

Trends in lipid-modifying agent use in 83 countries

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ABSTRACT

Background and aims: Lipid-modifying agents (LMAs) are increasingly used to reduce lipid levels and prevent cardiovascular events but the magnitude of their consumption in different world regions is unknown. We aimed to describe recent global trends in LMA consumption and to explore the relationship between country-level LMA consumption and cholesterol concentrations.

Methods: This cross-sectional and ecological study used monthly pharmaceutical sales data from January 2008 to December 2018 for 83 countries from the IQVIA Multinational Integrated Data Analysis System and total and non-high-density lipoprotein (non-HDL) cholesterol concentrations from the NCD Risk Factor Collaboration. Compound annual growth rate (CAGR) was used to assess changes in LMA consumption over time.

Results: From 2008 to 2018, use of LMAs increased from 7468 to 11,197 standard units per 1000 inhabitants per year (CAGR 4.13%). An estimated 173 million people used LMAs in 2018. Statins were the most used class of LMA and their market share increased in 75% of countries between 2008 and 2018. From 2013 to 2018, consumption of low-density lipoprotein lowering therapies increased (statins 3.99%; ezetimibe 4.01%; proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors 104.47%). Limited evidence supports a clear relationship between country-level changes in LMA consumption and mean total and non-HDL cholesterol concentrations in 2008 versus 2018.

Conclusions: Since 2008, global access to LMAs, especially statins, has improved. In line with international lipid guideline recommendations, recent trends indicate growth in the use of statins, ezetimibe, and PCSK9 inhibitors. Country-level patterns of LMA use and total and non-HDL cholesterol varied considerably.

1. Introduction

Lipid-modifying agents are widely recommended to reduce atherogenic lipid levels and to prevent atherosclerotic cardiovascular disease [1–3]. Over the last few decades, emerging evidence of the benefits and risks of different classes of lipid-modifying agents has informed updates to cholesterol guidelines and influenced treatment choices. Recommendations for the broader use of statins in the 2013 American College

of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline [4] raised concerns about extrapolating the available evidence, and subsequent worldwide ‘statinization’ [5]. It is unknown whether overall lipid-modifying agent use has continued to increase at the global level. Given the robust evidence of benefit for statins, their share of lipid-modifying agent use may have evolved over time.

Several developing regions now face a greater burden from elevated cholesterol levels, yet they have lower consumption of lipid-modifying

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agents as compared to high-income regions [6,7]. Since 1980, parts of Africa and East and Southeast Asia have experienced increases in total and non-high-density lipoprotein (non-HDL) cholesterol, while high-income Western countries have experienced decreases [6]. It is unknown whether recent consumption trends of lipid-modifying agents correspond to the observed changes in cholesterol levels. To date, there is also limited data on the use of lipid-modifying agents for many countries outside of Northern America and Europe.

In this study, we analyzed pharmaceutical market intelligence data from the IQVIA Multinational Integrated Data Analysis System (MIDAS) from 2008 to 2018. We aimed to describe contemporary trends in lipid-modifying agent use and to explore the relationship between the use of lipid-modifying agents and average total and non-HDL cholesterol concentrations. Regional and cross-country comparisons on trends of lipid-modifying agent consumption can be used to monitor progress on access to lipid-modifying treatment, to explore reasons for different patterns of use, and to connect information about an important cause of cardiovascular disease and its pharmacological treatment.

2. Materials and methods

2.1. Study design and data sources

We conducted a cross-sectional and ecological study using monthly pharmaceutical sales data collected by IQVIA in 83 countries from January 2008 to December 2018. Country-level data are collected from multiple distribution channels, such as wholesalers, direct distribution from manufacturers, retail, and hospital pharmacies and differs by country and data type. If required, the sampled data are then projected to represent 100% of the total sales channel in each country. Product information in MIDAS is classified according to Anatomic Therapeutic Chemical (ATC) codes, and undergoes various quality-control checks. The available data for this study provide an international view of medication use across 39 high-, 24 upper-middle, 13 lower-middle, and 7 low-income economies included in 67 MIDAS country panels (Supplementary Table 1). MIDAS countries can be defined as individual countries, regions or territories (e.g., Puerto Rico), or groups of countries (i.e., Central America and French West Africa). Annually, IQVIA internally estimates the accuracy of its data using manufacturer sales and reports 95% global precision in most years [8,9]. Detailed information on the methods of data collection, projection, and validation are proprietary and have not been externally audited limiting the assessment of data representativeness. Data from MIDAS have been used to assess global patterns in medicine consumption [7,10]. No information about patients or prescribers was available in our data; therefore, this study was exempt from ethical approval by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

We also used the mid-year population estimates from the United Nations (UN) World Population Prospects 2019 report [11]. The population of the constituent countries for French West Africa and Central America were summed for each year. Countries were then classified according to the UN geographical region (i.e. Africa, Latin America and the Caribbean, Oceania, Europe, Northern America, and Asia) and subregions. Gross domestic product (GDP) per capita was obtained from the World Bank [12]. Country-level estimates for mean total and non-HDL cholesterol were obtained from the NCD Risk Factor Collaboration. The NCD Risk Factor Collaboration used publicly available data from population-based surveys to estimate age-standardized total and non-HDL cholesterol for 200 countries, from 1980 to 2018, using a Bayesian model with the Markov chain Monte Carlo algorithm [6]. Although low-density lipoprotein (LDL) cholesterol is often the primary treatment target in lipid guidelines, both total and non-HDL cholesterol (the total mass of cholesterol in atherogenic lipoproteins) has been more widely measured [6]. To our knowledge, worldwide country-level estimates for triglycerides and LDL cholesterol are not available.

2.2. Lipid-modifying agent categories

The available data included sales of brand, generic, and combination lipid-modifying agents. Because of limited coverage by the WHO, IQVIA does not assign ATC codes or defined daily doses to combination products (e.g. C10B Lipid modifying agents, combinations) [13]. In addition, because the WHO ATC system groups ezetimibe, PCSK9 inhibitors, and omega-3 fatty acids under the “C10AX Other lipid modifying agents” category, we classified lipid-modifying agents into the following therapeutic categories: statins, fibrates, bile acid sequestrants, niacin, ezetimibe, omega-3 fatty acids, PCSK9 inhibitors, and others (Supplementary Table 2).

2.3. Consumption measurements

The primary variables of interest were the monthly number of standard units and consumption standardized for population, defined as standard units per 1000 inhabitants, either per quarter or per year. The measure of standard units captures the entire market of products in MIDAS and includes combination products. IQVIA defines a standard unit as the smallest common physical unit for each pharmaceutical product. This allows for comparisons between products of different dosage forms. For example, one standard unit for a statin equals a tablet or capsule while one standard unit for a PCSK9 inhibitor equals a pre-filled syringe.

2.4. Data analysis

We reported the total number of standard units sold per month for all lipid-modifying agents and by each drug class. For each calendar year from 2008 to 2018, monthly sales data were aggregated per quarter (Q1 = Jan, Feb, March; Q2 = April, May, June; Q3 = July, August, September; Q4 = October, November, December) and per year (January to December), and standardized per 1000 inhabitants. Consumption of all lipid-modifying agents by region and subregion was plotted. For all lipid-modifying agents and each class, we assessed consumption trends using the compound annual growth rate (CAGR). CAGR is the geometric mean of annual growth rates and is used to compare growth trends over several years and is defined as

$$\text{CAGR} = \left(\sqrt[\text{year}_2 - \text{year}_1]{\frac{\text{Annual sales volume year}_2}{\text{Annual sales volume year}_1}} - 1 \right) \times 100\% \quad [14].$$

Because CAGR is sensitive to the start and end years of the time period, we calculated it both for the overall study period (2018 vs 2008; or the earliest year of available data), and for the last five years of the study (2018 vs 2013). The latter five-year period is when most MIDAS country panel additions were completed and can capture consumption trends since the publication of the ACC/AHA 2013 cholesterol guideline (Supplementary Table 1) [4]. We estimated CAGR for PCSK9 inhibitors by comparing the annual sales in 2016 and 2018, since evolocumab and alirocumab were first approved in July 2015, and thus did not have a 12 months of sales data in 2015 [15,16].

Statin market share was estimated as the percentage of statin standard units sold relative to all lipid-modifying agent standard units in 2008 versus 2018. We estimated the number (%) of persons in each country who consumed lipid-modifying agents and statins in 2018 assuming consumption of one standard unit per person per day. We plotted lipid-modifying agent consumption versus sex-specific cholesterol concentrations (2018) and versus GDP per capita (2009, 2012, 2015, and 2018). Correlation was assessed using Spearman's ρ . Furthermore, we plotted the change in annual lipid-modifying agent consumption and mean concentrations of total and non-HDL cholesterol for 2008 to 2018. For these plots, we excluded countries with no consumption data or missing GDP data. Furthermore, for the MIDAS countries of French West Africa and Central America, we selected the mean cholesterol concentrations for Togo and El Salvador, respectively,

to represent changes for these MIDAS countries. These countries were arbitrarily selected since their cholesterol concentrations were approximately in the middle of the plots for average cholesterol in their respective MIDAS country. Two authors (JEB and YW) independently accessed the data and conducted the analysis using R software version 3.6.1 (R Core Team; Vienna, Austria).

2.5. Data availability statement

The underlying MIDAS data were provided by IQVIA under license. The terms of our agreement do not permit disclosure, sublicensing, or sharing of IQVIA MIDAS data.

The underlying cholesterol data are available from the NCD Risk Factor Collaboration: <http://www.ncdrisc.org/data-downloads-cholesterol.html>.

3. Results

The IQVIA MIDAS data included sales from 83 countries covering 74% of the estimated 2018 world population of 7,631,091,000 people. In 2018, an estimated 172.6 million people (3.1%) used lipid-modifying agents and 145.8 million people (2.6%) used statins (Supplementary Table 3). Use of all lipid-modifying agents increased from a total of 2,904,258,689 standard units in January 2008 to 5,509,412,107 in December 2018. Statins were the most commonly used class of lipid-modifying agent (Fig. 1A). Fibrates, ezetimibe, and omega-3 fatty acids were the most consumed nonstatins drugs (Fig. 1B). When accounting for the population of the included countries, the annual use of lipid-modifying agents increased at a CAGR of 4.13% from 2008 to

2018. In the latter five-year period (2013–2018), consumption slowed with a CAGR of 3.16% (Table 1). Statins experienced the largest average growth from 2008 to 2018 (CAGR 5.19%). Between 2013 and 2018, trends for nonstatins differed. There was increased consumption of other lipid-modifying agents, ezetimibe, and PCSK9 inhibitors. In contrast, consumption of fibrates, niacin, omega-3 fatty acids, and bile acid sequestrants decreased (Table 1).

The use of lipid-modifying agents varied widely according to region, subregion, and country. The overall use of lipid-modifying agents in Northern America remained similar in 2018 as compared with 2008, while other regions saw steady increases in consumption (Fig. 2A). In 2018, lipid-modifying agent consumption in Oceania was nearly 7.3 times greater than Asia, 6.1 times greater than Latin America and the Caribbean, and 16.1 times greater than Africa. At the subregion level, Central Asia, Central America, and Western Africa had the lowest use of lipid-modifying agents (Fig. 2B). In 2008, use of lipid-modifying agents in countries outside Northern America and Europe was low (Fig. 3A). By 2018, use had increased in most countries (Fig. 3B), notably in South America, Southern Europe, Northern Africa, and in East Asia.

Countries in Northern America and Europe were the greatest consumers of lipid-modifying agents. In 2008, the countries with the highest consumption of lipid-modifying agents were the United States (40,902 standard units/1000 inhabitants), Greece (39,827 standard units/1000 inhabitants), and France (39,751 standard units/1000 inhabitants). By 2018, Greece, Portugal, and Belgium were the greatest consumers of lipid-modifying agents (Supplementary Table 4). The estimated proportion of each country’s population that consumed lipid-modifying agents and statins in 2018 is shown in Supplementary Table 3. Over the most recent 5-year period, 59 (88.1%) of the IQVIA countries had

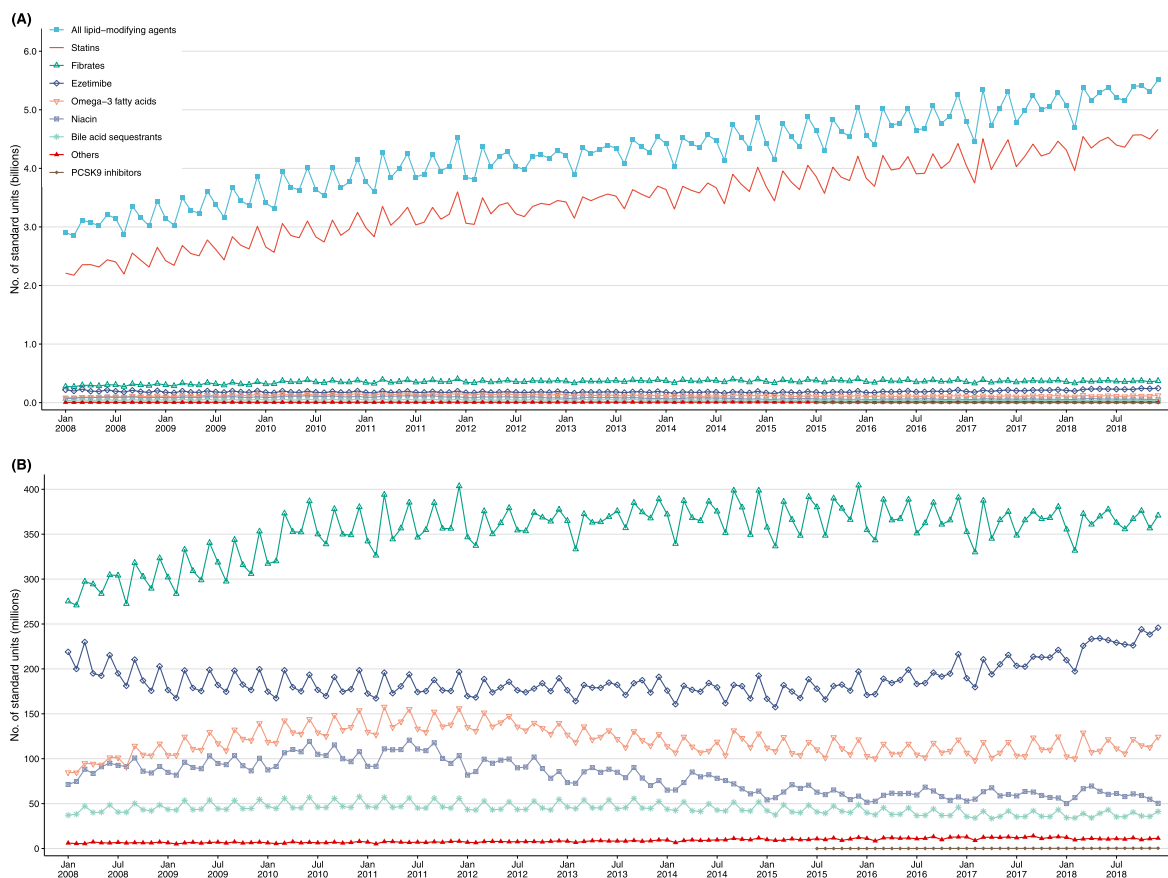


Fig. 1. Monthly number of lipid-modifying agent standard units used in 83 countries from 2008 to 2018. Monthly sales data are from IQVIA MIDAS. Lipid-modifying agents are categorized according to therapeutic categories (see Supplementary Table 2). (A) Number of standard units (billions) sold of all lipid-modifying agents and according to therapeutic category. (B) Number of standard units (millions) sold of fibrates, ezetimibe, omega-3 fatty acids, niacin, bile acid sequestrants, other lipid-modifying agents, and PCSK9 inhibitors.

Table 1
Use and growth rate of lipid-modifying agents by category in 83 countries between 2008 and 2018.

	Consumption (standard units per 1000 inhabitants)											CAGR (%)	
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2008–2018	2013–2018
All lipid-modifying agents	7467.86	8089.53	8694.76	9149.65	9289.57	9585.08	9839.76	10,064.89	10,464.85	10,767.08	11,197.07	4.13	3.16
Statins	5706.76	6261.74	6761.64	7223.41	7434.18	7780.26	8088.59	8367.84	8777.62	9071.05	9463.05	5.19	3.99
Fibrates	710.33	755.87	825.22	824.99	815.49	821.09	823.63	812.87	800.15	781.88	774.58	0.87	-1.16
Ezetimibe	482.86	439.23	422.83	411.14	402.27	400.70	390.03	386.46	410.38	441.26	487.67	0.10	4.01
Omega-3 fatty acids	237.89	282.92	311.55	320.67	309.58	276.16	256.37	245.67	236.51	237.44	241.83	0.16	-2.62
Niacin	210.98	221.82	243.05	241.01	205.69	180.94	159.89	135.73	128.18	128.16	126.45	-4.99	-6.92
Bile acid sequestrants	103.72	112.50	115.15	112.17	105.27	107.34	100.13	93.84	87.03	80.56	79.69	-2.60	-5.78
PCSK9 inhibitors	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.13	0.32	0.56	NA	104.47 ^a
Others	15.32	15.45	15.33	16.26	17.09	18.58	21.12	22.47	24.85	26.41	23.23	4.25	4.57

CAGR, compound annual growth rate; NA, not applicable.

^a CAGR calculated from 2016 to 2018.

increased use of lipid-modifying agents (Supplementary Table 4). During this time period, Belgium, Chile, Ecuador, France, Hungary, Luxembourg, the United States, and Venezuela all experienced decreased consumption of lipid-modifying agents.

When comparing 2008 to 2018, 17 countries (25%) had decreases in statin market share (Fig. 4), while statin market share increased in the remainder. Large increases in statin market share occurred in several countries from different regions, such as the Russian Federation, Venezuela, French West Africa, India, China, and the United States. In 2018, subregions with the highest proportion of statin use included Eastern, Northern, and Southern Europe, Western Africa, and Central Asia (Fig. 4B).

In 2018, there was a moderate positive correlation between lipid-modifying agent use and mean total cholesterol concentrations (Supplementary Fig. 1A and B). However, there was weaker evidence of a correlation for non-HDL cholesterol concentrations (Supplementary Fig. 1C and D). In contrast, lipid-modifying agent consumption was strongly correlated with GDP per capita (Supplementary Fig. 2). Distinct country-level patterns were observed when consumption of lipid-modifying agents and sex-specific total (Supplementary Fig. 3) and non-HDL cholesterol concentrations was compared in 2008 and 2018 (Supplementary Fig. 4). Many countries, such as Korea, Greece, and Puerto Rico, experienced large changes in consumption and small changes in total and non-HDL cholesterol. Others, such as French West Africa, China, and the Philippines, saw little change in the use of lipid-modifying agents, but had increases in cholesterol levels. In contrast, France and the United States experienced both reductions in use of lipid-modifying agents and total and non-HDL cholesterol concentrations.

4. Discussion

Our analysis shows a consistent increase in the use of lipid-modifying agents from 2008 to 2018 largely driven by the increased global consumption of statins. In the latter 5-year period, rapid uptake of LDL cholesterol lowering nonstatin treatments—PCSK9 inhibitors and ezetimibe—contrasts with declines in consumption of older nonstatin treatments (i.e., fibrates, nicotinic acid, and bile acid sequestrants). Distinct country-level patterns of changes in lipid-modifying agent use and lipid concentrations exist. Although statins have robust evidence of efficacy and safety from multiple randomized controlled trials and are a mainstay of lipid-lowering treatment, there was great diversity in statin market share between countries.

4.1. Comparison with previous studies

Few data are available on lipid-modifying agent use, and the market share of statins, in countries outside Northern America and Western Europe. The use of ezetimibe, fibrates, and niacin increased steadily in the United States and Canada from 2002 to 2009 [17–19]. In these studies, the overall use of nonstatins was higher in the United States than Canada and is reflected in our findings which saw an increased statin market share in the United States, but a relatively stable market share for statins in Canada. Increases in statin use and the use of generic statins occurred in the United States from 2002 to 2013 [20]. Previous reports from European countries describe consistent increases in consumption of lipid-modifying agents [21–24]. Statins were the predominant lipid-modifying agent although the market share of fibrates remained strong in France (~25%), Belgium (~25%) and Germany (~10%) in 2003 [21]. Sabo et al. reported lower use of statins in Serbia compared with Scandinavian countries [25]. Roth et al. reported cross-country comparisons of the proportion of the population treated with lipid-modifying agents and included data from three middle-income countries [26]. While in India growth in statin prescriptions and a large proportion of combination lipid-modifying agent product use was reported between 2006 and 2010 [27]. In East Asia, increased use of statins has been described in Hong Kong and Taiwan [28,29]. Taken

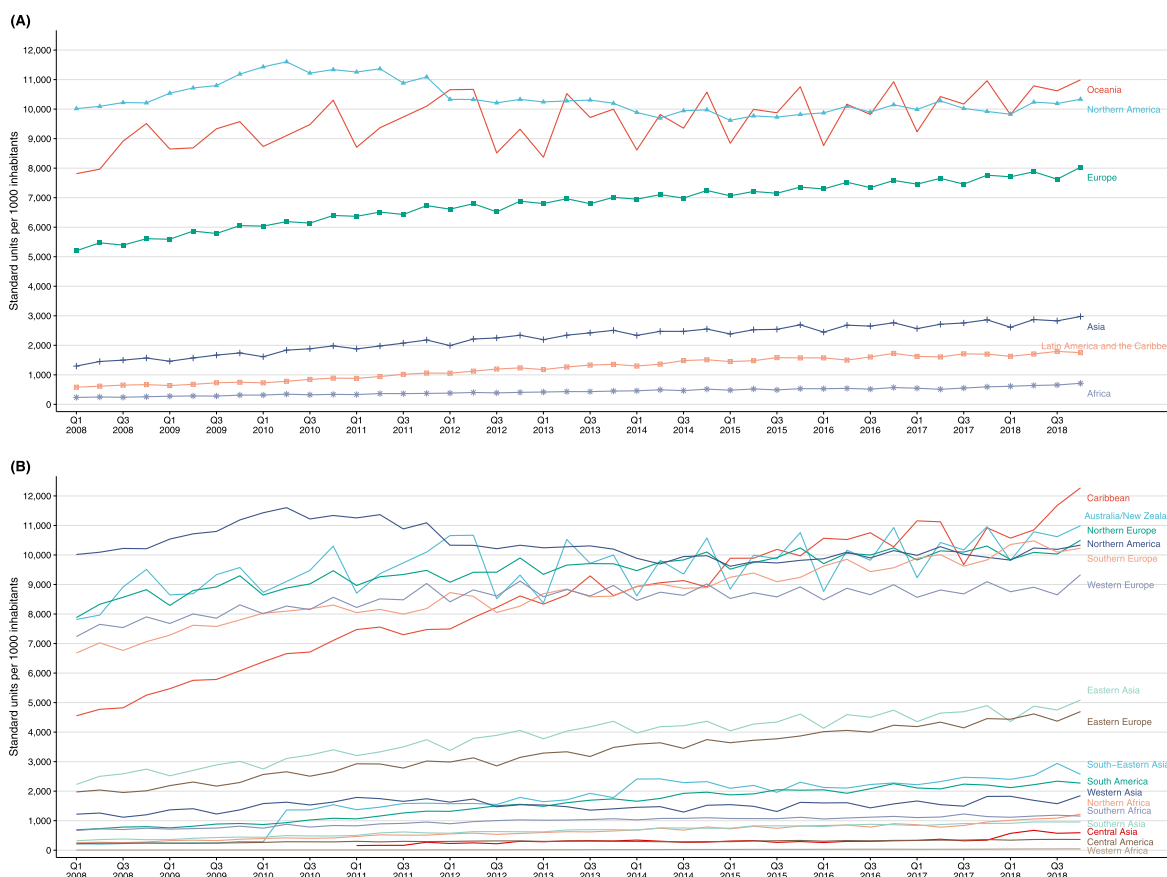


Fig. 2. Quarterly use of lipid-modifying agents by region from 2008 to 2018. Monthly sales data were aggregated on a quarterly basis. (A) Countries grouped according to UN geographical region. (B) Countries grouped according to UN geographical subregion (see [Supplementary Table 1](#)).

together, the global trends in increased use of lipid-modifying agents continued over the past decade, but appear to have weakened since 2013. In contrast to earlier reports from Northern America, recent trends point to an overall decreased use of fibrates and niacin.

4.2. Changes in consumption versus trends in cholesterol

The epidemiological transition of elevated blood cholesterol in several developing regions has now been quantified [6]. Rapid growth in the uptake of lipid-modifying agents has coincided with increases in cholesterol concentrations, particularly in countries located in East and Southern Asia, and Northern and Western Africa. However, lipid-modifying agent use in some countries has not kept pace with increases in total and non-HDL cholesterol. Statin use appears to be responsible for about one-third of reductions in total cholesterol in the United States and the United Kingdom [30,31]. For the countries in our analysis, it appears that country-level changes in non-HDL cholesterol over time do not necessarily coincide with a corresponding change in lipid-modifying agent consumption. Several countries had reductions in non-HDL cholesterol and had similar or reduced use of lipid-modifying agents from 2008 to 2018. The patterns observed in this study support the assertion that declines in non-HDL cholesterol are mostly due to lifestyle changes and not increased national use of lipid-modifying agents [31–34]. However, in several countries, the overall proportion of the population using lipid-modifying agents was likely too low to affect population-level cholesterol concentrations during the time period of this study. The stronger association between lipid-modifying agent consumption and GDP per capita reflects greater affordability and capacity to pay for chronic preventative drug use in higher income countries.

4.3. Cholesterol guidelines and trials

The timing of publication of key cholesterol guidelines and clinical trials aligns with the observed consumption trends for niacin, ezetimibe, and PCSK9 inhibitors. Evidence of the futility of adding niacin to statin therapy, led to the early stopping of the AIM-HIGH study (published December 2011) [35]. In our study, the use of niacin gradually increased and peaked in 2010–2011. Declining use of niacin further accelerated (2013–2018 CAGR -6.92%) after the global withdrawal of niacin-laropiprant in 2013 because it failed to reduce the incidence of major vascular events in the HPS2-THRIVE study [36]. The use of ezetimibe, in contrast, decreased up until 2015, because of the results of two clinical trials which suggested minimal evidence of benefit when ezetimibe was added to a statin: ENHANCE (published April 2008) [37] and SEAS (published September 2008) [38]. The resumption of increased use of ezetimibe since 2015 was likely influenced by the evidence of benefit of ezetimibe-simvastatin in the IMPROVE-IT study (published June 2015) [39], the introduction of generic ezetimibe (available in the United States in 2016) [40], and the recommendation to add ezetimibe to statins in high-risk individuals in the 2016 ESC/EAS cholesterol guideline [41]. Interestingly, ezetimibe’s U shaped trajectory means that consumption in 2018 was nearly unchanged from that in 2008. Use of PCSK9 inhibitors increased rapidly after their introduction in 2015, and their use was further supported by evidence of benefit from the FOURIER (published May 2017) [42] and the ODYSSEY OUTCOMES (published November 2018) trials [43]. Consumption of PCSK9 inhibitors will likely continue to increase beyond 2018, given the emphasis on lower LDL cholesterol goals, particularly in very high-risk patients in both the ACC/AHA 2018 [2] and European Society of Cardiology/European Atherosclerosis Society 2019 [1] cholesterol guidelines, and

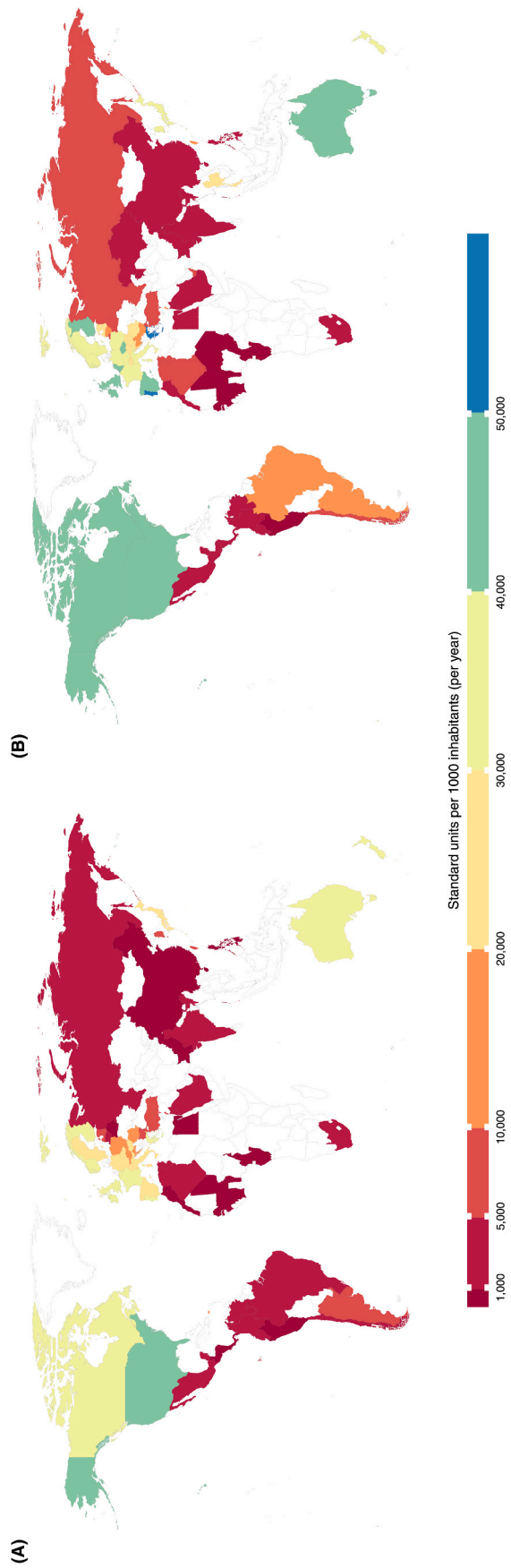


Fig. 3. Use of lipid-modifying agents by country in 2008 and 2018. (A) Consumption of lipid-modifying agents in 2008. (B) Consumption of lipid-modifying agents in 2018.

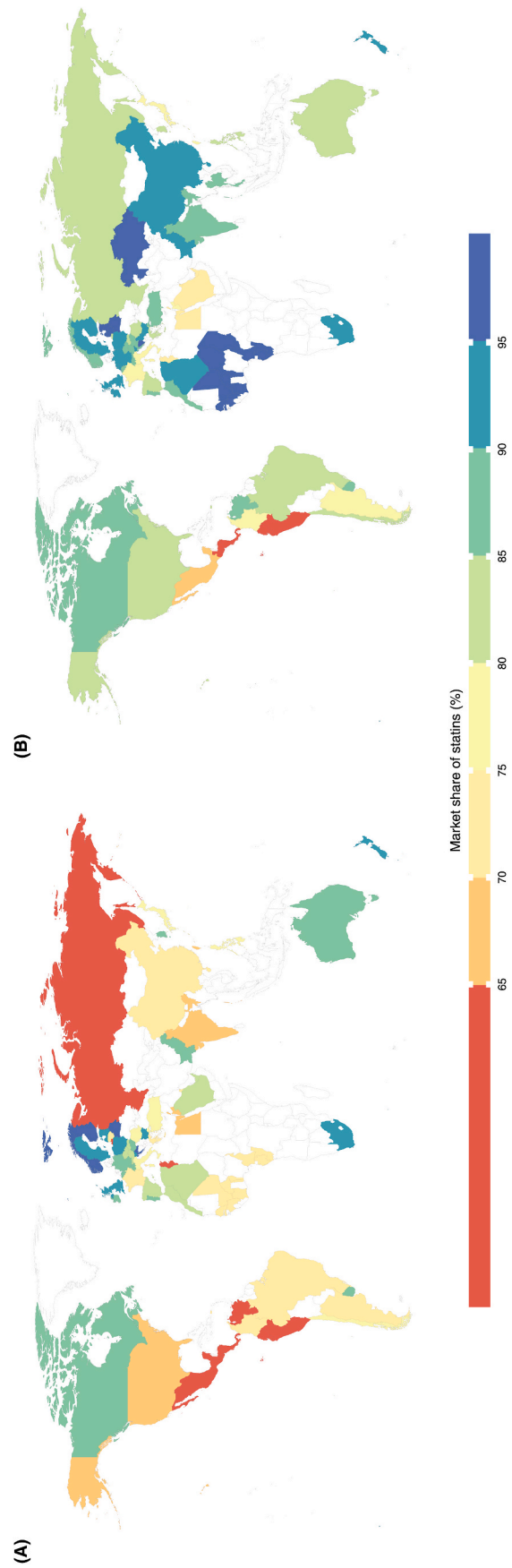


Fig. 4. Market share of statins by country in 2008 and 2018. (A) Market share of statins in 2008. (B) Market share of statins in 2018. Market share was calculated as the proportion of statin standard units to all lipid-modifying agent standard units.

potential further price reductions [44].

4.4. Strengths and limitations

We have identified diverse country-level trajectories by linking data on national lipid concentrations and lipid-modifying agent consumption. Another strength of our study is that it includes recent data from 83 countries, from different regions and with different income levels. To our knowledge, IQVIA MIDAS is the only platform which permits timely global and cross-country comparisons of medication consumption using locally collected data. Previous studies of lipid-modifying agents have tended to focus only on statin consumption, but we report consumption of all major classes of statin and nonstatin lipid-modifying agents. In particular, a current assessment of the recent trends in use of ezetimibe, PCSK9 inhibitors, and omega-3 fatty acids is needed since emerging evidence and clinical guidelines now suggest their use in select high-risk patients. Our study also has limitations. Comparisons between regions, subregions, and countries should be interpreted in the context of the available data and total market coverage of the included countries. Less than 100% market coverage underestimates the true consumption of lipid-modifying agents (e.g. Korea lacks hospital data). However, total pharmaceutical market coverage in most countries was greater than 80%. Lipid-modifying agents are taken on a chronic basis and are generally obtained from retail stores in countries that are not centered on the delivery of healthcare in hospitals; retail consumption data were available for all countries except for Taiwan and Thailand. Conclusions from our ecological study should not be interpreted as being applicable to individual inhabitants of each country. Furthermore, relationships between changes in lipid-modifying agent consumption and total and non-HDL cholesterol are not causal. However, distinct country-level patterns are useful for generating hypotheses for further research. We used aggregate data for each country and thus could not adjust for other factors that may influence lipid-modifying agent consumption such as population age structure, the proportion of the population with an indication for lipid-modifying treatment, access to healthcare services, affordability of medications, and dietary patterns. Commercial sales of lipid-modifying agents represent an estimate of the true level of drug consumption since they do not measure prescription volume nor patient adherence to therapy. Our choice of measuring physical units (i.e. standard units) also does not account for changes in lipid-modifying agent doses over time and might be better assessed using a measure such as the WHO defined daily dose.

4.5. Conclusion

Between 2008 and 2018, use of lipid-modifying agents increased globally and statins are the most used class of agent. However, three decades since the introduction of the first statin, their adoption in Africa, Asia, and Latin America and the Caribbean remains markedly lower than in Northern America and Europe.

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CRedit authorship contribution statement

Joseph E. Blais: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Yue Wei:** Formal analysis, Writing – review & editing. **Kevin K.W. Yap:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Hassan Alwafi:** Writing – review & editing. **Tian-Tian Ma:** Writing –

review & editing. **Ruth Brauer:** Writing – review & editing. **Wallis C.Y. Lau:** Writing – review & editing. **Kenneth K.C. Man:** Writing – review & editing. **Chung Wah Siu:** Writing – review & editing. **Kathryn C.B. Tan:** Writing – review & editing. **Ian C.K. Wong:** Resources, Supervision, Writing – review & editing, Funding acquisition. **Li Wei:** Resources, Writing – review & editing. **Esther W. Chan:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Man reports grants from C W Maplethorpe Fellowship, grants from National Institute of Health Research, UK, grants from European Commission H2020, personal fees from IQVIA, outside the submitted work. Prof Wong reports personal fees and non-financial support from IQVIA, outside the submitted work. Dr Chan reports honorarium from the Hospital Authority (Hong Kong), grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, and the Narcotics Division of the Security Bureau of the Hong Kong SAR, outside the submitted work. All other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2021.05.016>.

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