Author's response to reviews

Title: Economic impact of switching to fixed-dose combination therapy for Japanese hypertensive patients: a retrospective cost analysis

Authors:

Manabu Akazawa (makazawa@my-pharm.ac.jp)
Katsushi Fukuoka (fukuoka-k@nicho.co.jp)

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Author's response to reviews: see over
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BMC Health Services Research
Dr. Armando Arredondo
Associate Editor

Dear Dr. Arredondo

Enclosed is a revision of our manuscript entitled “Economic impact of switching to fixed-dose combination therapy for Japanese hypertensive patients: a retrospective cost analysis” (MS: 5925110668294243).

We thank reviewers for their important comments and suggestions that helped us to improve the quality of our manuscript. We addressed those comments in the revised manuscript and provided the point-by-point responses in this letter. Also, as suggested we added information of IRB and revised format of tables and figures.

We look forward to your review. Please contact me if further clarifications are needed.

Best regards,

Manabu Akazawa, PhD, MPH
Corresponding author
**Reviewer 1: Dr. Euna Han**

Comment:
Using a recent policy change regarding the prescription-term restriction as a policy instrument, the authors attempted to estimate the impact of FDC on treatment cost of hypertension. This study used a unique policy as an instrument to assess the causal impact of FDC on hypertension treatment, and potentially provides interesting evidence with regards to economic advantage of FDC. This is a well-written study with an interesting study topic and design. However, this study should more clarify the motivation and contribution of this study to the previous literature.

Response:
We agree. As suggested we have revised our introduction to help readers better understand our motivation and importance of the study. We summarized previous studies regarding to FDC antihypertensive drugs, the current policy changes in Japan and potential benefit of the study to overcome common limitation of the healthcare database studies. Below is the list of publications we added as references. All changes were highlighted in blue in the manuscript.


Stankus V, Hemmelgarn B, Campbell NR, Chen G, McAlister FA, Tsuyuki RT:


Comment:
The purpose of this study should be clarified. The authors said that they evaluated the economic benefit of FDC-switch in terms of adherence and drug costs in the Introduction section. However, throughout the paper, no evaluations were conducted in terms of adherence.

Response:
We revised our study purpose to focus on the antihypertensive drug costs. The reason why we could not evaluate the adherence of the antihypertensive treatments is explained in the discussion session as follow: “However, we could not confirm this benefit using pharmacy claims data in Japan. Because patients visited the doctor’s office regularly and received medications according to a schedule, the medication possession ratio (MPR) —which is defined as the total days of supply of drugs during the study period divided by the length of the follow-up period and is often used to measure adherence in claims-based studies—was almost 100% for most patients, regardless of whether they actually took the medications as indicated or not.”

Comment:
The policy change in Japan introduced the incentive for physicians to prescribe aggressive treatment option particularly for those with ARB and CCB in separate form. And thus, this policy change acts as an instrumental variable for FDC prescription, which would be endogenous for physician preference or patient case-mix. I would recommend the authors focus on this interpretation further, so that they can clarify that this study tries to shed light on the causal impact of FDC on hypertensive treatment cost. That being said, the authors may need to discuss limitation of the previous studies that showed cost savings of FDC in terms of causality.
Response:
Because limited information is available in the healthcare databases, unobservable confounding is the common limitation to assess treatment effects on outcomes (such as adherence and costs). In this study, using a policy change as an instrument, antihypertensive drug costs were compared pre and post of switching to FDC drugs. Also, population without switching was used as a baseline change during the study period. The common limitation of the previous studies and a potential benefit of this study were summarized in the last sentence of the introduction session.

Comment:
For total cost, the authors included “any drugs dispensed during the timeframe”. However, and it is not clear what is the implication of this total cost. If the authors intended to assess the indirect economic benefit of FDC, i.e., changes in any relevant treatment cost stemming from effective control of hypertension by using aggressive FDC, they should assess only those relevant drugs not “any” drugs. That is, the authors’ measurement of total cost does not accurately account for actual indirect economic benefit of FDC.

Response:
As suggested we changed the main outcome to the annual antihypertensive drug costs before and after the index date. All related figure (Figure 5) and tables (Table 1& 2) were also revised.

Comment:
The authors concluded that switching to FDC reduced the annual cost of antihypertensive treatments particularly for patients treated with a combination of ARB and CCB in separate forms. This finding does not seem to add any critical information to what we already know given the information about the listing price for FDC compared to respective hypertension treatment. What would be more interesting would be the net savings of FDC less the seemingly unnecessary use of aggressive FDC for patients with ARB alone.

Response:
As suggested a Canadian study estimated potential cost savings by assuming all combination therapies would switch to FDC drugs by using the listed price. However, because both brand-name and generic drugs were used for hypertensive treatments, we thought we should conduct the analysis using a real world prescription drug records by reflecting current medical practice in Japan. In addition, the study found that not all switching occurred from patients with taking combination therapies. As mentioned, the policy change may induce unnecessary use of aggressive FDC for patients with ARB alone. We have planned a further study to analyze data focusing on this population.

Comment:
The policy change in Japan is the key instrument of this study, and thus, it should be more clearly stated in the Abstract section which should stand alone without the main text.

Response:
As suggested the abstract section revised as follow: “In this study, we used the opportunity of this policy change in Japan as an instrument to assess the causal impact of switching to FDC on hypertensive treatment costs.”

Comment:
It is not clear the extent of the variation of the number of patients per physician, but if there is enough variation, I would recommend using physician-level mixed model given that physician preference toward prescription fee would vary and remains unobserved. Or controlling for some (assumingly) observed physician characteristics such as specialty (generalist versus specialist), gender, age, would help control variations stemming from physician side.

Response:
The database includes information about institutions where prescriptions were issued. We used information of the number of bed and name of department of the institutions to create variables indicating prescribers’ characteristics: clinics (no bed) or hospitals, as well as cardiovascular specialists or others. Because doctors at clinics and specialists were more likely to switch to FDC drugs (Table 1), subpopulation analyses were also performed using these variables as shown in Figure 5 and Table 2.
Comment:
Characteristics of case and control should be tested for statistical significance (Table 1).

Response:
\( \chi^2 \) tests were performed and results were added in Table 1.

Reviewer: Dr. CARLOS HERNANDEZ GIRON

Comment
Show the importance of the different cost of two treatment for recommendation: include the p value, in the tables, that show difference between different cost of treatments...

Response:
\( T \)-tests were performed to evaluate whether statistically significant changes were occurred between pre- and post- index periods. Results were described in Figure 5.