Reviewer's report

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

Version: 1 Date: 25 November 2012

Reviewer: Euna Han

Reviewer's report:

MS ID: 5925110668294243
Title: Economic impact of switching to fixed-dose combination therapy for Japanese hypertensive patients: a retrospective cost analysis
Authors: Manabu Akazawa and Katsushi Fukuoka

<Major compulsory revisions>
- 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.

- 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.

- 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.

- 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.
- 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.

- 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.

- 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.

- Characteristics of case and control should be tested for statistical significance (Table 1).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have no competing interests in relation to this paper.