PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Patterns of statin utilization for new users and market dynamics in South Korea: A 13-year Retrospective Cohort Study
AUTHORS	Son, Kyung-Bok; Bae, SeungJin

VERSION 1 – REVIEW

REVIEWER	Maria Garcia-Gil IDIAP Jordi Gol (IDIAJGol). Spain
REVIEW RETURNED	24-Oct-2018

GENERAL COMMENTS	This paper aimed at analising the use of statins for new users and assessing statin market dynamics between 2002 and 2015 in Korea. The study found that the number of statins users increased over time, they were mainly prescribed with monotherapy and moderate intensity statins, and the market was dynamic within the study period. I have some major remarks as well as some several comments on aspects of the manuscript that I thought could be improved and I hope the authors find to be constructive. Comments Title I think the title does not reflect the objective of the study and does not include the type of epidemiological study performed, that, is, a retrospective cohort. From what I can gather from the reading the study is not exactly aimed at evaluating the amount of moderate-intensity statins used by Koreans but describing patterns of statin prescription over time and market dynamics. I'd suggest aligning title, objectives and conclusions. Abstract - Line 37-45, page 2: the main outcome seems a repetition of the study objectives instead of the study variable definitions. Besides, the association between medical history of patients and intensity of statins should be stated as an objective (main or secondary) in the first paragraph. - Line 50, page 2: main results shown as a incidence (95%Ci) would be better measure than absolute numbers. This comment also applies to the results section (line 17, page 12) - Line 20, page 3: I think these conclusions cannot be directly drawn from these results. Strengths and limitations - Line 27-43: these sections seem conclusions and not strengths

	and limitations. Some comments on the quality and completeness of the dataset could be of interest for the reader, instead. Methods - Lines 21-35, page 8: I would suggest leaving out the entire paragraph as it seems a repetition of the study objective. - Line 50, page 8: would the authors clarify if the study dataset (2% of the Korean population) is a subset of the National Health Insurance Cohort or a whole dataset? Would also the authors explain in more detail how the random selection of the individuals was performed? Are they representative of the Korean general population? - Line 4, page 9. What does insurance eligibility mean? Is the study population covered by the health public system? - Line 9, page 11: It would be useful explain here the date of drug entry into the market so as to better understand the results, as well as, the way in which this information and the drug prices were considered in the models. In line, drug entry dates into the market are mentioned at some point in the results section (line 12 and 17, page 15) but I found it difficult to know if they were previously defined or were a result from the models. - Line 21, page 11: I cannot see the added value of modelling an interrupted time series. What additional information not already seen in the descriptive analysis are these models showing? If so, please explain the interrupted time series in more detail. Results - Line 17, page 12: see previous comment on the abstract. - Line 25, page 12: please, provide mean age with standard deviation. - Line 25, page 12: variable related to income was not previously defined in the methods section. - Line 24, page 14: variable related to healthcare institutions was not previously defined in the methods section. - Line 49, page 15: people with history of ischemic heart disease were also less likely to be prescribed with statins over time. Discussion Overall, I would suggest contextualizing the discussion talking into account local guidelines, Korean general practitioners o specialists practices regarding cholesterol goal attainment (which, in turn, is related with the implementation of local guidelines on lipid lowering therapy), and individuals characteristics of the study such as cardiovascular risk factors or history of cardiovascular disease. In addition, some comparisons beyond the regional area would be of interest. Patterns of prescription found in this study are quite different from other studies (Ferrajolo C. Plos One, 2014, Svensson E Clinical Epidemiology 2015, Garcia-Gil M, Journal of Clinical Lipidology, 2016). - Lines 27-43, page 18: This section should be moved to results section and replaced by some discussion on these results provided the authors could explain the added value of these models (see my previous comment on this).

REVIEWER	Brian Godman Karolinska Institutet, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK
REVIEW RETURNED	13-Nov-2018

GENERAL COMMENTS	Thank you. I enjoyed reading the paper. It is encouraging to see that physicians in Korea especially those in primary care are now prescribing higher doses of statins in line with guidelines. I have only minor comments to make. These are: a) Introduction i) Page 6 Line 22. Other landmark studies include the 4S study (first study to show statins lower CV events in secondary prevention - Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. Lancet. 1994;344:1383-9) - and the Heart Protection Study (landmark study in patients with diabetes) - MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22 and Gurm HS, Hoogwerf B. The Heart Protection Study: high-risk patients benefit from statins, regardless of LDL-C level. Cleveland Clinic journal of medicine. 2003;70(11):991-7 ii) page 6 line 33 - need a reference for these guidelines iii) Page 6 Line 48 - we have also seen an appreciable increase in statin utilisation among for instance Western European countries in recent years, e.g. Godman B et al. Policies to enhance prescribing efficiency in Europe: findings and future implications. Frontiers in pharmacology. 2010;1:141; Leporowski A et al. Ongoing activities to optimize the quality and efficiency of lipid-lowering agents in the Scottish national health service: influence and implications. Expert review of pharmacoeconomics & outcomes research. 2018;18:655-66; Woerkom M et al. Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. Journal of comparative effectiveness research. 2012;1:527-38 and Fraeyman J et al. The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium. Expert review of pharmacoeconomics & outcomes research. 2013;13:141-51 iv) Page 6 line 53/ 54 - Similarly health authorities in Europe recommend 40mg simvastatin following the Heart Protection study as well as more recent studies with atorvastatin (some references in Leprowski et al - above - and Bennie M et al. Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. Expert review of pharmacoeconomics & outcomes research. 2012;12:125-30). What doses are recommended in the US (to set the scene for the study) - good to include these? v) Page 7 lines 21 - 27. The reference from Norway was primarily to do with restricting the prescribing of patented atrovastatin when generic simvastatin became available at a much lower cost (plus some switching). Other European countries that instigated prescribing restrictions for atorvastatin at this time included Austria (Godman B et al. Impact of recent reforms in Austria on utilization and expenditure of PPIs and lipid-lowering drugs: implications for the future. Expert review of pharmacoeconomics & outcomes research. 2009;9:475-84) and Finland (Martikainen JE et al. Impact of restricted reimbursement on the use of statins in Finland: a register-based study. Medical care. 2010;48:761-6) vi) No mention anywhere whether there is any co-payment associated with statins in Korea - if so what is this - as we know co-payments do influence subsequent usage - Simoens S, Sinnaeve PR. Patient co-payment and adherence to statins: a review and case studies. Cardiovascular drugs and therapy.

	2014;28(1):99-109. This is also important to give a rationale why statin use may vary by income level (not necessary in e.g. Scotland, UK, where there is no patient co-payment or in Italy with Class A medicines) vii) Was there any health insurance activities in Korea during the course of the study to encourage physicians to prescribe higher dose statins (apart from similar prices, etc. - seen in the Discussion)? This is important as typically guidelines on their own have a variable impact on physician behaviour - typically multiple initiatives are needed (as seen in Europe). Good to comment on this. b) Methodology i) Page 9 - Dosages - do not mention the doses of fluvastatin, lovastatin or pitavastin that are available. Similarly Page 10 - what is low, medium or high dose for all the stains (pitavastatin seems left out) ii) Bottom of page 10 - The Heart Protection Study (mentioned above) - a justification for also looking at diabetes iii) No mention in the Methodology of key dates of generic availability - as this is very important later on - especially with generic availability appearing to appreciably increase statin use as seen with generic atorvastatin in Korea - Ref 17. Similarly, how were patients divided by income level (as do research this), i.e. what criteria were used to divide patients into the 5 income levels (Table 1) and what was the reference for this division (if any)? c) Results i) Page 12 - Lines 39 - 44 - any rationale for this that can be expanded in the Discussion ii) Figure 2 - when showing total statin use among the 3 statins - may be worth highlighting key date points, e.g. when generic atorvastatin and generic rosuvastatin became available in Korea to help illustrate why such dramatic changes d) Discussion i) Page 17 lines 4 - 15 - any rationale for this? ii) Page 17 - lines 38 - 40 - good to also convert Korean won into US$ for an international audience iii) Page 17 - line 49 - why was the price reduction for rosuvastatin deferred and what impact did this make? iv) Page 18 - line 19 - 27 - we have seen this before with atorvastatin in Korea - so worth mentioning this reference as well to back up the findings. Generic availability and relaxing reimbursement restrictions also appreciably increased statin use among Central and Eastern European countries, e.g. Lithuania - Garuoliene K et al. Differences in utilization rates between commercial and administrative databases: implications for future health-economic and cross-national studies. Expert review of pharmacoeconomics & outcomes research. 2016;16(2):149-52

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Maria Garcia-Gil

Institution and Country: IDIAP Jordi Gol (IDIAJGol). Spain

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This paper aimed at analising the use of statins for new users and assessing statin market dynamics between 2002 and 2015 in Korea. The study found that the number of statins users increased over

time, they were mainly prescribed with monotherapy and moderate intensity statins, and the market was dynamic within the study period.
I have some major remarks as well as some several comments on aspects of the manuscript that I thought could be improved and I hope the authors find to be constructive.

Comments

Title

I think the title does not reflect the objective of the study and does not include the type of epidemiological study performed, that, is, a retrospective cohort. From what I can gather from the reading the study is not exactly aimed at evaluating the amount of moderate-intensity statins used by Koreans but describing patterns of statin prescription over time and market dynamics. I'd suggest aligning title, objectives and conclusions.

-> Thank you for your comments. We changed the title of the manuscript.

"Patterns of statin utilization for new users and market dynamics in South Korea: A 13-year Retrospective Cohort Study"

Abstract

- Line 37-45, page 2: the main outcome seems a repetition of the study objectives instead of the study variable definitions. Besides, the association between medical history of patients and intensity of statins should be stated as an objective (main or secondary) in the first paragraph.
- Line 50, page 2: main results shown as a incidence (95%Ci) would be better measure than

absolute numbers. This comment also applies to the results section (line 17, page 12)

- Line 20, page 3: I think these conclusions cannot be directly drawn from these results.

-> I revised the abstract.

Strengths and limitations

- Line 27-43: these sections seem conclusions and not strengths and limitations. Some comments on the quality and completeness of the dataset could be of interest for the reader, instead.

-> Revised.

Given the market size of statins and a number of "me-too" drugs and generic statins, statin utilization, including switching drugs, in health systems has been the subject of considerable interest.

The National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort, provides public health researchers useful information regarding utilization of health services.

This 13-year longitudinal study of a sample cohort presented that the incidence of new statin user increase from 838.1/100,000 persons in 2003 to 1626.9/100,000 persons in 2015.

Patterns of prescription and market dynamics of statins found in this study is quite different from other studies in different regions.

Interestingly, discounted price of originals with the introduction of generics immediately expand markets or substitute the market particularly in primary healthcare institutions in Korea.

Methods

- Lines 21-35, page 8: I would suggest leaving out the entire paragraph as it seems a repetition of the study objective.

-> Deleted.

- Line 50, page 8: would the authors clarify if the study dataset (2% of the Korean population) is a subset of the National Health Insurance Cohort or a whole dataset?

Would also the authors explain in more detail how the random selection of the individuals was performed? Are they representative of the Korean general population?

-> Clarified and added.

This study used the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort established by the National Health Insurance Service [32]. The dataset is comprised of approximately 1 million individuals (approximately 2% of the population) selected randomly from South Koreans. The NHIS first built a target population of 46,605,433 individuals in 2002, and then 1,025,340 participants was randomly selected from the target population. Specifically, systematic stratified random sampling with proportional allocation within each stratum was conducted to construct the cohort
32.

- Line 4, page 9. What does insurance eligibility mean? Is the study population covered by the health public system?

-> Clarified.

The cohort dataset consists of four databases on participants' insurance eligibility, medical treatments, health care institutions, and general health examinations for the period from January 1, 2002, to December 31, 2015 [32]. The dataset provides information on demographic and socioeconomic characteristics, such as age, gender, and level of income. Income level was calculated based on the insurance premium that participant pays. Also, patients' disease diagnosis was coded based on the International Classification of Diseases-10th Revision (ICD-10), and the corresponding medical expenditure such as medical and prescription information are available. The prescription information covers the date and duration of the prescription, the prescribed drugs' international nonproprietary names (INN), dosage, the route of administration, prescribers' specialty and the types of the healthcare institution.

- Line 9, page 11: It would be useful explain here the date of drug entry into the market so as to better understand the results, as well as, the way in which this information and the drug prices were considered in the models. In line, drug entry dates into the market are

mentioned at some point in the results section (line 12 and 17, page 15) but I found it difficult to know if they were previously defined or were a result from the models.

-> Added in the Appendix.

- Line 21, page 11: I cannot see the added value of modelling an interrupted time series. What additional information not already seen in the descriptive analysis are these models showing? If so, please explain the interrupted time series in more detail.

-> Explained in detail.

Results

- Line 17, page 12: see previous comment on the abstract.

-> Modified.

- Line 25, page 12: please, provide mean age with standard deviation.

-> Added.

- Line 25, page 12: variable related to income was not previously defined in the methods section. -> Added in the section of method.

The cohort dataset consists of four databases on participants' insurance eligibility, medical treatments, health care institutions, and general health examinations for the period from January 1, 2002, to December 31, 2015 32. The dataset provides information on demographic and socioeconomic characteristics, such as age, gender, and level of income. Income level was calculated based on the insurance premium that participant pays. Also, patients' disease diagnosis was coded based on the International Classification of Diseases-10th Revision (ICD-10), and the corresponding medical expenditure such as medical and prescription information are available. The prescription information covers the date and duration of the prescription, the prescribed drugs' international nonproprietary names (INN), dosage, the route of administration, prescribers' specialty and the types of the healthcare institution.

- Line 24, page 14: variable related to healthcare institutions was not previously defined in the methods section.

-> Added in the section of method.

Lastly, this study has interest in health care institutions that prescribe statins. We sorted medical institutions by primary-, secondary-, and tertiary care institution. Primary care institutions include clinic-level medical institutions that provide medical services to outpatients. Secondary care institutions include hospital-level medical institutions that provide health services primarily to inpatients. Tertiary care institutions include superior general hospitals, designated by the Minister of Health and Welfare, that provide medical service requiring high level of expertise for treating serious disease.

- Line 49, page 15: people with history of ischemic heart disease were also less likely to be prescribed with statins over time.

-> Thank you for pointing this out.

Discussion

Overall, I would suggest contextualizing the discussion talking into account local guidelines, Korean general practitioners o specialists practices regarding cholesterol goal attainment (which, in turn, is related with the implementation of local guidelines on lipid lowering therapy), and individuals characteristics of the study such as cardiovascular risk factors or history of cardiovascular disease.

-> Added.

Korean guidelines for the management of dyslipidemia states that the first goal is LDL cholesterol. Statin is the first-choice drug for the treatment of hypercholesterolemia (class of recommendation I, level of evidence A) because it has a relatively low risk profile and proven effects of decreasing CVD by lowering LDL cholesterol. “Statins should be prescribed” and the dose adjusted to reach the LDL cholesterol target level for high-risk and very high-risk groups (I, A), whereas “statin use should be considered” if LDL cholesterol is not reduced to the first target even after lifestyle modification for weeks or months (IIa, B). The guidelines also provide dosage and administration of statins: lovastatin 20-80 mg/day, pravastatin 10-40 mg/day, simvastatin 20-40 mg/day, fluvastatin 20-80 mg/day, atorvastatin 10-80 mg/day, rosuvastatin 5-20mg/day, and pitavastatin 1-4 mg/day. Interestingly, atorvastatin and rosuvastatin, the top-2 best-selling statins in Korea, was recommended as moderate- and high-intensity dosage.

In addition, some comparisons beyond the regional area would be of interest. Patterns of prescription found in this study are quite different from other studies (Ferrajolo C. Plos One, 2014, Svensson E Clinical Epidemiology 2015, Garcia-Gil M, Journal of Clinical Lipidology, 2016).

-> Thank you for your critical comments.

I included the studies you mentioned. I think these comparisons make the manuscript more interesting.

- Lines 27-43, page 18: This section should be moved to results section and replaced by some discussion on these results provided the authors could explain the added value of these models (see my previous comment on this).

-> Moved.

Reviewer: 2

Reviewer Name: Brian Godman

Institution and Country: Karolinska Institutet, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you. I enjoyed reading the paper. It is encouraging to see that physicians in Korea especially those in primary care are now prescribing higher doses of statins in line with guidelines.

I have only minor comments to make.

These are: a) Introduction

i) Page 6 Line 22. Other landmark studies include the 4S study (first study to show statins lower CV events in secondary prevention - Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. Lancet. 1994;344:1383-9) -

and the Heart Protection Study (landmark study in patients with diabetes) - MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22 and Gurm HS, Hoogwerf B. The Heart Protection Study: high-risk patients benefit from statins, regardless of LDL-C level. Cleveland Clinic journal of medicine. 2003;70(11):991-7

-> Added.

ii) page 6 line 33 - need a reference for these guidelines

-> Added.

iii) Page 6 Line 48 - we have also seen an appreciable increase in statin utilisation among for instance Western European countries in recent years, e.g. Godman B et al. Policies to enhance prescribing efficiency in Europe: findings and future implications. Frontiers in pharmacology. 2010;1:141; Leporowski A et al. Ongoing activities to optimize the quality and efficiency of lipid-lowering agents in the Scottish national health service: influence and implications. Expert review of pharmacoeconomics & outcomes research. 2018;18:655-66; Woerkom M et al. Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. Journal of comparative effectiveness research. 2012;1:527-38 and Fraeyman J et al. The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium. Expert review of pharmacoeconomics & outcomes research. 2013;13:141-51 -> Added. Thank you for your interesting information.

iv) Page 6 line 53/ 54 - Similarly health authorities in Europe recommend 40mg simvastatin following the Heart Protection study as well as more recent studies with atorvastatin (some references in Leprowski et al - above - and Bennie M et al. Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. Expert review of pharmacoeconomics & outcomes research. 2012;12:125-30).

-> Added. Thank you for your interesting information.

What doses are recommended in the US (to set the scene for the study) - good to include these?

I replaced this reference with the reference you mentioned.

v) Page 7 lines 21 - 27. The reference from Norway was primarily to do with restricting the prescribing of patented atrovastatin when generic simvastatin became available at a much lower cost (plus some switching). Other European countries that instigated prescribing restrictions for atorvastatin at this time included Austria (Godman B et al. Impact of recent reforms in Austria on utilization and expenditure of PPIs and lipid-lowering drugs: implications for the future. Expert review of pharmacoeconomics & outcomes research. 2009;9:475-84) and Finland (Martikainen JE et al. Impact of restricted reimbursement on the use of statins in Finland: a register-based study. Medical care. 2010;48:761-6)

-> Added.

vi) No mention anywhere whether there is any co-payment associated with statins in Korea - if so what is this - as we know co-payments do influence subsequent usage - Simoens S, Sinnaeve PR. Patient co-payment and adherence to statins: a review and case studies. Cardiovascular drugs and therapy. 2014;28(1):99-109. This is also important to give a rationale why statin use may vary by income level (not necessary in e.g. Scotland, UK, where there is no patient co-payment or in Italy with Class A medicines) -> Thank you for your critical comments. Added.

In Korea, co-payment for medicines that prescribed for outpatients are 30% of total expenditure, including pharmacy preparation charge, thus financial burden is less likely to influence the statin adherence, unlike previous study 34.

vii) Was there any health insurance activities in Korea during the course of the study to encourage physicians to prescribe higher dose statins (apart from similar prices, etc. - seen in the Discussion)? This is important as typically guidelines on their own have a variable impact on physician behaviour - typically multiple initiatives are needed (as seen in Europe). Good to comment on this.

-> Thank you for your comments. I added local guideline of

statins. b) Methodology

i) Page 9 - Dosages - do not mention the doses of fluvastatin, lovastatin or pitavastin that are available. Similarly Page 10 - what is low, medium or high dose for all the stains (pitavastatin seems left out)

-> Added. Thank you for kind comments.

ii) Bottom of page 10 - The Heart Protection Study (mentioned above) - a justification for also looking at diabetes -> Added.

iii) No mention in the Methodology of key dates of generic availability - as this is very important later on - especially with generic availability appearing to appreciably increase statin use as seen with generic atorvastatin in Korea - Ref 17.

-> Added in the Appendix.

Similarly, how were patients divided by income level (as do research this), i.e. what criteria were used to divide patients into the 5 income levels (Table 1) and what was the reference for this division (if any)?

-> Added in the section of method.

The cohort dataset consists of four databases on participants' insurance eligibility, medical treatments, health care institutions, and general health examinations for the period from January 1, 2002, to December 31, 2015 32. The dataset provides information on demographic and socioeconomic characteristics, such as age, gender, and level of income. Income level was calculated based on the insurance premium that participant pays. Also, patients' disease diagnosis was coded based on the International Classification of Diseases-10th Revision (ICD-10), and the corresponding medical

expenditure such as medical and prescription information are available. The prescription information covers the date and duration of the prescription, the prescribed drugs' international nonproprietary names (INN), dosage, the route of administration, prescribers' specialty and the types of the healthcare institution. c) Results

i) Page 12 - Lines 39 - 44 - any rationale for this that can be expanded in the Discussion

-> Deleted.

ii) Figure 2 - when showing total statin use among the 3 statins - may be worth highlighting key date points, e.g. when generic atorvastatin and generic rosuvastatin became available in Korea to help illustrate why such dramatic changes

-> Thank you for your kind comments. Added.

d) Discussion

i) Page 17 lines 4 - 15 - any rationale for this?

-> Revised.

ii) Page 17 - lines 38 - 40 - good to also convert Korean won into US$ for an international audience

-> Added.

iii) Page 17 - line 49 - why was the price reduction for rosuvastatin deferred and what impact did this make?

-> Added.

However, the price reduction of original rosuvastatin was deferred until 2014 for the reason of valid patent that original rosuvastatin has until 2014, even though the follow on drugs were available in 2008.

iv) Page 18 - line 19 - 27 - we have seen this before with atorvastatin in Korea - so worth mentioning this reference as well to back up the findings. Generic availability and relaxing reimbursement restrictions also appreciably increased statin use among Central and Eastern European countries, e.g. Lithuania - Garuoliene K et al. Differences in utilization rates between commercial and administrative databases: implications for future health-economic and cross-national studies. Expert review of pharmacoeconomics & outcomes research. 2016;16(2):149-52

-> Added. Thank you for interesting information.

VERSION 2 – REVIEW

REVIEWER	Maria Garcia-Gil Institut Universitari d'Investigació en Atenció Primària Jordi Gol. IDIAPJGol
REVIEW RETURNED	31-Dec-2018

GENERAL COMMENTS	Thank you for your effort in addressing all the suggestions and questions I had. I think the message of the manuscript is clearer and more contextualised now.

REVIEWER	Brian Godman Karolinska Institutet, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK
REVIEW RETURNED	31-Dec-2018

GENERAL COMMENTS	Thank you for revising this paper building on my previous comments. My points are now only minor (apart from asking for help from the editor to help improve the English on some occasions): a) Page 9 Lines 34 to 41 - difficult to follow the dosing for moderate intensity statins as currently written b) I would like to see more discussion on why the dosing for statins increased in Korea as we have not seen this in some other countries unless for instance there has been health authority recommendations following for instance the Heart Protection Study (ref 14) and others as seen in e.g. Scotland - Ref 20. This would provide guidance to other health authorities across countries looking to enhance appropriate dosing of medicines prescribed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Maria Garcia-Gil

Institution and Country: Institut Universitari d'Investigació en Atenció Primària Jordi Gol. IDIAPJGol

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you for your effort in addressing all the suggestions and questions I had. I think the message of the manuscript is clearer and more contextualised now.

Reviewer: 2

Reviewer Name: Brian Godman

Institution and Country: Karolinska Institutet, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you for revising this paper building on my previous comments. My points are now only minor (apart from asking for help from the editor to help improve the English on some occasions):

a) Page 9 Lines 34 to 41 - difficult to follow the dosing for moderate intensity statins as currently written

Revised.

"High-intensity statins include atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day and simvastatin 80 mg/day. Low-intensity statins include simvastatin 10 mg/day, pravastatin 10–20 mg/day, lovastatin 20 mg/day, pitavastatin 1mg/day and fluvastatin 20–40 mg/day. Lastly, moderate-intensity statins include atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/ day, pravastatin 40–80 mg/day, lovastatin 40 mg/day, pitavastatin 2–4 mg/day and fluvastatin 80 mg/day."

b) I would like to see more discussion on why the dosing for statins increased in Korea as we have not seen this in some other countries unless for instance there has been health authority recommendations following for instance the Heart Protection Study (ref 14) and others as seen in e.g. Scotland - Ref 20. This would provide guidance to other health authorities across countries looking to enhance appropriate dosing of medicines prescribed.

Thank you for your kind comments. I think we need further studies to explain increased dosing of statins. Therefore, I added the following sentence to the manuscript (Limitations of the study).

"Lastly, we noted the dosing for statins increased in Korea, and partially explained this trends with the Korean guidelines for the management of dyslipidemia and the pricing and marketing strategies of manufacturers. However, further qualitative methods are needed to understand these interesting observations."