Mapping from visual acuity to utility in patients with macular oedema due to retinal vein occlusion using data from the LEAVO trial

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Objectives

- LEAVO was a multicentre phase III double-masked randomised controlled non-inferiority trial which compared intravitreal therapy with ranibizumab (Lucentis) versus aflibercept (Eylea) versus bevacizumab (Avastin) for macular oedema due to central retinal vein occlusion.
- LEAVO's primary outcome was the change in best corrected visual acuity (BCVA) in the study eye measured using early treatment for diabetic retinopathy study (ETDRS) letter score from baseline to 100 weeks.
- BCVA measures how many rows of letters (with decreasing size) patients can read. A higher BCVA score indicates better vision.
- To estimate the cost-effectiveness of ranibizumab, aflibercept and bevacizumab, we built an economic model which extrapolated study and non-study eye BCVA over a lifetime horizon.
- To estimate quality-adjusted life years required mappings to convert BCVA to utility.
- LEAVO contained three measures of utility: EQ-5D, EQ-5D with the vision bolt-on (EQ-5D V) and a vision specific utility instrument: the visual functioning questionnaire-utility index (VFQ-UI).
- We developed mappings to predict utilities using better-(BSE) and worse-seeing eye (WSE) BCVA, age and sex.

Methods

- Adjusted limited dependent variable mixture models (ALDVMM) are flexible parametric models that can be used to model the distinctive distribution of EQ-5D.
- Mixture models use multiple components – each component's distribution has different parameters. Variables predict the probability of each observation belonging to each component.
- We used data from six time points for 463 participants in LEAVO.
- We estimated ALDVMMs with one to four components.
- We included BCVA in the BSE and WSE, age and sex as independent variables to predict utility within each component.
- We considered BSE and WSE BCVA as predictors of component membership.
- We compared results across models using mean error, mean absolute error, root mean square error, Akaike information criteria, Bayesian information criteria, and visual inspection of predicted and observed utilities and the cumulative distribution functions.
- We followed ISPOR good practice guidance.

Results

- The EQ-5D and EQ-5D V data follow the typical multimodal distribution of EQ-5D and VFQ-UI is highly skewed with a long left tail (Figure 1).
- For EQ-5D and EQ-5D V, the two component model with within-component variables for BSE, WSE, age and sex, and component membership variables for BSE and WSE was the best fitting model (EQ-5D in Table 1). For VFQ-UI, the two component model with within-component variables for BSE, WSE, age and sex, and component membership variables for BSE and WSE was the best fitting model.
- The mean predicted and observed utilities for the best fitting models (Figure 2) show that predicted utilities lie furthest from the observed utilities at very low BSE and WSE scores, where the confidence intervals are wide because there are few observations.
- The mean predicted utilities lie closer to the observed utilities for VFQ-UI than EQ-5D and EQ-5D V, because VFQ-UI is focussed on vision whereas the EQ-5D and EQ-5D V measure other elements of health-related quality of life.

Figure 1: Distribution of utility data in the LEAVO study

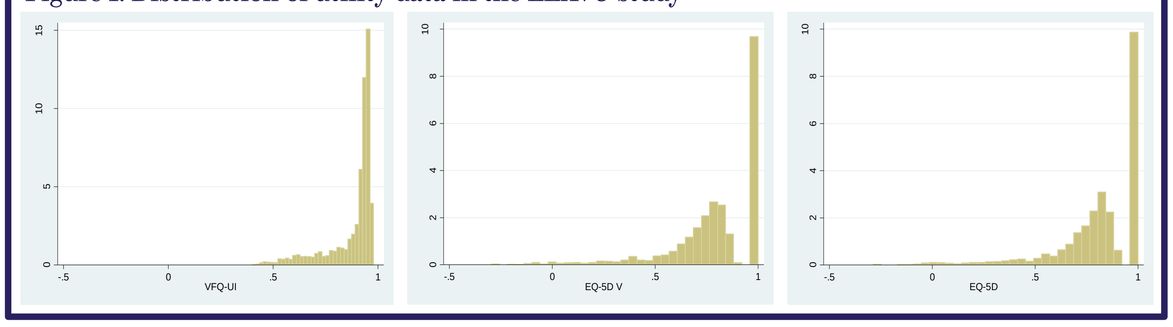
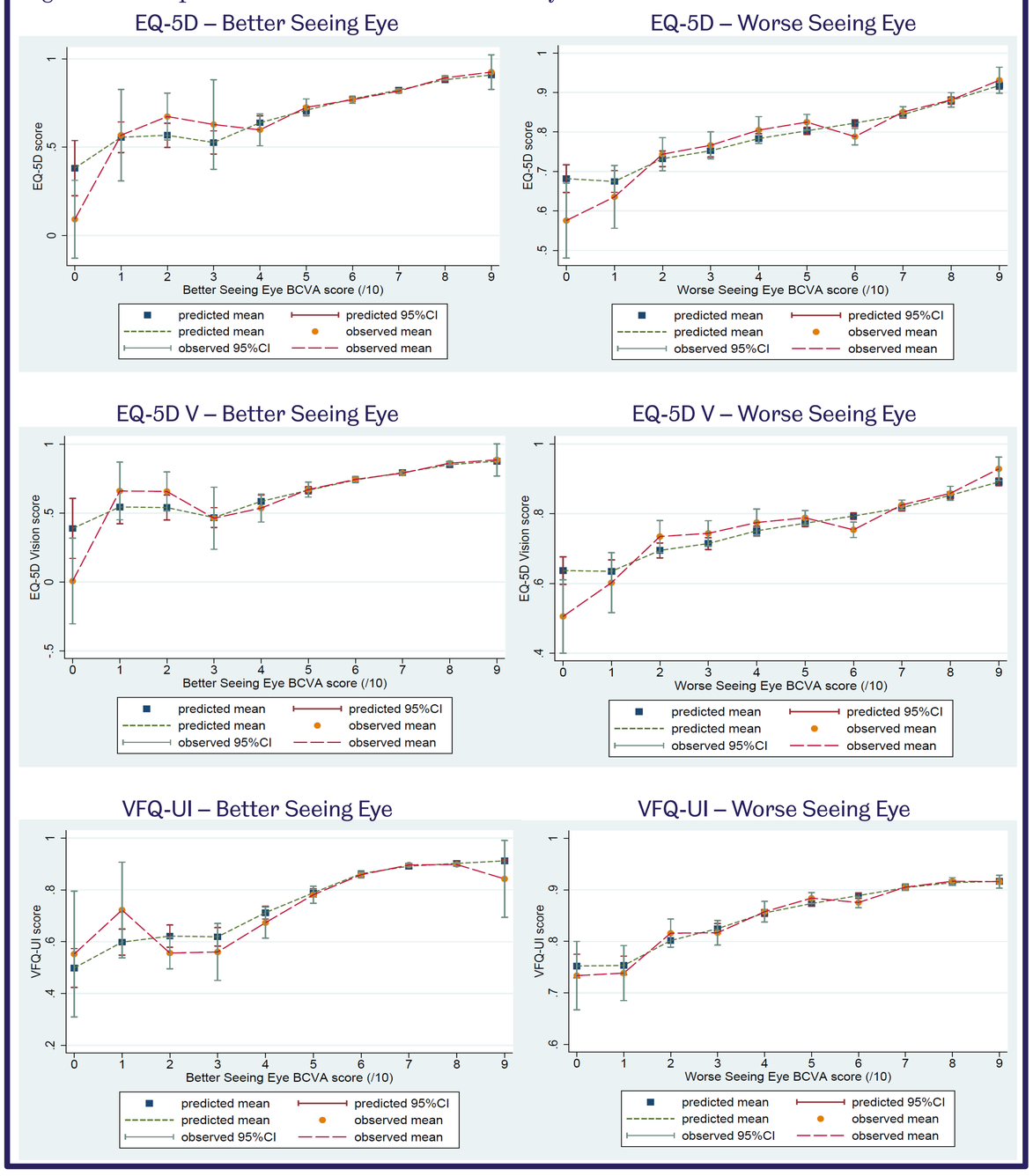


Table 1: EQ-5D Model fit statistics. Red = worst fitting model, Green = best fitting model.

Number of components	Within-component variables	Component membership variables	Log likelihood	Akaike information criteria	Bayesian information criteria	Mean error	Mean absolute error	Root mean square error
1	BSE, WSE, age, sex	NA	-704.413	1420.8250	1455.6970	0.0039	0.1445	0.1987
1	BSE, WSE, BSE*WSE, age, sex	NA	-704.412	1422.8240	1463.5080	0.0039	0.1445	0.1987
2	BSE, WSE, age, sex	Constant	-479.682	985.3648	1060.9200	-0.0017	0.1435	0.1986
2	BSE, WSE, BSE*WSE, age, sex	Constant	-477.872	985.7431	1072.9230	-0.0013	0.1437	0.1988
2	BSE, WSE, age, sex	BSE	-476.116	980.2326	1061.6000	-0.0006	0.1436	0.1987
2	BSE, WSE, age, sex	BSE, WSE	-467.949	965.8980	1053.0780	-0.0007	0.1435	0.1982
3	BSE, WSE, age, sex	Constant	-456.618	953.2355	1069.4750	-0.0009	0.1438	0.1986
3	BSE, WSE, age, sex	BSE, WSE	-449.198	946.3959	1085.8830	-0.0009	0.1437	0.1982
4	BSE, WSE, age, sex	Constant	-441.025	936.0499	1092.9730	-0.0012	0.1437	0.1985
4	BSE, WSE, age, sex	BSE, WSE	-419.682	905.3647	1097.1600	-0.0003	0.1421	0.1960

Figure 2: Mean predicted and observed visual acuity scores.



Conclusions

- Mappings with multiple components better predict utility for EQ-5D, EQ-5D V and VFQ-UI than those with one component.
- This is consistent with findings from other disease areas.
- Our ALDVMM models closely fit the distribution of the observed utility data and build on previous research in visual acuity that has been limited to ordinary least squares regression.

The LEAVO study:
Hykin P, Prevost AT, Vasconcelos JC, Murphy C, Kelly J, Ramu J et al. Clinical Effectiveness of Intravitreal Therapy With Ranibizumab vs Aflibercept vs Bevacizumab for Macular Edema Secondary to Central Retinal Vein Occlusion: A Randomized Clinical Trial. JAMA Ophthalmology. 2019. doi:10.1001/jamaophthalmol.2019.3305.

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