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Despite Increased Use And Sales Of Statins In India, Per Capita Prescription Rates Remain Far Below High-Income Countries

ABSTRACT Statin use has increased substantially in North America and Europe, with resultant reductions in cardiovascular mortality. However, little is known about statin use in lower-income countries. India is of interest because of its burden of cardiovascular disease, the unique nature of its prescription drug market, and the growing globalization of drug sales. We conducted an observational study using IMS Health data for the period February 2006–January 2010. During the period, monthly statin prescriptions increased from 45.8 to 84.1 per 1,000 patients with coronary heart disease—an increase of 0.80 prescriptions per month. The proportion of the Indian population receiving a defined daily statin dose increased from 3.35 percent to 7.78 percent. Nevertheless, only a fraction of those eligible for a statin appeared to receive the therapy, even though there were 259 distinct statin products available to Indian consumers in January 2010. Low rates of statin use in India may reflect problems with access to health care, affordability, underdiagnosis, and cultural beliefs. Because of the growing burden of cardiovascular disease in lower-income countries such as India, there is an urgent need to increase statin use and ensure access to safe products whose use is based on evidence. Policies are needed to expand insurance, increase medications' affordability, educate physicians and patients, and improve regulatory oversight.

Medications—along with diet, exercise, and smoking cessation—are a cornerstone of cardiovascular risk reduction. Statins are the medications of choice because of their proven value for both primary and secondary prevention—that is, for patients with and without known cardiovascular disease.^{1,2}

The use of statins has increased substantially in North America and Europe³ during the past three decades. As a result, cholesterol levels⁴ and cardiovascular mortality have been reduced in those regions.^{4,5} In contrast, cholesterol levels are increasing among people in low- and mid-

dle-income countries,⁴ where cardiovascular disease already accounts for more deaths than in higher-income countries.^{7–9} However, nationally representative estimates of the adequacy of statin prescribing in resource-poor settings are lacking.

Statin use in India is of interest because India has the highest burden of cardiovascular disease among less developed nations¹⁰ and because of the unique nature of the Indian prescription drug market. A limited number of statins are available in North America and Europe,¹¹ but India has a wide variety of “branded generic” products.¹² Statins in India are often sold in combination with other drugs, and there are few

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barriers to the entry of new products in response to changing market trends. The nature of statin use in India may also affect patients in other countries who purchase Indian products, often over the Internet, to avoid paying the high prices they would be charged in their local markets.¹³

We used data on prescription drug sales to estimate the prevalence of statin use in India, including the number and types of products available, and to estimate the proportion of people with coronary heart disease (CHD) who receive statins.

Study Data And Methods

DATA SOURCES We conducted an observational study using data collected by IMS Health for the period February 2006–January 2010. Our analyses were based on the Stockist Sales Audit database, which collects information from 4,000 of the 18,000 stockists in India. Stockists are intermediaries between manufacturers and the approximately 550,000 retail pharmacies in India.^{14,15} Indian stockists are selected for inclusion in the database based on their location. IMS Health uses stratified sampling to generate a sample that is representative of all of India as well as of individual regions, states, and town classes (a measure of town size used by the Indian census). IMS Health collects data from stockists and checks the data for quality control and accuracy.

The database contains information about the number and cost of packages of medication sold to pharmacies; the generic and brand name of each product; its manufacturer, dosage, and number of tablets per package; and whether or not the medication is sold in combination with other active ingredients. Information for different dosages (for example, ten milligrams versus twenty milligrams of atorvastatin) and individual manufacturers is also included.

OUTCOME MEASURES From the IMS Health data, we calculated the number of month-long supplies of medications sold (referred to in this article as prescriptions). We did this for each product by multiplying the number of tablets in the package (typically ten) by the number of packages sold and then dividing this amount by the number of days in the month.

We also calculated the number of doses of each medication sold each day, using the World Health Organization's "defined daily dose" (DDD). The DDD is the assumed average daily maintenance dose for a drug used for its main indication in adults. Using this measure makes it possible to make comparisons across medications with different relative potencies.¹⁶ For example, the DDDs for atorvastatin and lovastatin

are twenty milligrams and forty-five milligrams, respectively. DDDs for combination products were calculated based only on the statin component of each product.

Combination products were categorized into mutually exclusive groups based on the following nonstatin agent or agents that they contained: angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB); antiplatelet agent (aspirin or clopidogrel); ACE inhibitor or ARB and an antiplatelet agent; metformin; vitamin; other cholesterol-lowering agent; and other cholesterol-lowering agent and vitamin. The other cholesterol-lowering agents were ezetimibe, fibrates, and nicotinic acid, which could occur in combination.

STATISTICAL ANALYSIS We used descriptive statistics to summarize the statin products available in India in the last month for which data were available, January 2010. For each statin type, we assessed the number of products, proportion of products sold in combination with other drugs and the components of these products, number of prescriptions sold, average price, and total sales value. Prescription rates were standardized per 1,000 population based on data from the Indian Central Bureau of Health Intelligence in the Ministry of Health and Family Welfare.¹⁷

We estimated the prevalence of CHD using data from the report of the National Commission on Macroeconomics and Health,¹⁸ which provided projected rates of CHD for 2005, 2010, and 2015. Based on this information, we used linear regression to estimate trends and disease prevalence for 2006, 2007, 2008, and 2009.^{19,20}

We plotted the number of monthly medication supplies, DDDs, and value of sales in each month for all statins and stratified by statin type. Trends were evaluated using linear regression models that provided estimates of the trends' monthly rate of change. We assumed that errors were normally distributed.

All analyses were performed using the statistical software SAS, version 9.2. This study was approved by the Institutional Review Board of Brigham and Women's Hospital.

LIMITATIONS Our analyses were based on sales by stockists. This source of information does not include actual dispensing rates or numbers of prescriptions written. Although these measures should be highly correlated, our study might not have accurately captured the actual consumption of medications by patients. Validation studies have not been conducted using this data source. Furthermore, prices paid by consumers are generally higher than those paid by stockists. It is reassuring to note that any bias should be non-differential over time and thus should not mean-

ingfully influence our analyses of trends in use or of the products available.

Stockists' sales are estimated to account for 87–89 percent of total drug sales in India; they do not include manufacturers' direct sales to public hospitals. Therefore, we might have underestimated overall rates of statin use, and our results might not be generalizable to statin use in the public sector.

We used aggregate prescription sales data and did not have access to detailed patient-level clinical information. As a result, we could not determine whether or not the observed rates of statin use were clinically appropriate or were associated with any change in outcomes.

We did not have information on geographic or socioeconomic factors that affect access to statins. Although the data were from geographically diverse sources, it is possible that they did not describe the diversity of statin use in some parts of India.

We based our estimates of CHD prevalence on regression analyses applied to projections by the Government of India. Although our estimates are

consistent with published sources,⁸ inaccuracies in the projections could have influenced our estimates.

Study Results

STATIN AVAILABILITY AND SALES IN INDIA In January 2010, 259 unique statin products produced by sixty-five manufacturers were available to Indian consumers (Exhibit 1). Atorvastatin accounted for 81.1 percent of the available products and 84.8 percent of statin sales.

The rate of statin prescriptions sold daily in January 2010 was 3.4 per 1,000 population and 84.1 per 1,000 patients with CHD (Exhibit 1). The value of all sales in January 2010 was 725,731,281 rupees (US\$11,451,832), with a median price to retailers of 5.9 rupees (US\$0.09) per pill.

Combination products accounted for 55.2 percent of statin products (Exhibit 1) and 30 percent of statin prescriptions sold in January 2010. Ninety-three percent of the 143 combination products contained atorvastatin, as did 98 percent of the prescriptions (Exhibit 2). Products

EXHIBIT 1

Statins Available In India, January 2010

Statin category	Leading products	Rx per 1,000 people per day	Rx per 1,000 patients with CHD per day	Manufacturers		Unique products		Combination products		Sales		Mean price per Rx ^a	
				No.	%	No.	%	No.	%	Rupees	%	Rupees	Range
Atorvastatin	Storvas, Atorva, Tonact, Aztor, Lipicure	2.97	74.40	62	95.4	210	81.1	133	63.3	615,459,982	84.8	5.7	0.7, 24.6
Fluvastatin	Lescol XI	0.00	0.01	1	1.5	1	0.4	0	0.0	396,647	0.1	26.0	26.0, 26.0
Lovastatin	Rovacor, Lostatin, Lovacard	0.01	0.18	3	4.6	3	1.2	0	0.0	1,254,974	0.2	4.7	3.3, 6.0
Pravastatin	Pravator	0.00	0.00	1	1.5	1	0.4	0	0.0	40,496	0.0	13.7	8.5, 14.0
Rosuvastatin	Rosuvas, Rozavel, Crestor, Razel, Roseday	0.26	6.47	19	29.2	24	9.3	5	20.8	76,129,036	10.5	8.1	2.1, 40.3
Simvastatin	Simvotin, Zocor, Zosta, Simcard, Simvofix	0.12	3.08	12	18.5	20	7.7	5	25.0	32,450,146	4.5	7.2	0.9, 23.2
All	Storvas, Atorva, Tonact, Aztor, Rosuvas	3.36	84.10	65	— ^b	259	— ^b	143	55.2	725,731,281	— ^b	5.9	0.7, 40.3

SOURCE Authors' analysis of IMS Health's Stockist Sales Audit database. **NOTE** CHD is coronary heart disease. ^aTo retailers. ^bNot applicable.

that combined a statin and only one other agent made up 93 percent of the products and 94.5 percent of the prescriptions.

Antiplatelet agents and nonstatin cholesterol-lowering agents, particularly ezetimibe (combined with atorvastatin, rosuvastatin, or simvastatin) and fibrates (combined with atorvastatin or rosuvastatin), were the most common drug classes combined with statins. Combination products cost less than statins alone (5.0 versus 6.2 rupees per pill; $p < 0.001$). However, retail prices varied significantly.

Three separate products, collectively accounting for almost 4 percent of the prescriptions of combination products, contained a statin (atorvastatin), an ACE-I (ramipril), and aspirin. No products that combined a statin, thiazide, ACE inhibitor or ARB, beta-blocker, and antiplatelet agent—all of the components of the polypill discussed below—were available in India during the study period.

TRENDS IN STATIN USE IN INDIA In the study period, statin sales in India increased at a rate of 45,864 prescriptions per month (95% confidence interval: 42,928, 48,880; $p < 0.0001$), reaching 3,950,193 in January 2010 (Appendix A)²¹—or 84.1 per 1,000 population (Exhibit 3). The increase in sales was significant after we adjusted for population growth (an increase of 0.038 prescriptions per 1,000 popula-

tion per month [95% CI: 0.035, 0.040; $p < 0.0001$]) and the increasing prevalence of CHD (an increase of 0.80 prescriptions per 1,000 patients with CHD per month [95% CI: 0.74, 0.87; $p < 0.0001$]).

During this period, the proportion of the population receiving a DDD of a statin increased from 3.35 percent to 7.78 percent (see Appendix B; for results stratified by statin type, see Appendix C).²¹ Statin sales based on DDD increased at a faster rate than those based on prescriptions (there was a 106.8 percent increase in prescriptions and a 161.8 percent increase in DDD), which suggests a shift over time toward higher doses and more potent statins.

The average dose of atorvastatin sold was 16.2 milligrams per day in February 2006. The dose increased significantly during the study period, although the magnitude of the change was quite small (0.08 milligrams per month; $p < 0.0001$).

Atorvastatin accounted for more than 90 percent of prescriptions and DDDs (Exhibits 4 and 5). Rosuvastatin use increased in 2009, but that statin still had less than 5 percent of the market share. Simvastatin use declined during the study period ($p < 0.0001$), and in 2009 simvastatin's market share was less than 2 percent.

EXHIBIT 2

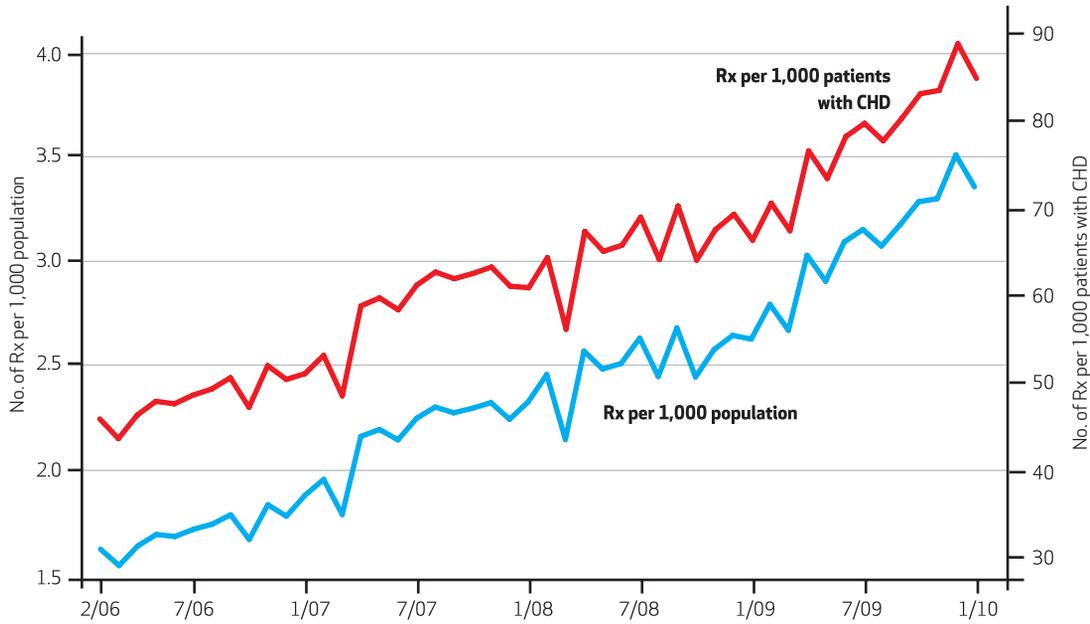
Statin Combination Products Available In India, January 2010

Characteristic	Products		Prescriptions	
	Number	Percent	Number	Percent
Statin combination products	143	100.0	1,205,203	100.0
Other agents combined with statins				
One agent with a statin	133	93.0	1,138,454	94.5
Two agents with a statin	10	7.0	66,749	5.5
Statins in combination products				
Atorvastatin	133	93.0	1,180,682	98.0
Rosuvastatin	5	3.5	19,704	1.6
Simvastatin	5	3.5	4,818	0.4
Nonstatin agents in combination products				
Nonstatin lipid agent ^a	112	78.3	548,070	45.5
Ezetimibe	55	38.5	226,790	18.8
Fibrates ^a	48	33.6	299,837	24.9
Nicotinic acid	5	3.5	8,174	0.7
Ezetimibe and fibrates	4	2.8	13,268	1.1
Antiplatelet ^b	13	9.1	588,804	48.9
ACE inhibitor or ARB	10	7.0	13,629	1.1
Metformin	1	0.7	679	0.1
Vitamin	5	3.5	9,404	0.8
ACE inhibitor or ARB and antiplatelet agent	3	2.1	46,858	3.9

SOURCE Authors' analysis of data from IMS Health's Stockist Sales Audit database. **NOTES** ACE is angiotensin-converting enzyme. ARB is angiotensin receptor blocker. ^aOne of the 112 combination products of a statin and a nonstatin lipid-lowering agent also contained a vitamin. ^bEither aspirin or clopidogrel. One of the combination products of a statin and an antiplatelet agent also contained a vitamin.

EXHIBIT 3

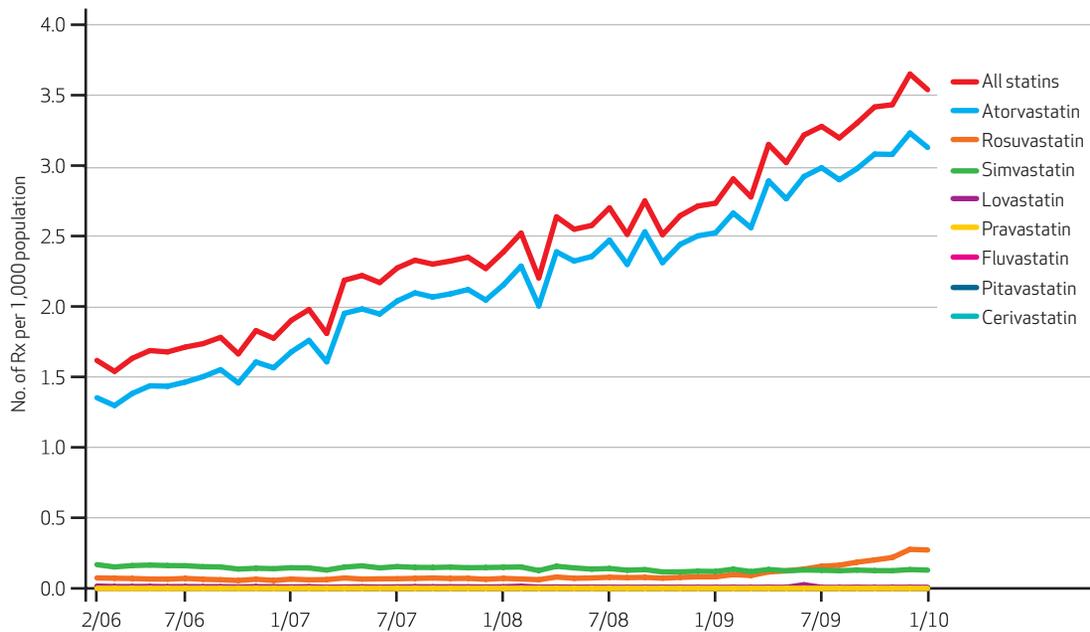
Statin Prescriptions Per 1,000 Population And 1,000 Patients With Coronary Heart Disease (CHD), February 2006–January 2010



SOURCE Authors' analysis of data from IMS Health's Stockist Sales Audit database. **NOTES** The blue line, prescriptions per 1,000 population, relates to the left-hand y axis. The red line, prescriptions per 1,000 population with CHD, relates to the right-hand y axis.

EXHIBIT 4

Statin Prescriptions Per 1,000 Population, By Statin Type, February 2006–January 2010



SOURCE Authors' analysis of data from IMS Health's Stockist Sales Audit database. **NOTE** Values for fluvastatin, pitavastatin, and cerivastatin are nearly identical to those of pravastatin and thus do not appear in this exhibit.

EXHIBIT 5

Annual Statin Sales In India, 2006-09

	2006	2007	2008	2009
Prescriptions				
Total	1,893,373	2,429,845	2,855,049	3,543,460
Per 1,000 population	1.70	2.15	2.49	3.05
Per 1,000 patients with CHD	48.03	58.26	64.89	76.55
Defined daily doses				
Total	1,452,613	2,103,356	2,600,359	3,334,354
Per 1,000 population	1.31	1.86	2.27	2.87
Per 1,000 patients with CHD	36.85	50.43	59.10	72.03
Total sales (rupees)	3,891,890,455	5,205,695,498	6,300,481,731	7,706,407,971
Average daily cost (rupees)	5.63 ^a	5.84 ^b	6.01 ^c	5.93 ^d
Market share				
Atorvastatin	91.46	94.08	95.05	93.58
Fluvastatin	0.00	0.01	0.02	0.02
Lovastatin	0.32	0.18	0.13	0.09
Pitavastatin	0.16	0.01	0.00	0.00
Pravastatin	0.05	0.02	0.01	0.00
Rosuvastatin	3.83	2.87	2.66	4.62
Simvastatin	4.19	2.83	2.13	1.69
No. of statin products	240	262	274	303
Combination products, % of total	48	53	55	55
No. of manufacturers	74	72	74	76

SOURCE Authors' analysis of data from IMS Health's Stockist Sales Audit database. **NOTES** Market share is percentage of defined daily doses. CHD is coronary heart disease. ^aStandard deviation: 0.04. ^bStandard deviation: 0.12. ^cStandard deviation: 0.05. ^dStandard deviation: 0.14.

Discussion

Our analysis of national sales data demonstrates substantial differences in statin use and availability in India compared to the situation in Western countries. The most distinctive feature of the Indian statin market is the number of products available to consumers and the number of manufacturers that produce the products. For example, during our study period, atorvastatin was produced by sixty-two manufacturers in India but by only one manufacturer in the United States.

Products that combined statins with other agents that are frequently prescribed with them—including clopidogrel, ACE inhibitors, and metformin—are widely available in India. In the United States, several combination products have been approved for sale by the Food and Drug Administration—most notably, simvastatin and ezetimibe—but they are not widely used.²² Surprisingly, in India combination products are less expensive than statins alone, which may create incentives for their adoption.

Combination products may increase adherence by reducing regimen burden,²³ which is a key motivation behind efforts to introduce a polypill—a single, multicomponent pill—to reduce cardiovascular risk.²⁴ No polypill was available in India during the study period, as noted above.

However, at least one is available now, and others have been submitted to the Central Drugs Standard Control Organization.^{25,26}

The results of randomized studies demonstrate that a polypill can reduce blood pressure,^{27–29} cholesterol,^{27,29} heart rate,^{27,28} and platelet activity^{27,28} and improve medication adherence.²⁹ The clinical effects of combination pills do not appear to be entirely equal to the effects of the drugs administered individually,²⁷ and it is possible that the simpler combinations that are available may not have predictable therapeutic effects.

The most commonly prescribed combination products in India contain statins and other cholesterol-lowering agents. Combinations of statins with fibrates appear to substantially increase the risk of rhabdomyolysis—that is, the rapid breakdown of muscle tissue—³⁰ and do not provide incremental benefits over the use of statins alone in patients with diabetes.³¹ Similarly, studies have raised questions about the benefits of combining statins and ezetimibe³² and of adding niacin to an optimal statin regimen.³³

Thus, the frequent use of these products in India may not be consistent with evidence-based practice. As a result, monitoring the sale, prescribing, and marketing of combination products in India should be a priority for the govern-

Only a minority of patients who would receive statin therapy in other countries appear to be receiving the therapy in India.

ment. Draft guidance on standards for the approval of combination products have been issued by the Central Drugs Standard Control Organization.³⁴ However, it is unlikely that the guidance will apply to existing products, and the date of implementation is uncertain. More generally, the wide range of statin products available in India increases the choices available to consumers, providers, and dispensers,¹² but it could also create drug safety problems. The bioequivalence of many drugs has not been rigorously evaluated.³⁵ In addition, many countries have difficulties monitoring the quality of legally produced prescription medications, as was seen when oral contraceptives were recalled because of a packaging error in the United States.³⁶ The volume of products available in India could conceivably increase these regulatory difficulties. However, the impact of the greater availability of statin products in India and the question of their safety have not been specifically evaluated.

Critics in India cite as evidence of the challenge involved in regulating the Indian pharmaceutical market the fact that some medications in India are sold despite the absence of data to support their efficacy and despite the fact that they are not sold in major developed countries.^{37–39} In addition, a report on the Indian Central Drugs Standard Control Organization expressed concerns about the adequacy of licensing mechanisms and called for significant reforms.³⁸

Atorvastatin accounted for 80 percent of all statin products and more than 90 percent of prescriptions sold in India in 2006–09 (Exhibit 5). In the United States simvastatin accounted for the greatest number of statin prescriptions in the same time period.⁴⁰ Atorvastatin's dominance in India reflects the fact that many "branded-generic" versions of this drug can be manufactured there, because international patents that protect brand-name drugs in the United States have not been respected in India until recently.

In 2005 India changed its Patent Act to become compliant with the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement.¹² However, the 2005 legislation provides patent protection only to new products that have been demonstrated to be superior to existing ones;⁴¹ it does not limit the production of statins that existed before the change in laws. Thus, atorvastatin—which was sold in the United States only as a brand-name drug during our study period—had a lower price in India than simvastatin does.

Other factors likely contribute to the dominance of atorvastatin in India. In a highly privatized health care system such as that in the United States, pharmaceutical companies provide financial incentives to hospitals to prescribe their drugs. In countries such as India, however, pharmaceutical manufacturers market their products heavily to physicians and pharmacists.

In India there are approximately 80,000 medical representatives⁴² who give physicians and pharmacists financial support to attend conferences, who sponsor their recreational trips,⁴³ and who provide them with smaller gifts⁴⁴—all on behalf of pharmaceutical manufacturers. Indian pharmacists, in turn, market brand-name drugs to consumers, who may have difficulty evaluating the quality of recommendations being made to them. The result is higher sales of brand-name medications than would be the case for patients with higher levels of health literacy.^{45,46}

In 2004 the fifty largest pharmaceutical manufacturers in India spent 290–1,025 percent more on drug promotion than they did on research and development.⁴⁷ In response, the Medical Council of India has urged physicians to prescribe generic drugs,⁴⁸ and a panel of Indian ministers of health has suggested capping the price of certain medications.⁴⁹ The council has also revised its code of conduct to deregister physicians who accept gifts worth more than 100,000 rupees (US\$1,577.97), but addressing potential conflicts of interest remains challenging.⁵⁰

We observed substantial increases in statin use between 2006 and 2009. However, with prescription rates of approximately 8,000 per 100,000 patients with CHD in January 2010, only a minority of patients who would receive statin therapy in other countries appear to be receiving the therapy in India. Per capita prescribing rates for statins in India are twenty times lower than those in the United States and Canada.²²

To our knowledge, no other nationally representative population-based estimates of statin use in India have been published. Cohort studies have found that statins are received by approxi-

20

Times lower

Per capita prescribing rates for statins in India are 20 times lower than those in the United States and Canada.

mately half of the Indians who have acute coronary syndromes when they are discharged from a hospital⁵¹ and only 20 percent of patients who have established CHD during a primary care visit.⁵² Our lower estimates are consistent with those from regionally conducted patient surveys⁵³ and probably reflect underprescribing in typical Indian care settings, the broad range of risk profiles in our sample, and the high rates of long-term nonadherence that are common for medications used to treat chronic disease.^{54,55}

More generally, the low rates of statin use in India may reflect a wide range of factors, including access to health care services, affordability, underdiagnosis, and cultural beliefs. For example, we did not have access to the prices that pharmacists charged patients, but we conservatively estimated that the price of statins in India was a few cents per pill, which is similar to what many US consumers pay for generic statins.⁵⁶ However, India's gross national income per capita is less than 3 percent of that in the United States (\$1,340 versus \$47,140 in 2010).⁵⁷

In addition, more than 80 percent of Indians have no health insurance and must pay out of pocket for all medications and health care services.⁵⁸ Several recent government efforts, including the national Rashtriya Swasthya Bima Yojna (the National Health Insurance Program), have sought to provide health insurance to lower-income Indians, but the impact of these efforts is unclear.^{59–61} The National Pharmaceutical Pricing Authority of India has recommended imposing a ceiling price for atorvastatin, limiting retailers to a margin of 16 percent.⁶² Whether this will increase overall rates of use remains unknown.

Conclusion

Our findings show that only a fraction of patients with CHD in India receive statin treatment.

The low rates of statin use in India may reflect a wide range of factors, including access to services, affordability, underdiagnosis, and cultural beliefs.

These results support the implementation of a broad range of policies, including the expansion of health insurance to make medications more affordable; educational activities targeted at physicians and patients to promote the prescribing and use of statins; raising awareness of the potential benefits of these drugs for selected patients; and perhaps even introducing quality measurement activities, which have been highly successful in the United States in increasing the use of evidence-based medications.⁶³

The wide variety of statins available in India suggests that to reduce the rapidly growing burden of cardiovascular disease, efforts to promote greater statin use should be accompanied by improvements in the regulatory oversight of pharmaceuticals in the country.^{34,37,38} These improvements should include confirming the bioequivalence of the many available drugs, improving the licensing process, and monitoring the prescribing and marketing of combination products. ■

NOTES

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