Reviewer's report

Title: Metformin use in patients with type 2 diabetes mellitus is associated with reduced risk of deep vein thrombosis: A Non-randomized, Pair-matched Cohort Study

Version: 3  Date: 9 September 2014

Reviewer: Ming-Ching Shen

Reviewer's report:

1. In the abstract section, the results (page 4, line 17) describe that "...44(0.6%) from the cohort with metformin and 16 (0.21%) from the control group...". The prevalence of DVT is higher in the metformin group than that in the non-metformin control group, how can the subjects with metformin use would experience a risk reduction in the development of DVT? Furthermore the prevalence rate of DVT in the context of "Results" (page 12, line 13 and 14) is a little bit different from those described in the abstract.

2. In the context of discussion (page 18, line 8-9) it is described that "...metformin may provide endothelial protection to reduce thromboembolic event...". The endothelial protection is more likely to reduce the arterial thrombosis event, e.g. CAD, stroke and PAOD, rather than to reduce the DVT event which is more blood flow and coagulation-related. The author spent too much time to discuss the mechanism to reduce the cardiovascular event not the DVT event.

3. In the study of co-morbidities, the author included mostly the cardiovascular risk factors, e.g. hypertension, coronary artery disease, hyperlipidemia, etc. The other important venous thromboembolic risk factors, e.g. cancer, surgery, immobilization, pregnancy, presence of antiphospholipid antibodies, myeloproliferative neoplasm or primary thrombophilia were unfortunately not included. These defects may cause serious bias.

4. Hyperhomocysteinemia is known to be associated with an increased risk of arterial and venous thrombosis. Hyperhomocysteinemia usually occurs when there are a MTHFR enzyme C677T homozygous mutation, which is found to present in about 7-10% of Taiwanese population, and low plasma level of folate, vitamin B6 or vitamin B12 coexist. Long term use of metformin has been shown to be able to induce vitamin B12 deficiency in 10 to 30% of patients. Therefore metformin use in patient with type 2 DM may cause B12 deficiency and homocysteinemia may occur when there is a MTHFR C677T homozygous mutation, therefore metformin-long term use in type 2 DM may be associated with increased, not reduced risk of DVT.

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal
Quality of written English: Acceptable

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

Declaration of competing interests:
I declare that I have no competing interests' below