Letter to the editor: Comparing iStent *versus* CyPass with or without phacoemulsification in patients with glaucoma: a meta-analysis

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To the Editor,

Recently we read with great interest the article by Fard and colleagues,[1] which conducted a systematic review and meta-analysis to compare the overall intraocular pressure (IOP)-lowering effect of iStent or CyPass as isolated procedures or in combination with cataract extraction. The authors concluded that "both iStent and CyPass either in combination with cataract extraction or as isolated procedures effectively decrease IOP. This effect is greatest with isolated implantation of CyPass followed by multiple iStents and then single iStent implantation and lasts up to 2 years". We would like to point out why results from this analysis should be interpreted with caution.

First, the authors stated that patients were stratified by baseline IOP $\geq$ 21 mmHg and $<$ 21 mmHg, however it was not specified if the values were washout or medicated IOP and what was included is a mix of these values. For example, the preoperative baseline IOP after the washout period was included for the Fernandez-Barrientos *et al.*[2] and Hoeh *et al.*[3] studies, while the medicated screening IOP values were computed for the Craven *et al.*[4] and Fea *et al.*[5] studies. IOP reductions based on preoperative washout or unmedicated IOP may report larger reductions in IOP from the same studies compared with preoperative medicated IOP as its baseline measurement. It is acknowledged in the World Glaucoma Association guidelines on design and reporting of glaucoma surgical trials that "in order to quantify the IOP reduction after surgery, a consistent definition of the baseline, or reference IOP is essential. This may be recorded as IOP before medication was started, the IOP after washout of medication or the IOP of the patient's full medical regimen just before surgery".[6] For data included in this type of meta-analysis, baseline IOP values should be consistent in whether they include washout or medicated IOP values to more appropriately compare IOP-lowering effect.

Second, the design of studies included in a systematic review can have a substantial impact on the estimation of the treatment effect and therefore should be considered within that context when considering the trial design of each individual study for inclusion in a meta-analysis. Changes in IOP are generally a function of medication use. For example, in the Katz study, postoperative glaucoma medication was started if IOP exceeded a prespecified target of 18 mmHg or in the case of optic nerve or VF changes.[7] Whereas, in the Garcia-Feijoo study, reintroduction of IOP-lowering medication was left to the discretion of the investigator and dependent on the target IOP of each subject.[8] Differences in study designs such as these will lead to differences in IOP and medication-reducing effects, which are an artifact of design rather than entirely due to the treatment effect of the intervention.

Third, while we agree with McAuley and colleagues, that meta-analysts should attempt to identify, retrieve, and include all reports, grey and published, that meet predefined inclusion criteria,[9] we take issue with basing the conclusion that CyPass has the greatest IOP-lowering effect among the comparators on Flowers,[10] Garcia-Feijoo,[8] Guguchkova, and Grabner[11]. In Figure 5 (a) it is reported that the IOP-lowering effect includes a weight of 88.2% from Flowers and colleagues. As the Flowers source is an abstract, limited information is available and it is not reported if this is computed with washout or medicated baseline IOP. Also, the corresponding medication reduction is not reported. Without this important information, interpretation of the meta-analysis is challenging. In addition to this, the Guguchkova study is not included in the references so the study design describing how medications were reintroduced could not be verified.

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Finally, the systematic review included only references that were published up to July 2016. Since then several studies have been reported including large randomized controlled trials such as COMPASS ($n = 374$),[11] ($n = 54$),[12] and the iStent inject pivotal study ($n = 380$).[13] Although, it is recognized that systematic literature reviews require a cut-off date, these recent large studies would heavily influence results. Results of this meta-analysis should be considered with the substantial amount of data now available and their contribution to the results presented by Fard and colleagues.[1]

We therefore urge interpretation of these results with caution. To better estimate the effect of these treatments the considerations described here should be taken into account.

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