

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	CALCIUM CHANNEL BLOCKERS AND CANCER: A RISK ANALYSIS USING THE UK CLINICAL PRACTICE RESEARCH DATALINK (CPRD)
<b>AUTHORS</b>	Grimaldi-Bensouda, Lamiae; Klungel, Olaf; Kurz, Xavier; de Groot, Mark; Maciel Afonso, Ana; De Bruin, Marie; Reynolds, Robert; Rossignol, Michel

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Christoph Meier Basel Pharmacoepidemiology Unit Division of Clinical Pharmacy and Pharmacoepidemiology Departement of Pharmaceutical Sciences University Of Basel Switzerland
<b>REVIEW RETURNED</b>	30-Aug-2015

<b>GENERAL COMMENTS</b>	<p>The authors of this large observational study used the UK-based CPRD to explore the risk of developing an incident cancer diagnosis in relation to use of calcium channel blockers (CCBs) or other antihypertensive drugs. The database they used is well-suited for this sort of analysis, and the methods and analyses are sound and valid. The paper is nicely written and clear. The authors found no evidence for an altered risk of cancer overall, nor of breast, prostate or colon cancer in particular. The null result was consistent across various exposure categories, i.e. across various categories of dose, duration and type of CCB.</p> <p>The study picks up an issue that was hot 20 years ago. I do not exactly know why they decided to study this association again. I am not aware of any current debate about the safety of CCBs. Nevertheless, it sort of brings the heated discussion of that time to an end, and it may therefore be worthwhile publishing. It is a null result and may therefore not be so attractive to journal editors, but in drug safety null results are often of great relevance and importance, since they provide reassurance to patients and health professionals, in case anyone was still worried about cancer risks of CCBs.</p> <p>I do have just two minor questions regarding the study population:</p> <p>The authors created three cohorts, the CCB cohort, the non-CCB cohort, and the cohort of users of other antihypertensive drugs. I assume these cohorts are mutually exclusive, but it is never clearly stated. Are they indeed mutually exclusive, and was the non-CCB cohort entirely untreated, despite the fact that 13.3% had a diagnosis of hypertension?</p>
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	Why did the authors match the non-CCB cohort to the CCB cohort, but not the cohort of users of other antihypertensive drugs too? This is a minor point as the analyses were adjusted for differences in age and other characteristics, but the authors may want to briefly discuss why they did not match the third cohort on age and sex as well.
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<b>REVIEWER</b>	Joji Ishikawa Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan
<b>REVIEW RETURNED</b>	31-Aug-2015

<b>GENERAL COMMENTS</b>	In the quite large national database, the author evaluated a risk of cancer associated with calcium channel blocker use. This paper was well-written and the negative results were reasonable.
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### VERSION 1 – AUTHOR RESPONSE

REVIEWER #1 - The authors created three cohorts, the CCB cohort, the non-CCB cohort, and the cohort of users of other antihypertensive drugs. I assume these cohorts are mutually exclusive, but it is never clearly stated. Are they indeed mutually exclusive, and was the non-CCB cohort entirely untreated, despite the fact that 13.3% had a diagnosis of hypertension?

REPLY: The CCB cohort was compared to two non-mutually exclusive comparators: no CCB use and anti-hypertensive drugs (other than CCB). The no CCB group contained individuals taking and not taking anti-hypertensive drugs other than CCB as no selection criteria other than not having been exposed to CCB was applied. It can be seen as a 'general population' comparison group. The second comparison group was restricted to individuals taking an anti-hypertensive drug (other than CCB) and can be seen as a subset of the general population comparator.

The last sentence of section on study population could be edited: "The second comparison cohort was a subset of the first, including unmatched patients with no CCB prescriptions but prescribed at least another antihypertensive drug from 1996 to 2009 (AHT cohort)."

REVIEWER #1 - Why did the authors match the non-CCB cohort to the CCB cohort, but not the cohort of users of other antihypertensive drugs too? This is a minor point as the analyses were adjusted for differences in age and other characteristics, but the authors may want to briefly discuss why they did not match the third cohort on age and sex as well.

REPLY - As explained above, the first comparison group was an unrestricted general population not taking CCB. Matching was used to make this group more comparable to CCB users. This procedure was not necessary with the AHT cohort as it was a priori 'naturally' comparable to a population taking CCB, nor desirable as this would have caused a loss in sample size.

No change proposed for the manuscript.