in patients at high risk of DME, which reflects a tendency to exclude patients that are predisposed to treatment complications. For example, data on file with Novartis indicate that 3.4% of the patients in DME trials treated with ranibizumab 0.5 mg had experienced a prior stroke or transient ischemic attack. More knowledge on the patients who are at greater risk of complications is warranted.

Such real-world evidence will be forthcoming in the LUMINOUS study [NCT01318941] being coordinated by Novartis, which has enrolled 30 000 patients at approximately 500 sites from >40 countries globally. The prospective 5-year observational study will evaluate the long-term safety and efficacy of ranibizumab in real-world clinical practice.

For now, there is no evidence to suggest any difference in safety between ranibizumab 0.5 mg and the control (sham/laser) in the 5 studies.

Methodological Shortcomings Revealed in Clinical Guidelines for Primary Open-Angle Glaucoma

Written by Brian Hoyle

A study examining 3 separate clinical practice guidelines governing primary open-angle glaucoma found that all 3 sets of guidelines require improvements, stated Annie Wu, MD, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA.

Glaucoma affects about 60.5 million people globally and is the second leading cause of blindness [Quigley HA, Broman AT. *Br J Ophthalmol.* 2006]. Although rigorous clinical practice guidelines are necessary for glaucoma, there are obstacles that can color the rigor of guidelines, including conflict of interest and quality of the evidence [Kung J et al. *Arch Intern Med.* 2012; Ransohoff DF et al. *JAMA*. 2013].

The present study evaluated the quality of guidelines for primary open-angle glaucoma published in recent years by the American Academy of Ophthalmology (AAO) [AAO Glaucoma Panel, Primary Open-Angle Glaucoma Preferred Practice Patterns, 2010], Canadian Ophthalmological Society (COS) [COS, *Can J Ophthalmol.* 2009], and the National Institute for Health and Care Excellence (NICE) [National Collaborating Center for Acute Care. Glaucoma: Diagnosis and management of chronic open-angle glaucoma and ocular hypertension. London (UK), 2009].

Four evaluators independently appraised each set of guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool [Brouwers M et al. *CMAJ.* 2010]. AGREE II contains 6 domains: Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence. The overall assessment score across all domains uses a 7-point scale; a score of 7 indicates 100% adherence to the particular guideline.

Application of AGREE II–produced scores ranged from 28% to 85% for the AAO guidelines, 51% to 96% for the COS guidelines, and 55% to 97% for the NICE guidelines. Scope and Purpose was the strongest domain for all 3 sets of guidelines. Clarity of Presentation was a strong domain for the COS and NICE guidelines. The

Table 1. Comparison of AGREE II Scores in Evaluation of Glaucoma Guidelines

Agree II Domain	AAO	COS	NICE
Scope and Purpose, %	85	86	93
Stakeholder Involvement, %	28	51	79
Rigor of Development, %	63	72	92
Clarity of Presentation, %	78	96	97
Applicability, %	58	67	92
Editorial Independence, %	64	77	55
Overall assessment	**4.75/7.0**	**5.50/7.0**	**6.25/7.0**

AAO, American Academy of Ophthalmology; COS, Canadian Ophthalmological Society; NICE, National Institute of Health and Care Excellence.

weakest domains were Editorial Independence for all 3 guidelines, and Stakeholder Involvement for the AAO and COS guidelines.

Comparison of the AGREE II evaluation of the 3 guidelines revealed variability that sometimes could be considerable between the individual guideline domain scores; for example, scores for the Stakeholder Involvement domain varied from 28% for the AAO guidelines to 79% for the NICE guidelines (Table 1).

The overall assessment favored the NICE guidelines, followed by the COS and AAO guidelines. The results of the study have prompted several primary and additional recommendations.

Primary recommendations concerned clarifying stakeholder involvement, using a guideline development process that is transparent and rigorous, and acknowledging competing interests and their possible influence.

The researchers concluded that the use of the AGREE II assessment instrument revealed shortcomings in methodologies in all 3 association guidelines in the domains of Stakeholder Involvement, Rigor of Development, and Editorial Independence. This appraisal highlights the importance of regularly assessing clinical practice guidelines. Such a regular assessment, and the resulting improvements, will result in meaningful recommendations for clinical practice.

Intravitreal Aflibercept Has Long-Term Benefits in Treatment of DME

Written by Brian Hoyle

Quan Dong Nguyen, MD, MSc, University of Nebraska Medical Center, Omaha, Nebraska, USA, described the 2-year outcomes of the Intravitreal Alfibercept Injection in Vision Impairment Due to DME [VIVID; NCT01331681] trial as well as the Study of Intravitreal Administration of VEGF Trap-Eye (BAY86-5321) in Patients With Diabetic Macular Edema [VISTA; NCT01363440]. VIVID and VISTA are both phase III, randomized, double-blind global studies in which intravitreal aflibercept was injected to treat diabetic macular edema (DME).

VIVID was a 73-center study involving 406 patients; VISTA enrolled 466 patients at 54 centers. Patients with clinically significant DME and eye chart–rated best corrected visual acuity (BCVA) of 20/40 to 20/320 were randomized in a 1:1:1 fashion to receive injections of intravitreal aflibercept 2 mg every 4 weeks (2Q4; n = 136 in VIVID and n = 154 in VISTA), 2 mg every 8 weeks (2Q8; n = 135 in VIVID and n = 151 in VISTA), or the control procedure of laser photocoagulation (n = 132 in VIVID and n = 154 in VISTA). The primary end point of mean change in BCVA was assessed at week 52, with treatment and assessment continued through year 3. Key secondary end points included change in optical coherence tomography and change in the diabetic retinopathy severity scale (DRSS).

At baseline, patients' age, sex, race, mean level of glycated hemoglobin, duration of diabetes, and body mass index were similar in the 3 arms of both studies. Baseline disease characteristics of BCVA and central retinal thickness were also similar between the study arms. Prior treatment with anti-vascular endothelial growth factor medication was more variable and higher in VISTA participants.

In VIVID, the week 100 completion rates were 77.8%, 84.6%, and 81.5% for the control, 2Q4, and 2Q8 arms, respectively, with an overall completion rate of 81.3%. The respective values for the 3 arms of the VISTA trial were 85.3%, 80.1%, and 82.5%, with an overall completion rate of 82.6%.

Through week 100, the mean number of laser treatments was 2.4 in VIVID and 3.5 in VISTA. The mean numbers of injections in the 2Q4 and 2Q8 arms were 22.6 and 13.6, respectively, in VIVID and 21.3 and 13.5, respectively, in VISTA. Rescue treatment was necessary in 34.6%, 7.4%, and 11.1% of the VIVID patients in the control, 2Q4, and 2Q8 arms, respectively, and 40.9%, 3.2%, and 8.6% of the VISTA patients in the respective arms.

In both trials, the significant improvement in BCVA noted at 4 weeks was maintained through week 100 ($P < .001$ for both trials).

Gain of BCVA of ≥ 10 and ≥ 15 letters at week 100 was significant for the 2Q4 and 2Q8 arms in VIVID (58.1% and 49.6%, and 38.2% and 31.1%, respectively) compared with the control (25.0% and 12.1%) and in VISTA (63.6% and 59.6%, and 38.3% and 33.1%, respectively) compared with the control (27.9% and 13.0%). The improvements in the treatment arms were similar. The mean change in retinal thickness through week 100 in both trials significantly favored both treatments compared with the control (both $P < .001$).

In both trials, there was a higher proportion of patients in the treatment arms with ≥ 2-step improvement in DRSS at week 100 compared with the control arms. The safety profile in both trials was acceptable, with no treatment-related ocular adverse events or systemic serious adverse events, no increased rate of arterial thrombotic events, and no safety signals related to death.

The week 100 findings demonstrate the effectiveness of intravitreal aflibercept in the treatment of DME and confirm the safety of both treatment regimens.