PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Consumption and market share of cholesterol-lowering drugs in high-risk patients before and after the release of the 2013 ACC/AHA cholesterol guidelines—A retrospective observational study
AUTHORS	Kuo, Tzu-Tsen; Huang, Yaw-Bin; Hsieh, Ching-Jung

VERSION 1 – REVIEW

REVIEWER	Stanley S. Levinson VAMC and University of Louisville 800 Zorn Avenue Louisville, KY 4020
REVIEW RETURNED	30-Jan-2020

GENERAL COMMENTS	Use of cholesterol lowering drugs BMJ 2020. This is an interesting paper. But 1. I am not sure of its usefulness, 2. In a few places, the paper seems to state that the 2013 guidelines “resulted in” these changes. Implying the guidelines caused these changes. which cannot be proven and 3. The information can be given in ¼ the space with the need for only 2 Tables and no Figures, possibly as a letter to the Editors. It is unclear what units are inside the parenthesis in Table 2. These data are for only one Center. Perhaps the doctors were guided by advice from the Center rather than the guidelines. Moreover, there seems to have been absolute increases in fibrates and ezetimibe that were not recommended by the guidelines, although the market share does seem to have fallen. I suggest simplifying this paper, reducing its length by about ¾ with 2 Tables to provide the important descriptive information and simply describe what happened in 2012 and 2015 and simply stating to what degree the 2013 guidelines affected these changes is unclear.

REVIEWER	Ariela Orkaby MD MPH New England GRECC, VA Boston Healthcare System Harvard Medical School
REVIEW RETURNED	10-Feb-2020

GENERAL COMMENTS	Kuo and colleagues present data from the Kaohsiung Chang Gung Memorial Hospital in Taiwan to examine the impact of cholesterol-lowering drug prescribing following the 2013 ACC/AHA cholesterol guidelines vs the years prior. Results indicate an absolute 1.77% increase in statin prescription, primarily driven by an increase in use of atorvastatin, rosuvastatin and Pitavastatin, with simvastatin and Fluvastatin decreasing. There was also a 2.41% absolute reduction in fibrates, and 0.42% reduction in cholesterol absorption inhibitors. The paper is generally well written. I have several suggestions for the authors to consider. Major comments:

	Abstract: - More detail on the cohort is needed in the results - Clarity on how many patients were in each of the risk group is needed (also in the manuscript, as noted below) - Avoid introducing new data in the conclusion Introduction: - Consider shortening and focusing the introduction. The aims can be clarified as well, is the goal to examine changes in cholesterol-lowering drug use among specific high-risk groups, or overall? - At various points in the paper different groups are referred to (e.g. prior ASCVD, FH, DM2, LDL >190, prior stroke, PAD), please clarify which groups will be examined at the outset Methods: - Why was lovastatin not included? - It would be informative to show data according to the indication of use – for example, one would hope that rates of cholesterol-lowering medications, particularly statins, would have increased for those with prior ASCVD. - The statistical approach appears very simplistic. Were any adjustments made to account for secular trends, such as the aging of the population? At the very least, age-standardized rates to compare utilization between years would be useful for comparisons. - Results: - To guide the reader, please add details on the demographics of the population at least as a table. This could be done for all 4 high risk groups (which as noted above, should be clearly identified). - If the goal is to examine cholesterol-lowering drug use generally over time, this should be clearly specified. If, however, the goal is to look at use within specific populations, additional information should be shown clarifying rates and change within each population. - Related: the text seems to refer to Fig 1 according to 4 high risk groups, but this is not - What is the clinical meaning of a 1% increase in statin use? This data would be particularly useful if shown according to primary vs secondary prevention Discussion: - The Discussion refers to data not shown, particularly within risk groups. Showing this data in the results will make it easier to follow Minor comments: Introduction: - The statement “Those are considered the origins of atherosclerosis” seems out of place. Discussion: - Consider focusing the discussion on the importance of the findings, namely the changes in prescribing patterns and the impact that this might have on clinical outcomes

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name:
Stanley S. Levinson

Institution and Country:
VAMC and University of Louisville

800 Zorn Avenue
Louisville, KY 40206

1. Please state any competing interests or state ‘None declared’:
Reply: We have stated Declarations of interest: None

2. I am not sure of its usefulness
Reply: Thank you for your comment. The results of this drug-use analysis show an increased use of fixed-dose, high-intensity, and moderate-intensity monotherapy and combined therapy statins in high-risk groups, which matches the 2013ACC/AHA guidelines’ suggestion to use high-intensity or moderate-intensity statins in high-risk groups. One of the impacts of this was that according to the results of clinical effectiveness and side effects in patients with diabetes, statins were found to be effective and were associated with fewer side effects. Also, since the database used is for a hospital in Taiwan, compared with studies in other countries, the data accessed and the patients are actually from Taiwan. Therefore, the conclusions might be reflective of what the situation really is in Taiwan, and make contributions to Taiwan’s Medical treatment.

3. In a few places, the paper seems to state that the 2013 guidelines “resulted in” these changes., implying the guidelines caused these changes, which cannot be proven
Reply: Thank you for pointing this out. We have accordingly revised it to imply that these changes were observed after release of the guidelines.

4. The information can be given in ¼ the space with the need for only 2 Tables and no Figures, possibly as a letter to the Editors.
Reply: Thank you for your comment. We do not believe that the data here can be condensed as suggested and we believe that this detailed explanation is required,

5. It is unclear what units are in the parenthesis in Table 2.
Reply: The unit in Table 2 corresponds to tablets/month (%).

6. These data are for only one Center.
Reply: Yes. As accurately noted, our data are from one Center. This is a limitation of our study.

7. Perhaps the doctors were guided by advice from the Center rather than the guidelines.
Reply: The 2013 ACA/AHA cholesterol guidelines were followed, and not advice from the Center.

8. Moreover, there seems to have been absolute increases in fibrates and ezetimibe that were not recommended by the guidelines, although the market share does seem to have fallen.
Reply: The guideline suggested that high- or very-high-risk patients need to reduce their LDL levels to 50%. Only atorvastatin at a dose of 40 mg or more, rosuvastatin at a dose of 20 mg or more, and vytorin (ezetimib 10 mg and simvastatin 20 mg) tablets could help achieve these treatment goals. Patients using statins faced some challenges and considered discontinuing statin therapy, primarily to overcome its side effects and high costs. Symptoms included muscle pain, discomfort, and elevated creatine kinase levels up to 5 times the normal level. In fact, patients probably reduced or even stopped the treatment at that time, which is a major concern. If they continued to use it, side effects

became a serious problem. Patients reducing or stopping therapy due to the severity of side effects is concerning. Another concern is the new onset of diabetes, following successful completion of treatment. Using statin is beneficial for patients for long-term outcome, and since its benefits outweigh its adverse effects, the use of statins remains necessary. This was the reason for the absolute increases in fibrates and ezetimibe that were not recommended by the guidelines, although the market shares had fallen.

9. I suggest simplifying this paper, reducing its length by about ¾ with 2 Tables to provide the important descriptive information and simply describe what happened in 2012 and 2015 and simply stating to what degree the 2013 guidelines affected these changes is unclear.
Reply: Thank you for your comment. We have shortened the article as much as we could, without compromising the quality of the manuscript and data. Any further reduction would possibly reduce the impact of the study.

We observed an increase in the use of different types of cholesterol-lowering drugs, of which, the use of HMG CoA reductase inhibitors was the highest. In terms of specific forms of cholesterol-lowering drugs, the use of Rosuvastatin increased the most. The use of rosuvastatin 10 mg was three-fold greater than that of rosuvastatin 5 mg. The use of atorvastatin 10 mg increased by nearly twice that of atorvastatin 40 mg. Specifically, the average monthly consumption of fluvastatin and simvastatin were significantly lower in 2015 than in 2012. In terms of combined therapy for cholesterol-lowering drugs, the use of Vytorin was the highest among all FDCs in 2015. After adjusting the demographics (age and sex) and types of drugs, comparing 2015 with 2012, each prescribed dosage increased by 0.5 tablet per year.
In other words, in 2012, each average prescribed dosage consisted of 23.7 tablets; in 2015, each prescribed dosage increased by 0.5 tablet to 24.2 tablets (P<0.001).
After adjusting for cholesterol-lowering drug therapies (monotherapy vs combined therapy), age, and sex, in 2015, each prescribed dosage increased by 0.5 tablets on an average, whereas in 2012, each average prescribed dosage was 25.3 tablets of the adjusted drug. Thus, in 2015, each average prescribed dosage was 25.8 tablets, (P<0.001).
Conclusion: Adjusting for the drug type, or adjusting between monotherapy and combined therapy resulted in the same margin of increase in the average prescribed dosage, which was 0.5 tablets.

Response to Reviewer's Comments

Reviewer: 2
Reviewer Name
Ariela Orkaby MD MPH

Institution and Country
New England GRECC, VA Boston Healthcare System
Harvard Medical School

1. Please state any competing interests or state "None declared."
Reply: We have accordingly revised this section to "None declared."

Major comments:
Abstract:

1. More detail on the cohort is needed in the results.
Reply: Thank you for your suggestion. The cohort included in this study comprised entirely of high-risk patients. Additional details can be found in the Methods section.

2. Clarity on how many patients were in each of the risk group is needed (also in the manuscript, as noted below)
Reply: The cohort of this study consisted entirely of high-risk patients.
The number of patients under ambulatory care increased from 36,367 in 2012 to 41,807 in 2015.

3. Avoid introducing new data in the conclusion
Reply: Thank you for your suggestion. We have deleted the sentences describing results that were not pertinent to this study

Introduction:
1. Consider shortening and focusing the introduction. The aims can be clarified as well, is the goal to examine changes in cholesterol-lowering drug use among specific high-risk groups, or overall?
Reply: Thank you for your suggestion and question. The aim of this study was to investigate changes in the usage of cholesterol-lowering drug among all high-risk patients. As advised, the introduction section has been revised, and we hope it is now to your satisfaction.

2. At various points in the paper different groups are referred to (e.g. prior ASCVD, FH, DM2, LDL >190, prior stroke, PAD), please clarify which groups will be examined at the outset.
Reply: The Introduction contains definitions of our high-risk criteria/groups. All high-risk patients were investigated as a cohort in this study.

Methods:
1. Why was lovastatin not included?
Reply: Lovastatin was excluded since it is a fixed-dose combination drug. Thus, we analyzed it as a combination: Linicor (lovastatin 20 mg + niacin ER 500 mg)/tablet.

2. It would be informative to show data according to the indication of use – for example, one would hope that rates of cholesterol-lowering medications, particularly statins, would have increased for those with prior ASCVD. The statistical approach appears very simplistic. Were any adjustments made to account for secular trends, such as the aging of the population? At the very least, age-standardized rates to compare utilization between years would be useful for comparisons.
Reply: Thank you for your comment and question.
Results: Statistical methods of analyses were used to evaluate differences between groups.
Comparisons of adjusted populations (age and sex) and drug types between 2012 and 2015 showed that each prescribed dosage increased by 0.5 tablets in 2015.
That is, the average number of tablets per prescription in 2012 was 23.7, whereas in 2015, it increased by 0.5 tablets to 24.2 ($P<0.001$).
After adjustments for single-combination cholesterol-lowering drugs, age, and sex, each prescribed dosage increased by an average of 0.5 tablets in 2015. The average number of tablets per prescription in 2012 was 25.3 and in 2015 was 25.8 ($P<0.001$).
The increase remained the same (0.5 tablets increase) irrespective of adjustments for drug types or single-/fixed-dose combinations.

1. To guide the reader, please add details on the demographics of the population at least as a table. This could be done for all 4 high risk groups (which as noted above, should be clearly identified).

Reply:
These demographics are indicated in Table 2.
1. Age:
In 2012, the number of patients was 36,367 and their mean age was 69.2 years. In 2015, the number of patients was 41,807 and their mean age was 67.2 years.
Comparison between the overall data in 2012 and 2015 showed a P value of <0.001, indicating that the difference between 2012 and 2015 was statistically significant.
2. Sex:
In 2012, there were 16,824 (46.3%) females and 19,543 (53.7%) males, whereas in 2015, there were 19,032 (45.5%) females and 22,775 (54.5%) males.
Comparison between the overall data in 2012 and 2015 showed a P value of <0.05, indicating that the difference between 2012 and 2015 was statistically significant.

2. If the goal is to examine cholesterol-lowering drug use generally over time, this should be clearly specified. If, however, the goal is to look at use within specific populations, additional information should be shown clarifying rates and change within each population.
Reply: The cohort of this study comprises high-risk patients only. There was no subgroup. The major aim was to improve clinical outcomes of these high risk patients.
Secondary goal of the study was to decrease cardiovascular disease risk of these high risk patients.

3. What is the clinical meaning of a 1% increase in statin use? This data would be particularly useful if shown according to primary vs secondary prevention.
Reply: Clinical meaning of a 1% increase in statin use is that the use of statins, especially cholesterol-lowering drugs, in high-risk patient populations increased by 1% in 2015 compared with that in 2012.

Discussion:
1. The Discussion refers to data not shown, particularly within risk groups. Showing this data in the results will make it easier to follow
Reply: As there was no subgroup (four groups of high-risk patients) in this study, no data were obtained. We have repositioned new data from the discussion.

2. Minor comments:
Introduction:
1. The statement “Those are considered the origins of atherosclerosis” seems out of place.
Reply:
Thank you for your suggestion. High-risk groups include patients with atherosclerotic cardiovascular disease (ASCVD), which is defined as an acute coronary syndrome or a history of myocardial infarction (MI), stable angina, coronary or other arterial revascularization, stroke, transient ischemic stroke, or peripheral arterial disease (PAD), presumed to be of atherosclerotic origin. We have revised the corresponding text in the manuscript to accurately convey this.

Discussion:

1. Consider focusing the discussion on the importance of the findings, namely the changes in prescribing patterns and the impact that this might have on clinical outcomes

Reply: As recommended, we have discussed the importance of these findings in the discussion and conclusion sections of the manuscript.
Effectiveness and side effects before and after treatment with statins for 1 and 2 years in patients with diabetes
In terms of effectiveness, high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride values in the 2,398 patients treated with statins for a year showed statistically significant improvements (all $p < 0.001$). Probability of de novo diabetes among some of the 2,398 patients treated was also significant ($p < 0.001$), but the probability of myalgia, myositis, rhabdomyolysis, peripheral neuropathy, headache, and dyspepsia was not statistically significant. There was no incidence of either myopathy or cognitive impairment.

Significant improvements in high- and low-density lipoprotein, total cholesterol, and triglyceride levels were observed in the 1,633 patients treated with statin for two years (all $p < 0.001$). These patients also showed statistically significant probability of myalgia ($p = 0.004$), myositis ($p = 0.004$), and de-novo diabetes ($p < 0.001$), whereas the probability of rhabdomyolysis ($p = 1.000$), peripheral neuropathy ($p = 1.000$), headache ($p = 0.581$) and dyspepsia ($p = 0.500$) was not statistically significant. The incidence of myopathy and cognitive impairment was 0.
Regarding effectiveness, the probability of high-density lipoprotein ($p = 0.016$), low-density lipoprotein ($p < 0.001$), and total cholesterol ($p = 0.027$) levels in the 1,633 patients treated continuously with statin for a year was statistically significant. The change in triglyceride levels in the 1,633 patients treated continuously with statin for a year was not statistically significant ($p = 0.576$).

Regarding side effects, the resultant changes in myalgia and myositis were statistically significant (each $p = 0.008$). The resultant probability of rhabdomyolysis, peripheral neuropathy, headache, and dyspepsia ($p = 1.000$) as well as de novo diabetes ($p = 0.058$) was not statistically significant. There was no incidence of either myopathy or cognitive impairment.

VERSION 2 – REVIEW

REVIEWER	Ariela Orkaby, MD MPH New England GRECC, VA Boston Healthcare System Harvard Medical School
REVIEW RETURNED	26-May-2020

GENERAL COMMENTS	Please trim and focus the Introduction further. Please do not delete the information on data sources in the methods. A 1% increase in statin use is not necessarily clinically meaningful. Consider explaining what this might mean as far as prevented events.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2
Ariela Orkaby, MD MPH
New England GRECC, VA Boston Healthcare System
Harvard Medical School

1. Please state any competing interests or state ‘None declared’: None
Reply: We thank you for the comment. We have provided the necessary information in the manuscript accordingly.
“COMPETING INTEREST: None”

2. Please trim and focus the Introduction further.
Reply: We thank you for your suggestion. We have condensed the Introduction accordingly.

3. Please do not delete the information on data sources in the methods.
Reply: Assuming that you want us to provide information on Data source, we have provided the following information in the manuscript.
“In this retrospective observational study, data were obtained from the electronic database of Kaohsiung Chang Gung Memorial Hospital for 2012 and 2015. The number of patients using cholesterol-lowering drugs was estimated on the basis of drug-consumption rate. The encounter form consisted of patient identification code, diagnostic information indicating the reason for high-risk designation, diagnostic code, and drug prescription. Drug information included monthly and annual prescriptions, brand and generic names, dosages, and prescription dates. The electronic database focused on the annual use of drugs in the four pharmaceutical drug categories (Table 1) and presented single- and fixed-dose combination (FDC) products.”

4. 1% increase in statin use is not necessarily clinically meaningful. Consider explaining what this might mean as far as prevented events.
Reply: Because the purpose of using statins is to reduce low-density lipoprotein and in turn reduce the occurrence of cardiovascular events, a 1% increase in statin use may not necessarily be clinically meaningful, but it may prevent the occurrence of cardiovascular events.