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RESEARCH ARTICLE

USE OF STATINS IN INDIA: A SURVEY TO UNDERSTAND THE PRESCRIBING PATTERNS OF PHYSICIANS IN INDIA- SCORE STUDY

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ABSTRACT

Background: Hyperlipidemia is a modifiable risk factor for cardiovascular disease (CVD) and is primarily treated by statins. The present survey was conducted to understand the prescribing practices of physicians and cardiologists in managing patients of dyslipidemia with various statins.
Methods: This was a prospective, cross sectional, questionnaire-based survey of Indian physicians and cardiologists managing the patients of dyslipidemia with statins. The questionnaire consisting of 10 questions related to the use of statins in the management of dyslipidemia in real-world clinical settings was prepared, validated and then administered to physicians and cardiologists attending CSI 2016.
Results: Responses from 358 physicians and cardiologists were received. Compared to other statins, most physicians experienced maximum reduction in the low-density lipoprotein cholesterol (56.7%), triglycerides (47.2%) and maximum increase in high-density lipoprotein cholesterol (48.3%) with rosuvastatin. Rosuvastatin was reported as the most preferred statin by the physicians in their clinical practice for primary prevention (50.6%) and secondary prevention (49.4%) of CVD followed by atorvastatin (38.5% and 31%, respectively). Physicians preferred rosuvastatin over atorvastatin in patients with diabetes mellitus or metabolic syndrome (53.4% vs 27.7%), while atorvastatin was preferred over rosuvastatin in patients with chronic kidney disease (44.4% vs 32.4%) and chronic heart failure (46.9% vs 34.6%). Amongst the statins, the highest dose tolerable was that of rosuvastatin 40 mg (39.9%).
Conclusion: The survey findings suggest that rosuvastatin was the most preferred stat in among cardiologists and physicians, followed by atorvastatin in the management of patients with hyperlipidaemia and for primary and secondary prevention of CVD.

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INTRODUCTION

Worldwide, cardiovascular disease (CVD) is the leading cause of death and CVD related mortality rates are higher in low- and middle-income countries (Fuster *et al*., 2010; Doupa *et al*., 2014).According to World Health Organization (WHO), the prevalence of CVD will double by 2020 (Mathers *et al*., 2004). Hyperlipidemia is a major modifiable risk factor for CVD and progression of atherosclerotic lesions. The prevention of CVD is critically dependent on lowering of low density lipoprotein cholesterol (LDL-C). In dyslipidemia, statins are the most widely prescribed class of drugs worldwide, and results into reduction of cardiovascular (CV) events by 25% to 45% (Jukema *et al*., 2012). Statins are thus, the mainstay treatment for reduction of LDL-C and increase in high density lipoprotein cholesterol (HDL-C)for primary and secondary prevention of CVD (Minder CM *et al*., 2013).Various clinical trials and observational studies have established lipid lowering efficacy and safety of rosuvastatin and atorvastatin in patients with dyslipidemia (Rubba P *et al*., 2009; Jones PH *et al*., 2005).Various statins differ from each other in their ability to reduce LDL-C and triglyceride (TG) levels and also in safety profilewhich may affect the choice of physician in choosing the statin in a desirable patient (Nelson RH *et al*., 2013; Ramkumar S *et al*., 2016). Amidst the availability of literature on superiority of one statin over other in different subsets of patients and considering the fact that none of the dyslipidaemia guidelines recommend preference of

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one statin over the other, it becomes really important to understand the practice followed in real-world clinical settings. Therefore, the present survey was conducted to understand the prescribing practices of physicians and cardiologists in managing patients of dyslipidaemia with various statins.

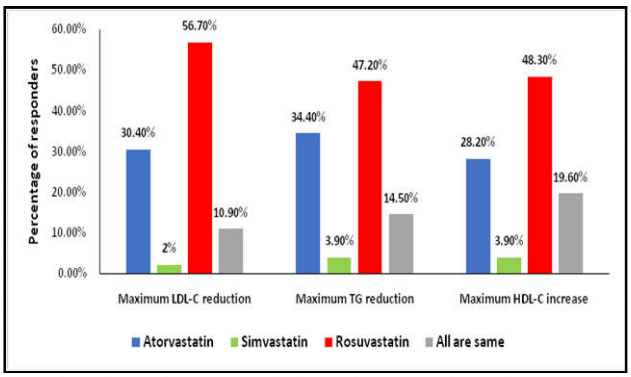
MATERIALS AND METHODS

This was a prospective, cross sectional, questionnaire-based survey of physicians and cardiologists managing the patients of dyslipidemia with statins across different geographic areas in India. A survey questionnaire consisting of 10 questions related to the use of statins in the management of dyslipidemia in real-world clinical settings was prepared. The questions were pertaining to experience of physicians with the use of different statins for maximum reduction in LDL-C, TG and increase in HDL-C; their preferred choice of statin for primary and secondary prevention; in patients with different co-morbidities like chronic kidney disease (CKD), chronic heart failure (CHF) and in patients with diabetes mellitus/metabolic syndrome. The questionnaire was also designed to understand the safety of statins in real-world clinical settings as perceived by physicians. The questionnaire was later validated in a small group of physicians and then administered to physicians and cardiologists at the 68th Annual Conference of Cardiological Society of India (CSI), December 2016, Kochi. Delegates attending CSI 2016 conference were approached, explained the objective of doing this survey and those willing to provide their opinion were given the questionnaire. No remuneration was given to the participants for filling these survey questionnaire. The completed questionnaire were collected and analyzed. Physicians' and cardiologists' responses from the questionnaire were entered in a Microsoft excel sheet and descriptives were calculated as frequencies.

RESULTS

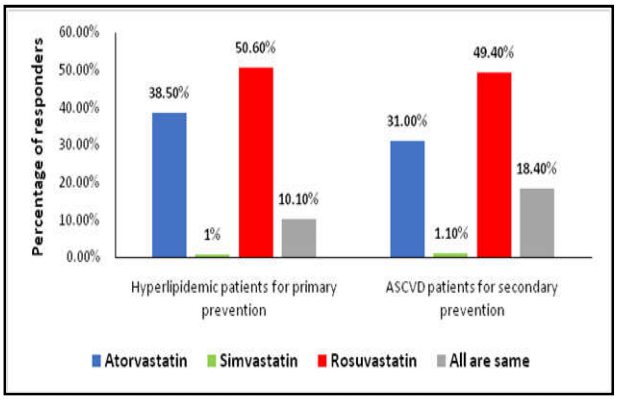
In the survey, responses from 358 physicians and cardiologists were obtained. Among the currently available statins, in clinical practice, rosuvastatin showed the maximum reduction in LDL-C and triglyceride and maximum increase in HDL-Cas reported by most of the physicians (56.7%, 47.2% and 48.3% physicians respectively) (Figure 1).

While, other physicians were of the opinion that in their clinical practice, myopathy occurred more commonly with atorvastatin (25.4%), followed by simvastatin (18.4%) and rosuvastatin (14.5%).Most of the physicians reported that among the various statins at their highest doses, rosuvastatin 40 mg is best tolerated (39.9%) compared to highest doses of atorvastatin 80 mg (35.8%) and simvastatin 80 mg (3.1%); while 21.2% physicians reported that all statins were equally tolerated at their highest doses (Figure 3).



LDL-C – low-density lipoprotein cholesterol, TG – triglyceride, HDL-C – high density lipoprotein cholesterol

Figure 1. Physicians' clinical experience with different statins for maximum reduction in LDL-C & TG and increase in HDL-C



ASCVD – Atherosclerotic cardiovascular disease

Figure 2. Statin preference by physicians for primary and secondary prevention

Table 1. Statins preferred by physicians in comorbid conditions

Comorbidities	Atorvastatin n (%)	Simvastatin n (%)	Rosuvastatin n (%)	All are same n (%)
Preferred statin of choice in patients with CKD	159 (44.4%)	16 (4.5%)	116 (32.4%)	67 (18.7%)
Preferred statin of choice in patients with CHF	168 (46.9%)	13 (3.6%)	124 (34.6%)	53 (14.8%)
Preferred statin of choice in patients with DM /MS	99 (27.7%)	13 (3.6%)	191 (53.4%)	55 (15.4%)

CKD – Chronic kidney disease, CHF – Chronic heart failure, DM – Diabetes mellitus, MS – Metabolic syndrome

As shown in figure 2, most of the physicians preferred rosuvastatin over other statins for primary prevention in patients of hyperlipidemia (50.6%) as well for secondary prevention in patients with Atherosclerotic cardiovascular disease (ASCVD) (49.4%).

As presented in table 1, in presence of comorbid conditions, rosuvastatin was preferred by physicians in patients with diabetes or metabolic syndrome (53.4%) while atorvastatin was preferred in those with CKD (44.4%) and CHF (46.9%). Majority of physicians (41.6%) reported that myopathy as an adverse effect was observed similarly across all statinsin their patients.

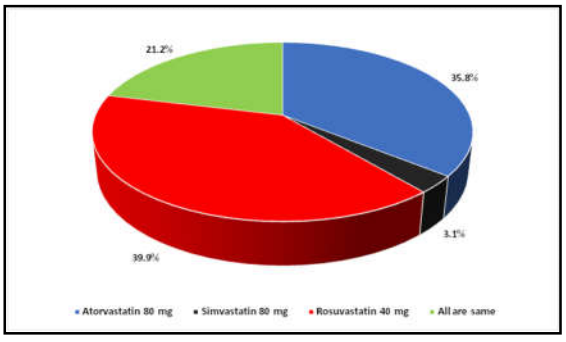


Figure 3. Tolerability of highest doses of statins reported by physicians

DISCUSSION

In this survey, rosuvastatin emerged as the most preferred statin by the physicians in their clinical practice. It was observed that among the currently available statins, survey physicians experienced maximum reduction in the LDL-C, TG and maximum increase in HDL-C with rosuvastatin followed by atorvastatin. Rosuvastatin also emerged as the most preferred statin in clinical practice for primary prevention in patients of hyperlipidemia and for secondary prevention in patients with ASCVD followed by atorvastatin. In various comorbid conditions, physicians preferred rosuvastatin over atorvastatin in patients with diabetes mellitus or metabolic syndrome, while atorvastatin was preferred over rosuvastatin in patients with CKD and CHF. Amongst the statins, the highest dose tolerable was that of rosuvastatin. These observations in the present survey are in concordance with clinical study evidences comparing different statins. In a systematic review and meta-analysis by Weng *et al*, 75 randomized controlled trials (RCT) of head-to-head comparisons of various statins were analysed to generate pooled estimates of the cholesterol lowering effect of statins and the differences between statins. It was observed that the only two statins that could reduce LDL-C more than 40% were rosuvastatin at 10 mg or higher dose and atorvastatin at a daily dose of 20 mg or higher (Weng *et al*., 2010). In STELLAR trial, in patients of hypercholesterolemia, rosuvastatin showed significant maximum reductions of LDL-C, total cholesterol (TC) and TG compared to atorvastatin, simvastatin and pravastatin across doses at 6 weeks of treatment (Jones PH *et al*., 2003). Rosuvastatin reduced non-HDL-C by 42.0% to 50.9% compared with 34.4% to 48.1% with atorvastatin and 26.0% to 41.8% with simvastatin. Thus, rosuvastatin 10 to 40 mg was found to be more efficacious than milligram-equivalent doses of atorvastatin and milligram-equivalent or higher doses of simvastatin in improving the lipid profile of patients with hypercholesterolemia. In PULSAR study, which was a head to head RCT of rosuvastatin with atorvastatin in high risk patients with hypercholestrolemia, it was found that rosuvastatin was more effective than atorvastatin in reducing LDL-C, LDL-C/HDL-C ratio and increasing HDL-Clevels while similar efficacy was noted for reduction in TG and TC (Clearfield *et al*., 2006). LDL-C levels were significantly reduced with rosuvastatin 10 mg than with atorvastatin 20 mg at week 6 (44.6% vs. 42.7%, $p<0.05$).

It is commonly observed that many patients at high risk of CVD do not achieve recommended LDL-C goals. But, PULSAR trial showed that significantly more patients achieved National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) goal of less than 100 mg/dL and 2003 European LDL-C goal of less than 2.5 mmol/L in patients with atherosclerotic disease, type 2 diabetes (T2DM), or at high risk of CV events with rosuvastatin 10 mg compared with atorvastatin 20 mg (68.8% vs. 62.5%, $p < 0.05$; 68.0% vs. 63.3%, $p < 0.05$, respectively) (Clearfield *et al*., 2006). The findings of these robust clinical trialsare also reflected in real-world clinical practice. These study findings have found an influence in clinical practice of physicians and made rosuvastatin as the most preferred statin. Evidences from the STELLAR and PULSAR trials demonstrated higher efficacy of rosuvastatin compared to other statins in patients of hypercholesterolemia. This could probably explain rosuvastatin as the most preferred statin of choice among the survey physicians for primary prevention in patient of hyperlipidemia and for secondary prevention in patients with ASCVD (Jones PH *et al*., 2003; Clearfield MB *et al*., 2006). In CVD prevention, statins are among the most studied drugs. Statins substantially reduce CV morbidity and mortality in both primary and secondary prevention as evidenced in various large-scale trials. Statins have established place in slowing the progression or even promoting regression of coronary atherosclerosis. Current available evidence suggests that the clinical benefits depend on the extent of LDL-C lowering and are largely independent of the type of statin used (Colhoun *et al*., 2004). In the large Cholesterol Treatment Trialists (CTT) analysis data, 26 RCTs involving>170000 patients treated with statins were studied (Baigent *et al*., 2010). It was observed that all-cause mortality was reduced proportionally by 10% and CAD mortality was reduced by 20% per 40 mg/dL reduction in LDL-C. Moreover, every 40 mg/dL reduction in LDL-C resulted in reduction in the risk of major coronary events by 23% and reduction in the risk of stroke by 17% (Baigent *et al*., 2010). Statins have been extensively studied specifically in primary prevention in various meta-analyses (Ray KK *et al*., 2010; Mills EJ *et al*., 2008; Mihaylova *et al*., 2012). The largest of these meta-analyses in primary prevention was Cochrane review by Taylor F *et al* published in 2013 (Taylor F *et al*., 2013).In this meta-analysis, each 40 mg/dL reduction in LDL-C resulted in reduction in all-cause mortality by 14%, CVD events by27%, fatal and non-fatal coronary events by 27% and stroke by 22%. Larger reduction in LDL-C with rosuvastatin than atorvastatin as experienced by survey physicians in clinical practice justifies their preference for rosuvastatin in primary and secondary prevention.

In this survey, rosuvastatin also emerged as the most preferred statin by physicians in patients of diabetes mellitus or metabolic syndrome. This can be justified from the results of a study by Barakat L *et al*.in patients of diabetic dyslipidemia, wherein, rosuvastatin was clinically found to be the most effective statin in comparison to atorvastatin and pravastatin in terms of maximum reduction of TC, LDL-C and TG and increase in HDL-C (Barakat *et al*., 2013).The Use of Rosuvastatin versus Atorvastatin iN type 2 diabetes mellitUS (URANUS) study also demonstrated that rosuvastatin was significantly more effective than atorvastatin at reducing LDL-C and at week 16, significantly more patients achieved their LDL-C goal with rosuvastatin compared with atorvastatin (94% vs 88%, $p < 0.05$) (Berne C *et al*., 2005). The results of a prospective randomised, open-label study by Sindhu S *et al*. further highlighted that rosuvastatin should be preferred over atorvastatin in obese T2DM patients in whom LDL-C and TC levels are elevated (Sindhu *et al*., 2011). CKD is a risk factor for atherogenic dyslipidaemia and hence, management of dyslipidaemia can potentially reduce mortality in these patients. Lipid Association of India (LAI) in their Expert Consensus Statement on Management of Dyslipidemia in Indians published in 2017 has recommended statins/statin plus ezetimibe for all adults CKD patients over the age of 40 years with eGFR< 60 mL/min/1.73 m^2 (Iyengar *et al*., 2017).In the present study, most of the physicians preferred atorvastatin over rosuvastatin in patients with CKD. This preference of surveyphysicians can be justified based on the available evidences of differential effects of atorvastatin and rosuvastatin in patients with CKD. A recently published data of 484 patients with diabetes who received statin treatment for more than 12 months showed that moderate-intensity dose of atorvastatin has fewer detrimental effects on renal function

than that of rosuvastatin (Han E *et al*., 2017). In fact, a recent meta-analysis demonstrated that statins caused modest reduction in proteinuria, which indicates its beneficial property in patients of hyperlipidemia with chronic kidney disease (CKD) (Sandhu *et al*., 2006). PLANET 1, a RCT in patients with diabetes who had progressive renal disease showed that atorvastatin 80 mg reduced urine protein: creatinine ratio (UPCR) significantly more than rosuvastatin 10 mg (-15.6%, p=0.043) and rosuvastatin 40 mg (-18.2%, p=0.013) (de Zeeuw D *et al*., 2015). PLANET 1 trial, therefore emphasized that despite higher lipid lowering efficacy of rosuvastatin than atorvastatin, atorvastatin seems to have more reno-protective effects in patients with CKD. The use of statins in CHF patients has been controversial due to conflicting results from various RCTs and smaller studies. The results of two large, prospective, randomized, placebo-controlled trials; the CORONA trial and the GISSI-HF trial have largely contributed to the disagreement for the use of statins in patients with CHF (Kjekshus *et al*., 2007; Maggioni *et al*., 2008). Both the trials failed to demonstrate beneficial effects of rosuvastatin in CHF patients. Physicians in present study preferred atorvastatin in patients with CHF and is well supported by the results of meta-analysis published in 2010 (Xu M *et al*., 2010). In this meta-analysis, there was significant reduction in all-cause mortality, CV mortality and sudden cardiac death in patients of CHF treated with atorvastatin compared to placebo. There was also a significant reduction in the risk of hospitalization due to worsening CHF with atorvastatin therapy compared with placebo. In any case, there is no evidence for harm in patients who develops HF while on treatment with statin. Therefore there is no need for discontinuation of statin in the event of occurrence of HF as recommended by recent 2016 ESC/EAS Guidelines for the Management of Dyslipidemias (Catapano *et al*., 2016).Lipid Association of India (LAI) in their Expert Consensus Statement on Management of Dyslipidemia in Indians published in 2017 has also recommended continuation of statins if a patients of CAD who was on statin develops symptomatic HF (Iyengar SS *et al*., 2017). Generally, the use of statin in patient with advanced HF is not recommended. However, if statins is to be administered, rosuvastatin 10 mg should be preferred in these patients as recommended by Lipid Association of India (Iyengar *et al*., 2017).

Myotoxicities are the most commonly reported adverse effects with statins and include myopathy, myalgia, rhabdomyolysis and myositis (Tomaszewski *et al*., 2011). The physicians in present study reported that they did not observe differences between the different statins in regards to occurrence of myopathy. These findings are in concordance with findings of a network meta-analysis of 22 RCTs with 129,680 patients randomized to different statins (Khan *et al*., 2017). ESC 2016 guidelines for management of dyslipidemia has recommended LDL-C target of <100 mg/dL in high-risk and <70 mg/dL in very high risk patients (Catapano AL *et al*., 2016). Lipid Association of India (LAI) in their Expert Consensus Statement on Management of Dyslipidemia in Indians published in 2016 has recommended little stringent LDL-C goals for (Iyengar *et al*., 2016). LAI has recommended LDL-C goal of <70 mg/dL in high risk patients and <50 mg/dl in very high risk patients. To attain these goals, many patients will need statins at high dosesbut at the cost of increased risk of side effects. LAI has also recommended that at least moderate- or high intensity statin therapy is required to bring about a clinically meaningful reduction in LDL-C in most patients (Iyengar *et al*., 2016). Although low and moderate doses of statins show a favourable safety profile, there is always a concern about the tolerability of intensive doses of statins. This issue should be taken into account in clinical practice as tolerability profile of statins plays a significant role in deciding the compliance of patients with high dose statins and thereby influence the efficacy to reduce LDL-C values. The survey findings suggest that majority of physicians experienced better tolerability with highest dose of rosuvastatin (40 mg) followed by highest dose of atorvastatin (80 mg) in their clinical practice. In India, rosuvastatin and atorvastatin are widely used statins in management of dyslipidemia. Among them, rosuvastatin is the most preferred statin among Indian physicians for most of their patients probably due to its proven better efficacy and tolerability compared to other statins. Whereas, atorvastatin is also a part of their clinical practice in managing patients of dyslipidaemiaspecially in subsets of patients including those with CKD and CHF, thereby signifying the individualized approach. The practices of survey physicians in choosing rosuvastatin and atorvastatin are in accordance with the available scientific evidences and reflect evidence-based medicine practice.

Limitations of study: The major limitation of this survey is that it was physicians' opinion and practices based on their individual experience in managing patients with statin which may account for subjectivity; the actual prescription patterns were not traced and analysed basis comparative cholesterol lowering efficacy, preference in comorbidities and safety of different statins. However, we strongly believe that practices in real-world clinical settings captured in this survey are largely based on the available evidences with individual experiences accounting for differential use of statins amongst the physicians.

Conclusion

The survey findings suggest rosuvastatin as the most preferred statin among cardiologists and physicians followed by atorvastatin in the management of patients with hyperlipidemia and for primary and secondary prevention. Better cholesterol lowering efficacy and better tolerability of rosuvastatin than other statins as evidenced in published clinical trials largely drive the clinical decision making among Indian practitioners, there by affirming the evidence-based medicine approach adopted in their clinical practice. This survey further emphasizes the individualized approach adopted by the practitioners in managing patients of dyslipidemia.

REFERENCES

Baigent C, Blackwell L, *et al*. 2010. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet. 376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5.*

Barakat L, Jayyousi A, Bener A, Zuby B, Zirie M. 2013. Comparison of Efficacy and Safety of Rosuvastatin, Atorvastatin and Pravastatin among Dyslipidemic Diabetic Patients. *ISRN Pharmacol. 2013:146579. doi:10.1155/2013/146579.*

Berne C, Siewert-Delle A. 2005. URANUS study investigators. Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus:

results from the URANUS study. *Cardiovasc Diabetol.;4(1):7. doi:10.1186/1475-2840-4-7.*

Catapano AL, Graham I, De Backer G, *et al*. 2016. ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J. 2016;37(39):2999-3058. doi:10.1093/ eurheartj/ ehw272.*

Clearfield MB, Amerena J, Bassand J.P, *et al*. 2006. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia--Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). *Trials.7:35. doi:10.1186/1745-6215-7-35.*

Colhoun HM, Betteridge DJ, Durrington PN, *et al*. 2004. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet. 364(9435):685-696. doi:10.1016/S0140-6736(04)16895-5.*

de Zeeuw D, Anzalone DA, Cain VA, *et al*. 2015. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. *Lancet Diabetes Endocrinol. (3):181-190. doi:10.1016/S2213-8587(14)70246-3.*

Doupa D, Seck SM, Dia CA, *et al*. 2014. Dyslipidemia, obesity and other cardiovascular risk factors in the adult population in Senegal. *Pan Afr Med J., 19:181. doi:10.11604 /pamj. 2014.19.181.4872.*

Fuster V, Kelly BB. 2010. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health*. Washington (DC): National Academies Press (US).*

Han E, Kim G, Lee JY, *et al*. 2017. Comparison between Atorvastatin and Rosuvastatin in Renal Function Decline among Patients with Diabetes. *Endocrinol Metab (Seoul, Korea)., 32(2):274-280. doi:10.3803/EnM.2017.32.2.274.*

Iyengar SS, Puri R, Narasingan SN, *et al*. Lipid Association of India (LAI) expert consensus statement on management of dyslipidaemia in Indians 2017: part 2. *Clinical Lipidology, 2017;12:1,56-109.*

Iyengar SS, Puri R, Narasingan SN, *et al*. Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2016: Part 1. *J Assoc Physicians India. 2016 Mar;64(3):7-52*

Jones PH, Davidson MH, Stein EA, *et al*. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol. 2003;92(2):152-160. http://www.ncbi.nlm.nih.gov/pubmed/12860216. Accessed January 30, 2018.*

Jones PH, McKenney JM, Karalis DG, Downey J. Comparison of the efficacy and safety of atorvastatin initiated at different starting doses in patients with dyslipidemia. *Am Heart J. 2005;149(1):e1-e8. doi:10.1016/j.ahj.2004.07.025.*

Jukema JW, Cannon CP, de Craen AJM, Westendorp RGJ, Trompet S. The Controversies of Statin Therapy. *J Am Coll Cardiol. 2012;60(10):875-881. doi:10.1016/j.jacc.2012.07.007.*

Khan MS, Riaz H, Siddiqi TJ, *et al*. Do Individual Statins Differ in the Incidence of Myopathy? A Network Meta-analysis of Randomized Controlled Clinical Trials. *Circulation. 2017;136(Suppl 1).http://circ.ahajournals.org/ content/136/Suppl_1/A14584. Accessed February 3,2018.*

Kjekshus J, Apetrei E, Barrios V, *et al*. 2007. Rosuvastatin in Older Patients with Systolic Heart Failure. *N Engl J Med., 357(22):2248-2261. doi:10.1056/NEJMoa0706201.*

Maggioni AP, Marchioli R, *et al*. 2008. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet. 372(9645):1231-1239. doi:10.1016/S0140-6736(08)61240-4.*

Mathers C, Fat D, Boerma J. 2008. For World Health Organization. *The Global Burden of Disease: 2004 Update. Geneva.*

Mihaylova B, Emberson J, *et al*. 2012. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet. 380(9841):581-590. doi:10.1016/S0140-6736(12)60367-5.*

Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. 2008. Primary Prevention of Cardiovascular Mortality and Events With Statin Treatments. *J Am Coll Cardiol.52(22):1769-1781. oi:10.1016/j.jacc.2008.08.039.*

Minder CM, Blumenthal RS, Blaha MJ. 2013. Statins for primary prevention of cardiovascular disease. *Curr Opin Cardiol. 28(5):554-560. doi:10.1097/ HCO. 0b013e32836429e6.*

Nelson RH. 2013. Hyperlipidemia as a risk factor for cardiovascular disease.*Prim Care.40(1):195-211. doi: 10.1016/j.pop.2012.11.003.*

Ramkumar S, Raghunath A, Raghunath S. 2016. Statin Therapy: Review of Safety and Potential Side Effects. *Acta Cardiol Sin., 32(6):631-639. doi:10.6515/ACS20160611A.*

Ray KK, Seshasai SRK, Erqou S, *et al*. 2010. Statins and All-Cause Mortality in High-Risk Primary Prevention. *Arch Intern Med., 170(12):1024. doi:10.1001/ archinternmed.2010.182.*

Rubba P, Marotta G, Gentile M. 2009. Efficacy and safety of rosuvastatin in the management of dyslipidemia. *Vasc Health Risk Manag.;5(1):343-352. http://www. ncbi.nlm.nih.gov/ pubmed/19436657. Accessed February 14, 2018.*

Sandhu S, Wiebe N, Fried LF, Tonelli M.2006. Statins for Improving Renal Outcomes: A Meta-Analysis. *J Am Soc Nephrol.17:2006-2016. doi:10.1681/ASN.2006010012.*

Sindhu S, Salman M, Verma V, Singh H, Fatima J. 2011. Effects of atorvastatin and rosuvastatin on high-sensitivity C-reactive protein and lipid profile in obese type 2 diabetes mellitus patients. *J Pharmacol Pharmacother. 2(4):261. doi:10.4103/0976-500X.85954.*

Taylor F, Huffman MD, Macedo AF, *et al*. 2013. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev., (1):CD004816. doi:10.1002/ 14651858.CD004816.pub5.*

Tomaszewski M, Stępień KM, Tomaszewska J, Czuczwar SJ.2011. Statin-induced myopathies. *Pharmacol Rep.;63(4):859-866. http://www.ncbi.nlm.nih. gov/ pubmed/22001973. Accessed February 3, 2018.*

Weng TC, Yang YHK, Lin SJ, Tai SH. 2010. A systematic review and meta-analysis on the therapeutic equivalence of statins.*J Clin Pharm Ther., 35(2):139-151. doi:10.1111/j.1365-2710.2009.01085.x.*

Xu M, Yuan G, Wei F. 2010. Effect of atorvastatin in patients with chronic heart failure - insights from randomized clinical trials. *Arch Med Sci., 6(6):866-873. doi: 10.5114/aoms.2010.19293.*

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