recommend only 20 mg atorvastatin/day for people >10% risk, unlike much higher doses (80 mg atorvastatin) recommended for secondary prevention.[7] This suggests that >10% risk over 10 years is not perceived as truly high-risk, but only a threshold to warrant statin therapy.
- **Canadian guidelines (Feb 2013)** used a cut-off of 20% to define high risk.[3]
- **Australian guidelines (May 2012)** used a cut-off of 15% over 5 years (equivalent to >30% over 10 years) to define high risk.[3]
- **World Health Organization risk prediction charts** also use >20% 10-year risk as the definition for high risk.[8]

However, regardless of what definition is used for defining high CV risk, there is ample evidence to suggest that statin therapy is beneficial even in individuals at much lower risk of vascular events. Accordingly, the recently published American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend statin therapy in all individuals with >7.5% 10-year risk of CV events, with an option to use statin therapy even in those with 5–7.5% CV risk.[9]

Contrary to the perception by Enas A. Enas and colleagues, the present Indian consensus document does not restrict use of statins only to individuals with >20% 10-year risk. The document clearly recommends statin therapy for all individuals having 10-year risk >10%, regardless of the baseline LDLC levels and without the need to wait for the effect of lifestyle interventions. Further, even in those with <10% risk (which means everyone else other than those with >10% risk), statin therapy is recommended if LDLC is persistently above 130 mg/dL despite adequate lifestyle modification. These recommendations are in agreement with most of the latest guidelines, including those of the ACC/AHA. In contrast, the IAS guidelines only mention that lipid-lowering drug therapy should be considered (and do not make it mandatory) in those who are at moderately high CV risk. The Indian recommendation of statin therapy in all individuals (even if their 10-year CV risk is <10%) with LDLC >130 mg/dL despite adequate lifestyle measures also addresses, to a great extent, the issue of young individuals having low short-term risk despite a high lifetime CV risk.

It is also noteworthy, that the Indian consensus document has proposed a hybrid approach for lipid management, combining 'LDLC goal-based strategy' with the one based on the magnitude of LDLC reduction, even though this was in stark contrast with the ACC/AHA recommendations. It was recommended that once initiated, the aim of the statin therapy should be to lower LDLC by at least 50% (i.e. high-intensity therapy) in those at high CV risk or those with established atherosclerotic vascular disease and by at least 30–50% (i.e. moderate-intensity therapy) in all the other subjects. It is heartening to note that these recommendations have been fully supported by the recent National Lipid Association recommendations, which were published at a time when the Indian consensus document was already in print.[6]

Conflicts of interest

The authors have none to declare.

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