SPECIFIC COMMENTS TO AUTHORS

Please, discuss the patho-physiology of the diabetes microvascular complications. You can underline the microvascular complication in coronary artery system.

Reply:

As requested, we have discussed the patho-physiology of diabetes microvascular complications and added texts about the microvascular complication in coronary artery system. Please refer to the first paragraph of the introduction.

Reviewer's code: 00506409

SPECIFIC COMMENTS TO AUTHORS

This manuscript presents a meta-analysis on the incidence of macrovascular and microvascular complications in patients with type 2 diabetes. This is an important topic in the management of the ever-expanding population of patients with type 2 diabetes. This report is a revision of the original manuscript. This reviewer has not contributed to the review of the original manuscript, and there is only one statement in the response by the authors on the comments made on the original manuscript. It is therefore not possible to judge whether there were more comments on the original manuscript: changes in the manuscript are not indicated. This reviewer has therefore not conducted a thorough review of the revised manuscript as is done in the review of an original manuscript, but only conducted a review as done in the process of a revision. Some comments are as follows:

• The flow diagram of the selection procedure of publications for this analysis does not include the selection criteria mentioned in the section "Study selection".

Reply:

In fact, the selection criteria have already been reflected in the reasons for exclusion in the flow chart. For example, "animal research" and "not diabetes patients" correspond to the selection criterion "not patients with T2DM aged ≥18 years; "lack of outcomes needed" corresponds to the selection criterion "no data for MACEs and SMICs". However, the inconsistency between selection criteria and flow chart is indeed confusing. To avoid confusion, the reasons for exclusion have been rephrased. Please refer to the revised Figure 1.

• In the selection process it is not mentioned whether studies included those in which special drugs were tested, i.e., what was the aim/focus of individual manuscripts selected? This is not clear in Table 1. In the results it is stated that "…12 eligible studies, participants from five studies …. were considered representative of the general patients with T2DM." This needs clarification and detail, as this differs from the selection criteria.

Note that the study includes cohort studies and clinical trials, but the nature of the clinical trials is not disclosed.

Reply:

We added the information of treatment in four clinical trials to Table 1 and described it in the result section. Please refer to the Table 1 and the last paragraph in page 9 for details.

Regarding representativeness, we would like to clarify that there was no requirement for representativeness in the selection criteria. A study was included as long as it was conducted in patients (N>1000) with T2DM aged ≥18 years, and reported absolute number of cases or incidence for both MACEs and SMICs, no matter how representative the participants are. The evaluation of representativeness of T2DM patients was one aspect of the quality assessment for the included studies. Better representativeness means that the study findings would be more applicable to the general T2DM patients. However, it does not mean the studies whose participants were less representative could not be included in our review.

• In the results it is stated "Finally, eight cohorts from eight cohort studies[33-40] and eight cohorts from four clinical trials[41-45], were eligible and finally included in the analyses." This makes 16 studies, but only 13 references are given, and there are 12 studies in Table 1 and Figure 1: in contrast, there are 16 studies in Figure 2, and 16 cohorts is mentioned in the first sentence of the discussion. The different numbers are quite confusing, and need a careful check. Apparently there are some studies which provided more than one cohort, but this is insufficiently detailed.

Reply:

Sorry for the confusion. Twelve studies (8 cohort studies and 4 clinical trials) were finally eligible. So, in Table 1 we described the baseline characteristic of these 12 eligible studies. The reason for having 13 references for 12 eligible studies is that the incidence of MACEs and that of SMICs in the ACCORD study were reported separately by two different papers derived from the study.

As explained in method section, the intervention and control arms of clinical trials were considered as two sub-studies in the data analysis. Therefore, there seemed to be 16 studies (8 cohort studies plus 8 sub-studies from 4 clinical trials) in Figure 2.

The third paragraph in page 9 and the third paragraph in page 10 have been revised to avoid confusion.

• The results present data on analysis of subgroups according to age, study design, length of follow-up and duration of diabetes (Table 2). There is no rationale presented in the selection of subgroups. Normally this follows a multivariate analysis in which potential parameters that affect the outcome (microvascular or macrovascular complications) are analyzed. This is not done in the present study.

Reply:

Previous studies found that age, follow-up time, and diabetes duration were associated with macrovascular and microvascular events in patients with type 2 diabetes mellitus. Besides, different types of study (cohort vs trial) were included in our review. In theory, the drugs tested in trials may affect the incidence of complications, thus affecting the risk ratio (although the result of subgroup analysis showed no significant difference). So, we did subgroup analyses according to these factors to investigate the potential sources of heterogeneity.

Due to the limited number of eligible studies (<10 times the number of factors mentioned above), the statistical efficiency of multivariate meta-regression analysis is very low. Therefore, as recommended by Cochrane Handbook, we did not conduct multivariate meta-regression analysis.

Please refer to the first paragraph in page 9 for more details.

• In Table 1 it appears that there are huge differences in incidence of macrovascular and microvascular complications between the various studies. This needs an explanation with regard of the definition/characteristics of the various studies. It is questionable to present data after combination of data from these studies, even restricting this to the RR

as parameter. The section on study limitations needs revision in this regard.

Reply:

We would like to clarify that the percentage shown in Table 1 is the prevalence, not the incidence, of macrovascular and microvascular complications in type 2 diabetes patients at baseline. The reason for including such studies is that almost all studies are of this kind, making them the currently best available evidence. This point has been discussed in the limitation part.