

# Sharing best practice and landmark evidence in glaucoma care

BY KEITH BARTON, GUS GAZZARD AND HARI JAYARAM

Evolving technology, best practice and landmark evidence in glaucoma care were reviewed by an international expert faculty in session presentations and debates during the 11th Moorfields International Glaucoma Symposium 2019. The authors were meeting chairs and provide an overview of symposium proceedings.

## OCT imaging and AI in ophthalmology

Hans Lemij, Rotterdam Eye Hospital, the Netherlands, discussed glaucoma optical coherence tomography (OCT) imaging and automated segmentation issues, noting several common image artefacts.

Paul Foster highlighted research by the UK Biobank Eye and Vision Consortium related to cognitive function and the expanding use of OCT imaging in dementia and neurodegeneration research. Findings show that a thinner retinal nerve fibre layer (RNFL) is associated with worse cognitive function in individuals without known neurodegenerative disease, as well as a greater likelihood of future cognitive decline [1]. The Rotterdam Study also revealed an association of retinal neurodegeneration on OCT with an increased risk of dementia, including Alzheimer's disease [2]. Worsening vision in older adults may be adversely associated with future cognitive functioning, suggesting that maintenance of good vision may mitigate age-related cognitive decline [3]. For clinical practice, however, the use of OCT imaging to predict individual risk of cognitive decline has not yet been proven.

Sameer Trikha noted the rising burden of glaucoma care and new opportunities using artificial intelligence (AI). For validation, AI technology needs to be comprehensively tested across different devices, with clear explainability of algorithm results [4]. Future trends identified include use of AI machine learning tools to support clinical decision-making capabilities, development of transparency and trust, together with a changing clinician skill set entailing wider use of AI support.

Artificial intelligence is a fast-evolving technology that will likely lead to changes in ophthalmic clinical practice and AI-assisted science may provide new insights into disease, observed Pearse Keane. Nonetheless, robust prospective clinical validation of AI in ophthalmology is required. Intended uses of deep learning systems include initial clinical deployment as decision support

tools, for example, in rapid access virtual macular clinics, as well as medical education and training applications [5]. Preliminary research results using deep learning to predict conversion from dry age-related macular degeneration (AMD) to neovascular (wet) AMD are promising.

## New therapy for old problems: what will we be using in a decade?

Intraocular pressure (IOP) homeostasis is regulated within the trabecular meshwork / Schlemm's canal, explained Daryl Overby, Imperial College London, in a review of the role of nitric oxide (NO) in the trabecular meshwork [6]. Increasing IOP stimulates NO production by Schlemm's canal cells and NO may act as a mechanosensory feedback signal to decrease outflow resistance. Latanoprostene bunod (Vyulta, Bausch+Lomb), approved in 2017 by the US Food and Drug Administration as a new treatment option for open-angle glaucoma (OAG) and ocular hypertension (OHT), is composed of latanoprost acid linked to a NO-donating moiety (butanediol mononitrate), providing a dual mechanism action through the uveoscleral and trabecular meshwork / Schlemm's canal pathways to reduce elevated IOP [7].

Patrick Yu Wai Man discussed mitochondrial dysfunction, retinal ganglion cell (RGC) disease and potential therapeutic approaches. Retinal ganglion cell survival is critically dependent upon normal mitochondrial function. Mitochondrial optic neuropathies represent an important cause of chronic visual morbidity. Several promising treatment paradigms have emerged targeted at specific disease mechanisms, including stabilisation of the mitochondrial membrane and gene replacement therapy.

Jonathan G Crowston, University of Melbourne, Australia, explored visual recovery in glaucoma, including evidence that exercise boosts RGC recovery following injury. It is known that exercise is associated with improved cognitive function, while

preliminary evidence suggests that vigorous physical activity may reduce glaucoma risk [8]. Animal studies show that exercise reverses age-related vulnerability of the retina to injury by preventing complement-mediated synapse elimination via a brain derived neurotrophin-dependent pathway [9]. Fry et al. outlined experimental research showing that functional recovery can occur following a prolonged course of RGC dysfunction [10]. Research also supports the therapeutic use of vitamin B3 in glaucoma and potentially other age-related neurodegenerative diseases [11].

Anthony Khawaja explained that genetics underlies IOP variability between individuals and that developmental and anatomical factors are important. Lymphangiogenic factors represent a potential treatment target. Collectively, loci have predictive value for primary open-angle glaucoma (POAG), underscoring the potential for targeted screening and prevention of late presentation with timely therapy [12]. Susan Williams, University of the Witwatersrand, Johannesburg, South Africa, said she believes that genetics will herald an era of precision medicine involving customised care for POAG, as new insights improve understanding of disease pathogenesis and the genetic factors that affect the risk of developing POAG (Table 1).

## MIGS: where are we now?

Alex Huang, Doheny Eye Institute, USA, discussed advances in structural and functional evaluation of aqueous humour outflow (AHO). Impairment of AHO can lead to elevated IOP, optic nerve damage and concomitant glaucoma [13]. Assessment of AHO patterns after trabecular microbypass in glaucoma patients revealed different patterns of aqueous angiographic outflow improvement, although it is unclear which types portend better outcomes [14]. Greater understanding of AHO may prove useful in improving glaucoma surgeries aimed at trabecular meshwork bypass, with the aim of individualised surgery.

Compared with trabeculectomy using

**Table 1: Glaucoma risk alleles in the Ocular Hypertension Treatment Study: Cox Proportional Hazards Analysis.\***

	Hazard Ratio	95% Confidence Interval	P Value
TMCO1 (per risk allele)	1.73	1.28–2.34	0.00036
Vertical cup-to-disc ratio (per 0.19 [SE])	1.62	1.33–1.96	0.00000096
Central corneal thickness (per 37µm [SE])	1.57	1.30–1.89	0.0000028
Male gender	1.53	1.05–2.23	0.025
Age (decade)	1.40	1.14–1.71	0.0011
Intraocular pressure (per 2.7mmHg [SE])	1.28	1.03–1.46	0.021
Visual field defect (PSD, per 0.25 [SE])	1.20	0.99–1.45	0.070

\* Data show a three-fold increased risk (for two glaucoma risk alleles) of incident glaucoma in an analysis of the OHTS cohort. Abbreviations: PSD, pattern standard deviation. Adapted from Sheetz, et al. *Ophthalmology* 2016;**123**(12):2527–36.

Mitomycin C (MMC), minimally invasive glaucoma surgery (MIGS) implantation produces a more predictable IOP gradient across the sclera, with less risk of hypotony, bleb leak, infection and discomfort, noted Professor Paul Palmberg, Bascom Palmer Eye Institute, USA. A prospective study showed surgery utilising the InnFocus microshunt (Santen) with MMC, alone or in combination with phacoemulsification, achieved IOP control in the low teens in most subjects up to three years' post-surgery [15]. Achieving low IOP stabilises more people and may protect and help improve vision, noted Prof Palmberg. In the future, it may be possible to stage glaucoma patients and to evaluate treatment efficacy based on real-time assessment of neuronal cell apoptosis [16]. Cordeiro et al. recently demonstrated that the level of apoptosis (detected using, detecting apoptosing retinal cells (DARC) in vivo) correlated with glaucoma, increased glaucoma progression, decreased central corneal thickness and increasing age [16].

Herbert A Reitsamer, University Clinic Salzberg, Austria, shared his experience with ab interno XEN implant (Allergan) surgery for lowering of IOP in glaucoma. He said the most important considerations in determining which patients are suitable for a XEN procedure are target IOP, tolerance to eye drops, anatomical considerations and whether cataract surgery is necessary. Results from the APEX study group showed that the XEN implant, with or without phacoemulsification, effectively reduced IOP and need for medication over two years in POAG uncontrolled medically [17]. Professor Norbert Pfeiffer, Mainz University Medical Center, Germany, discussed glaucoma surgery using the Hydrus Microstent (Ivantis). At 24 months in the HORIZON study, the proportion of POAG subjects achieving a 20% reduction from baseline in washed-out modified diurnal IOP was 77.2% in the cataract surgery plus Hydrus Microstent group (n=369) versus 57.8% in the phaco only group (n=187), difference 19.5% (P<0.001) [18].

Paul Harasymowycz, University of Montreal, Canada, provided a personal viewpoint on choice of MIGS devices. He suggested that for patients well controlled on antiglaucoma medications but who wanted to get off topical drops, he would probably choose a MIGS procedure.

With the rapid adoption of MIGS as primary surgery for glaucoma, there is a need for assessment of patient-centric outcomes in studies of MIGS devices to complement randomised clinical trial data, observed Nathan Kerr [19]. The International Glaucoma Surgery Registry provides a secure, web-based clinical tool for ophthalmologists to track and audit surgical as well as patient-reported outcomes (migs.org/registry). The registry has seen rapid take-up, with users in over 20 countries.

Keith Barton described device enhancements aimed at improved insertion and placement and continuing MIGS developments. Investigational MIGS device iStent inifite (Glaukos), comprising three heparin-coated trabecular bypass stents preloaded into an auto injection system, is designed to be less invasive, allow faster recovery and have fewer complications than conventional procedures. Novel glaucoma surgery devices and alternative drug delivery systems in the pipeline include MINiject (iSTAR Medical), the MIMS ab-interno procedure (Sanoculis), iDOSE travoprost (Glaukos) and bimatoprost sustained release (SR) intracameral implant (Allergan). iDOSE travoprost is a titanium implant designed for continuous drug delivery directly into the anterior chamber; preliminary phase II data show average IOP reductions of more than 30% from baseline through 12 months.

### The Debates

Debate discussions addressed pre-perimetric glaucoma, phasing of diurnal IOP, use of intravitreal bevacizumab for non-neovascular glaucoma surgery and the impact of glaucoma surgery on the corneal endothelium.

Prof Paul Palmberg underscored the benefit

of detecting structural loss before visual field damage, supporting close follow-up and monitoring of pre-perimetric glaucoma. Visual fields are notoriously variable, while OCT RNFL loss is highly predictive of functional loss.

Philip Bloom, Western Eye Hospital, London, argued that monitoring of diurnal IOP during follow-up of glaucoma is inconvenient, costly, may delay clinical decision-making and is of little or no proven utility. Phasing with all day measurements of eye pressure may be appropriate and useful in a number of different case scenarios, explained Debbie Kamal. For example, to establish a diagnosis in normal tension glaucoma, to differentiate between a suspect and 'likely' glaucoma or where there is progression or disc haemorrhage despite controlled clinic IOP. Phasing validates the management regime and patients are the winners with respect to tailored treatment, concluded Ms Kamal.

Vascular endothelial growth factor (VEGF) is a major driver of scar formation. Adjunctive intravitreal bevacizumab inhibits fibrosis and will help improve outcomes in certain individuals at higher risk of excess fibrosis, observed Mr Crowston. Alex Huang commented that anti-VEGF treatment changes blebs, that anti-scarring measures are available and attention should be focused on promoting outflow.

### Landmark trials

The Zhongshan Angle Closure Prevention (ZAP) and Effectiveness in Angle-closure Glaucoma of Lens Extraction (EAGLE) trials have helped define optimal management of primary angle closure glaucoma (PACG), explained Mr Foster. The ZAP trial found that prophylactic peripheral iridotomy (PI) in primary angle closure suspects (PACS) had no proven benefit over the planned three-year trial, although there was a significant but modest benefit over six years. Trial investigators concluded that PI should only be offered to suspects with the very highest risk of PACG. Table 2 details estimates of the number of people with glaucoma worldwide.

The EAGLE trial demonstrated the effectiveness of early clear lens extraction for the treatment of PACG (Table 3)[20]. Investigators recommended lens extraction as the preferred initial intervention for high IOP PAC/PACG [20]. Mean postoperative corrected distance visual acuity in patients undergoing lens extraction for angle closure glaucoma appeared stable over the three-year study period [21].

Gus Gazzard reviewed findings from the LiGHT randomised study, which assessed initial selective laser trabeculoplasty (SLT) followed by conventional medial therapy as required versus conventional medical therapy without laser in newly diagnosed OAG and OHT patients [22]. At three years' follow-up, initial SLT provided drop-free disease control at stringent target IOPs in

**Table 2: Number of people with glaucoma worldwide.**

		Primary open-angle glaucoma	Primary angle closure glaucoma
Affected	2010	45 million	16 million
	2020	59 million	21 million
Blind from glaucoma	2010	4.5 million	3.9 million
	2020	5.9 million	5.3 million

Adapted from Quigley, et al. *Br J Ophthalmol* 2006;**90**:262-7.

**Table 3: EAGLE trial: primary outcome European Quality of Life-5 Dimensions (EQ-5D) questionnaire.**

EQ-5D score	Lens extraction		Laser peripheral iridotomy	
	N	Mean (SD)	N	Mean (SD)
Baseline	204	0.87 (0.19)	204	0.88 (0.18)
36 months	176	0.87 (0.21)	175	0.84 (0.23)

Difference in change between groups, baseline vs. 36 months (95% CI): 0.052 (0.015 to 0.088); P=0.005

Adapted from Azuara-Blanco, et al. *Lancet* 2016;**388**(10052):1389-97.

**Table 4: Clinical outcomes at three years in the LiGHT Trial Study.**

Outcomes at 36 months	Medicine-first group (n=312)	SLT-first group (n=314)
VA (logMAR), mean (SD)	0.08 (0.17)	0.07 (0.18)
IOP (mmHg), mean (SD)	16.29 (3.87)	16.63 (3.62)
Visual field MD (dB), mean (SD)	-3.21 (3.76)	-3.19 (3.92)
Total number of clinic visits	2907	3441
Number of clinic visits excluding two-week IOP check	2907	2976

Abbreviations: IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; MD, mean deviation; SLT, selective laser trabeculoplasty; VA, visual acuity.

Adapted from Gazzard, et al. *Lancet* 2019;**393**(10180):1505-16.

three-quarters of patients, with lower surgery and glaucoma progression rates compared with the medicine-first group. Results suggest that primary SLT should be considered for all newly diagnosed patients with POAG or OHT (Table 4). Further studies might consider more sensitive quality of life instruments, with bolt-on studies of additional risk factors such as ocular surface disease.

The UK Glaucoma Treatment Study (UKGTS) represents the first placebo-controlled trial to show preservation of the visual field with an IOP-lowering drug in patients with OAG [23]. Ted Garway-Heath considered that future protocols of studies of disease progression in glaucoma should evaluate visual field progression using rate-based analysis as the primary outcome, with secondary outcomes capturing spectral domain OCT features and quality of life measures. Combining OCT and visual field data can more rapidly identify worsening vision and produce more accurate estimates of the progression rate than visual field-only methods [24].

The Primary Tube Versus Trabeculectomy Study (PTVT) demonstrated a higher surgical success rate for trabeculectomy with MMC compared with tube shunt implantation in patients with medically uncontrolled glaucoma and no previous incisional ocular surgery [25]. Tube shunt surgery had a higher success rate compared with augmented trabeculectomy during five years of follow-

up in the Tube Versus Trabeculectomy (TVT) study [26]. Surgical techniques and different baseline characteristics may partly explain outcome differences between these trials, noted Sheng Lim. The randomised single-centre PEACE trial will evaluate trabeculectomy with MMC versus Baerveldt tube implantation with or without MMC in black African Caribbean or African adults with POAG that is uncontrolled on tolerated medical therapy.

The Treatment of Advanced Glaucoma Study (TAGS), a multicentre randomised controlled trial comparing primary medical treatment with primary trabeculectomy for people with newly diagnosed advanced glaucoma, is expected to report two-year results in 2020 [27]. Anthony King, Nottingham University Hospital, Nottingham, emphasised that subjects with greater visual field loss at presentation face an increased risk of bilateral glaucoma blindness [28]. The TAGS trial will help address current uncertainty between guidelines and ophthalmology practice regarding the best initial treatment option for people with severe glaucoma.

**Back to basics**

W Daniel Stamer, Duke University, USA, reviewed the ocular pharmacology of topical drug administration and future glaucoma therapeutics, including sustained drug delivery systems. Topical application of medication is an inefficient route of administration, the corneal

epithelium being the primary barrier to ocular entry for drops. Dosing frequency depends on lipophilicity of the drug and its ability to depot in relevant tissues. A single bimatoprost sustained release implant (Allergan) has been shown to control IOP up to 16 weeks in 91% of patients and for six months in 71% of patients [29].

Kazuo Tsubota, Keio University School of Medicine, Japan, explained that glaucoma eye drops decrease tearing, resulting in dry eye. A prospective crossover trial in healthy subjects highlighted the negative effects of antiglaucoma medication and its preservatives on the corneal tear film, effects that worsen with increasing drop instillation [30]. Latanoprost showed the most statistically significant reduction in break-up time, and brimonidine showed the most significant reduction in basal secretion of all the glaucoma medications used in this study [30]. Although the precise mechanism of reduced tearing is not clear yet, a neuronal approach may reveal the real mechanism of lowering tear production by topical glaucoma medications.

The global market withdrawal of the CyPass micro-stent over concerns of endothelial cell loss has highlighted broader considerations with respect to the corneal endothelium and glaucoma surgery. Leon Au, Manchester Royal Eye Hospital, Manchester, explained that pre-existing glaucoma has a significantly higher risk of corneal graft failure. There is evidence that glaucoma patients have a lower corneal endothelial cell count than normal controls [31], which is most likely IOP related. Mr Au stressed the importance of considering the impact of surgery on the cornea. Tube drainage implantation is associated with endothelial cell density loss of between 11.5% and 18.6% [32,33].

Martin Watson also emphasised considerations with respect to the epithelium, encouraging glaucoma specialists to minimise drops and minimise preservative use. Endothelial risk should also be considered when planning glaucoma surgery.

W Daniel Stamer reviewed the acute transient effects of intravitreal anti-VEGF injection therapy on IOP [34]. Approximately ~6% of non-POAG/OHT patients receiving repeated anti-VEGF injections will develop sustained ocular hypertension, with OHT patients being particularly susceptible to sustained IOP elevation (>6-8mmHg) after anti-VEGF injections [35]. Brad Fortune, Devers Eye Institute, USA, explained that glaucoma exerts a mechanical impact on the retina and proposed a role for optic nerve head deformation. Manifestations include paravascular inner retinal defects / paravascular defects, peripapillary retinoschisis and inner nuclear layer pseudocysts. Peripapillary retinoschisis is associated with existing RNFL defects and faster progression, while inner nuclear layer pseudocysts are associated with moderate to severe loss and rapid progression.



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