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International Glaucoma Review

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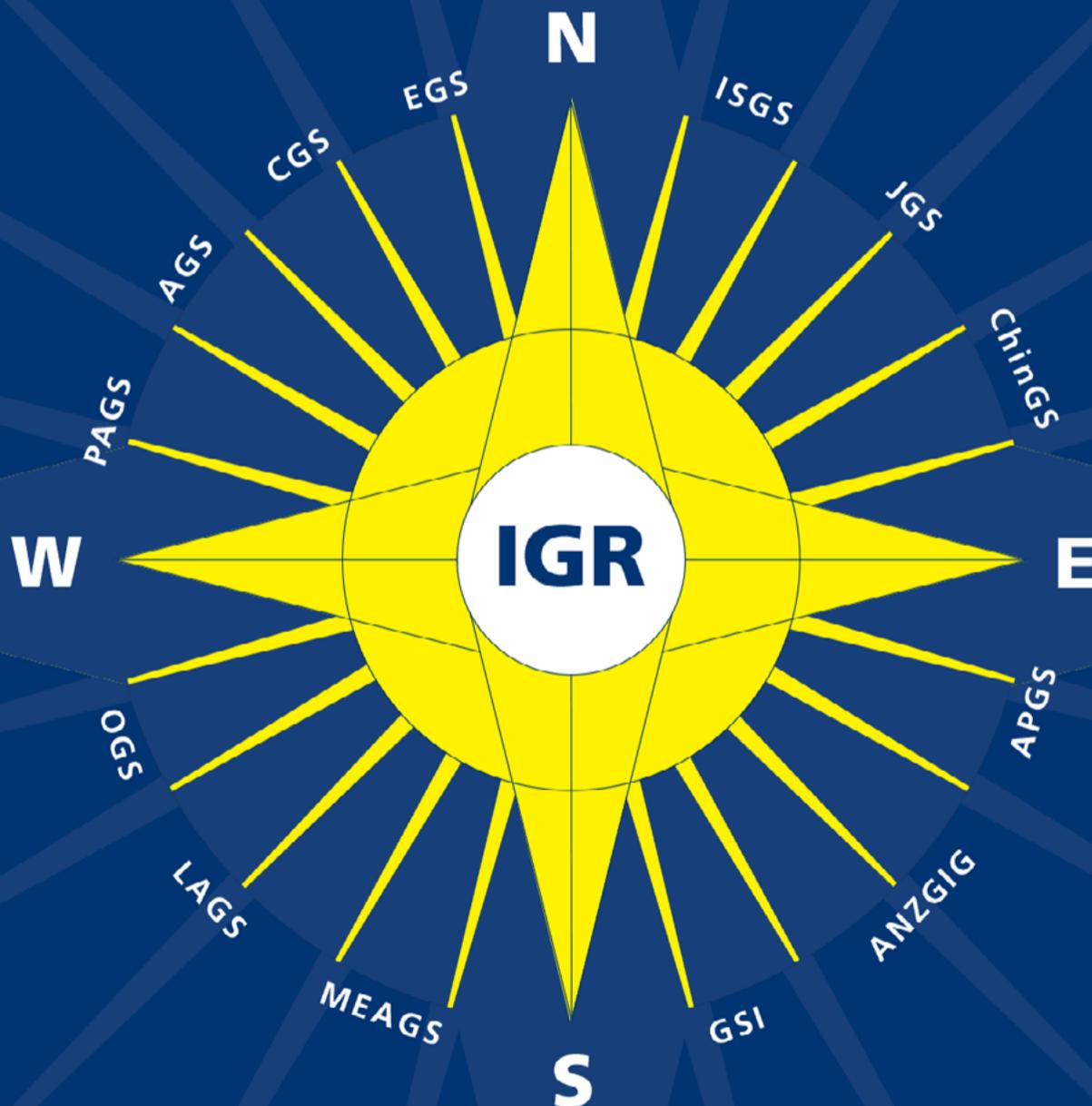
The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

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The Global Glaucoma Network
The Journal of the World Glaucoma Association

INTERNATIONAL GLAUCOMA REVIEW

A Quarterly Journal

Volume 17 no. 2



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From the WGA Executive Office

We wish to thank everyone who helped to make the World Glaucoma Week 2016 a true success. This global awareness event always is a major undertaking for the WGA and it would have not happened without our strong support base throughout the world. Every act, regardless of its size, brings us a step closer to our core vision: **creating awareness about glaucoma and mobilizing people to take a stand against this eye disorder by getting their eyes checked!**

With that being said, the WGA welcomes everyone to participate in next year's World Glaucoma Week **#WGW2017**, March 12–18, 2017. So please keep an eye out!

In addition, I want to take the opportunity to thank our loyal advertisers. It is clear that the uniqueness of the **International Glaucoma Review** is acknowledged by the glaucoma industry members.

In sight of the release of **IGR 17-3**, I am pleased to announce that this issue will be circulated right before the start of the European Glaucoma Congress 2016 in Prague, upcoming June. This special edition will include some extra material which will make a stop at our WGA booth in Prague worth your while!

More closely to date, the 10th Consensus Meeting on Diagnosis of Primary Open-Angle Glaucoma will be held on April 30, 2016 (preceding ARVO Seattle) with as WGA Consensus Initiative Chair: Professor Robert N. Weinreb, MD.

The program will entail the following sessions and co-leaders:

- | | |
|--------------------------------------|---|
| 1. Structure | Chris Leung, Linda Zangwill, Tae-Woo Kim |
| 2. Function | Ted Garway-Heath, Gustavo De Moraes, Aiko Iwase |
| 3. Structure/Function | Felipe Medeiros, Gustavo De Moraes, Ki Ho Park |
| 4. Risk Assessment (Ocular) | Felipe Medeiros, Jamie Brandt, Mingguang He |
| 5. Risk Assessment (Systemic) | Jeffrey Liebmann, Janey Wiggs, Fotis Topouzis |
| 6. Screening | Jeffrey Liebmann, David Friedman, Jost Jonas, Tanuj Dada |

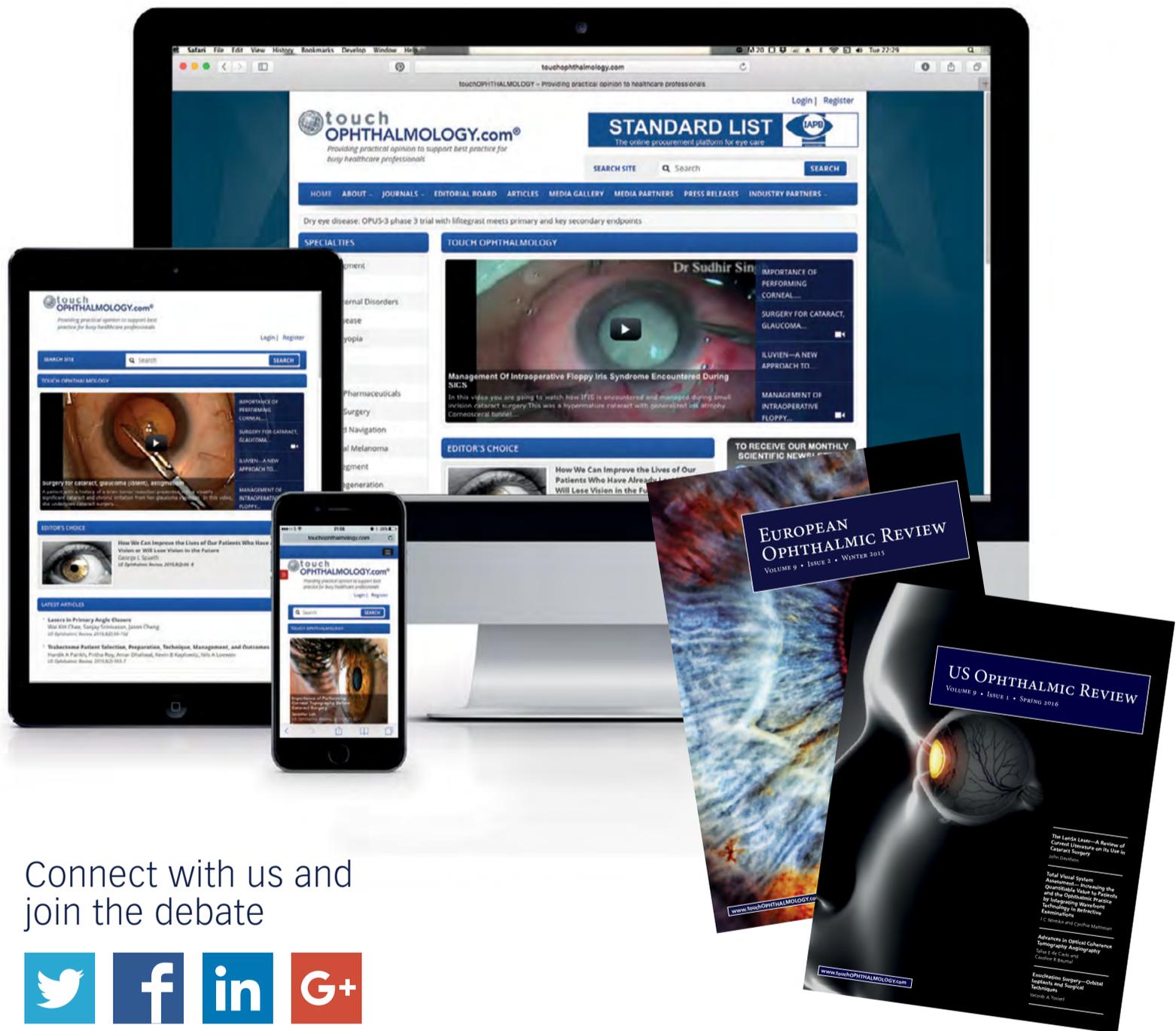
The program can be found via the WGA website: www.worldglaucoma.org/consensus-10. If you are interested in attending the Consensus meeting as an observer, please send an email to the WGA Executive Office: info@worldglaucoma.org.

Please enjoy this IGR and let me know your thoughts regarding our efforts in this and all WGA initiatives. You can reach me at (fechtner@worldglaucoma.com). You can also contact our WGA Executive Office (info@worldglaucoma.org) if you need any information or have questions on IGR or WGA related matters. I look forward to hearing from you.



Professor Dr. Robert D. Fechtner, Executive Vice President

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Neuroprotective therapies in glaucoma: I. Neurotrophic factor delivery

Nafissi N, Foldvari M

(abstract no. 64918)

Wiley Interdisciplinary Reviews Nanomedicine and Nanobiotechnology 2016;8(2):240-254

The Function of Matricellular Proteins in the Lamina Cribrosa and Trabecular Meshwork in Glaucoma

Wallace DM, Pokrovskaya O, O'Brien CJ

(abstract no. 65125)

Journal of Ocular Pharmacology and Therapeutics 2015;31:386-395

Uveitis and glaucoma: new insights in the pathogenesis and treatment

Sng CC, Ang M, Barton K

(abstract no. 65230)

Progress in Brain Research 2015;221:243-269

Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential

Feng Y, LoGrasso PV, Defert O, Li R

(abstract no. 65599)

Journal of Medicinal Chemistry 2016;59(6):2269-2300

Ocular Perfusion Pressure vs Estimated Trans-Lamina Cribrosa Pressure Difference in Glaucoma: The Central India Eye and Medical Study (An American Ophthalmological Society Thesis)

Jonas JB, Wang N, Nangia V

(abstract no. 65707)

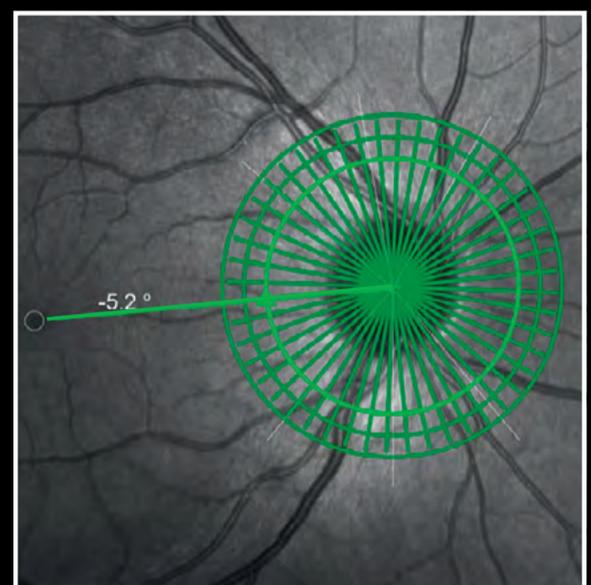
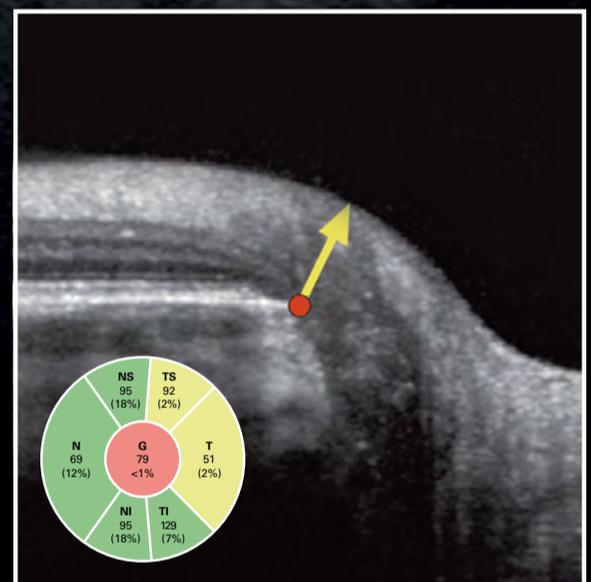
Transactions of the American Ophthalmological Society 2015;113:T61-T613

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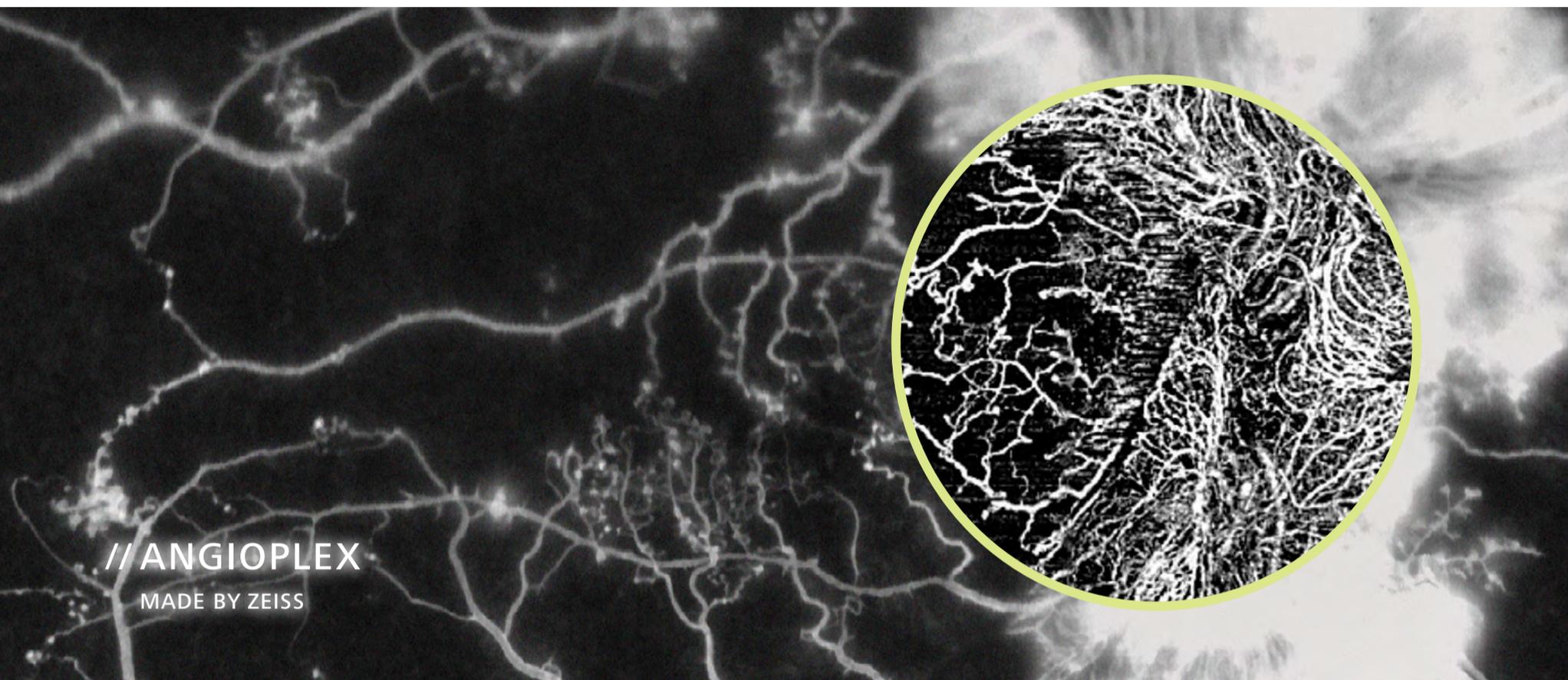
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Meeting Highlights

Top-Five of the annual Belgian Glaucoma Society Session

The National Ophthalmological Congress, Brussels, Belgium, January 16, 2016



Sayeh Pourjavan, Cliniques Universitaires St. Luc, Brussels, Belgium

This session included, lectures given by an invited speaker and the board members and challenging cases in glaucoma treatment and surgery.

1. Combined phaco-trabeculectomy versus phacoemulsification alone for angle-closure glaucoma

We reviewed RCTs comparing phacoemulsification with combined phaco-trabeculectomy. Compared to phacoemulsification alone, phaco-trabeculectomy offered only a small additional IOP reduction (mean=1.5 mmHg) and additional reduction of the number of glaucoma medications (mean=1). However, phaco-trabeculectomy was associated with significantly more post-operative complications. Phacoemulsification alone is probably the best first option in patients with medically controlled and uncontrolled angle-closure glaucoma. RCTs are needed to compare phacoemulsification alone with combined phaco-MIGS (minimally invasive glaucoma surgery). (Thierry Zeyen, Leuven, Belgium (President of BGS))

2. Translaminar pressure gradient. Is it relevant for NTG? And is it accurate?

Translaminar pressure (TLP) has recently gained interest in the study of normal tension glaucoma. Applying physics however reveals major flaws in this concept. In fact neither the force nor the area under the force is known for a calculation of TLP. The concept needs to be improved. A recent study on 37 Caucasians did not confirm a connection of TLP to glaucomatous field defects. (Hanspeter E. Killer, Aarau, Switzerland)

3. Preservative free drops: treatment or prevention of ocular surface disease (OSD)?

In two studies we demonstrated that BAK induces low grade chronic inflammation not only on the ocular surface but also in the anterior chamber of the eye. Recent findings implicate Thelper 17 memory cells in the vicious cycle of inflammation and OSD. Therefore, preservative free medication should be used from the start in our glaucoma patients, as prevention is better than treatment. (Annemie Stevens, Ghent, Belgium)

4. New glaucoma drugs and devices in the pipeline

The future looks bright for the treatment of glaucoma. There are many promising drugs in clinical trials, such as ROCK-inhibitors, endothelin antagonists, adenosine agonists, cannabinoids, latrunculins, angiotensin blockers, and possibly even neuroprotective agents. We also discussed new mechanisms of drug delivery, such as Helios insert, drug-eluting punctal plugs, Durasert and other injectables. (Kathy Hodeghem, Antwerp, Belgium)

5. Can elderly patients with early glaucoma be followed initially without treatment?

According to the Guidelines of the European Glaucoma Society, the goal of glaucoma treatment is to maintain the patient's visual function and related quality of life, at a sustainable cost. Therefore, when considering treatment in a glaucoma patient, the benefit and risks of treatment should be weighed against the risk of significant visual loss during the patient's life span. In some elderly patients with early glaucoma, an initial follow-up without treatment may be warranted. (Ingeborg Stalmans, Leuven, Belgium)

Top-Five of the 25th American Glaucoma Society Meeting

Fort Lauderdale, Florida, USA, March 3–6, 2016



Christopher A. Girkin and Steven J. Gedde

An Ab-Interno Gelatin Stent for the Treatment of Primary Open-Angle Glaucoma: Three-Year Follow-up

A prospective, multicenter study investigated ab-interno implantation of a transscleral gelatin stent (Xen implant) for patients with medically uncontrolled primary open-angle glaucoma. Mean IOP decreased from 22.7 mmHg to 13.5 mmHg at 36 months, and the mean number of ocular hypotensive medications was reduced from 2.8 medications to 0.8 medication. (Rohit Varma, Los Angeles, CA, USA)

A Novel Bayesian Retinal Nerve Fiber Layer Thickness Deviation Map Improves Glaucoma Diagnosis

A prospective cross-sectional study evaluated a novel Bayesian deviation map, which uses information from both healthy and glaucomatous eyes to generate topographic maps and estimate the probability that a specific location shows RNFL damage. The Bayesian deviation map trained on both glaucoma and healthy eyes had a ROC curve area of 0.95, which was significantly higher than those of average peripapillary RNFL thickness and the standard deviation map ($p < 0.05$ for all comparisons). (Felipe A. Medeiros, La Jolla, CA, USA)

Postoperative Complications in the Ahmed Baerveldt Comparison Study during Five Years of Follow-up

The Ahmed Baerveldt Comparison (ABC) Study is a multicenter randomized clinical trial comparing the safety and efficacy of the Ahmed glaucoma valve and Baerveldt glaucoma implant. The cumulative rates of late complications were similar after placement of an Ahmed valve (46.8%) and Baerveldt implant (56.3%) during five years of follow-up ($p = 0.082$). Serious complications associated with vision loss or reoperation developed more frequently after Baerveldt implantation (24.7%) than Ahmed implantation (15.9%) ($p = 0.037$). (Donald L. Budenz, Chapel Hill, NC, USA)

A Comparison of Outcomes of Laser Trabeculoplasty Surgery Performed by Optometrists versus Ophthalmologists in the State of Oklahoma

Health care claims data were used to compare the outcomes of laser trabeculoplasty performed by optometrists and ophthalmologists in Oklahoma. The proportion of eyes requiring subsequent laser trabeculoplasty was significantly higher when the initial treatment was done by an optometrist (35.0%) rather than an ophthalmologist (14.9%) ($p < 0.0001$). (Joshua D. Stein, Ann Arbor, MI, USA)

PhS-OCT Imaging of Synchronous Trabecular Meshwork and Collector Channel Entrance Motion in Vivo in Human Subjects

A laboratory prototype spectral domain, phase-sensitive OCT system was used to image and quantitate pulse-dependent aqueous system outflow system motion in five human subjects. A new algorithm was used to remove background in-vivo tissue motion and enhance motion detection of the trabecular meshwork and collector channel entrance providing high-resolution images. (Murray J. Johnstone, Seattle, WA, USA)



ANZGIG Auckland 2016 Top-Five

The 2016 Annual Scientific Meeting of the Australia and New Zealand Glaucoma Interest Group, Auckland, New Zealand, 12–13 February, 2016



Anne M.V. Brooks, Chair, ANZGIG

1. A Tale of Two Cities: The City of Physicians and the City of Patients

This presentation reminds us that the worlds in which patients and physicians live are as different as the City of Man and the City of God – the cities dominating the Middle Ages. Physicians think in terms of readily accessible quantifiable data, such as – for glaucoma specialists – intraocular pressure (IOP) and dB of field loss. But patients are persons whose world focuses on how they feel and how they function. “Feeling” is best assessed by careful history. The quantitative surveys, such as NEI-VFQ-25, actually contribute little to the clinical examination. Function is best evaluated by direct assessments, such as reading speed or comprehensive tests such as ADREV or CAARV. Visual acuity and Visual Field are but surrogates, even for function, and are only roughly predictive. Surrogates for disease, such as IOP and age are even more distant and are not indicators that relate well to what is important to patients.

In order to enter into the City of Patients, physicians must listen to the patients attentively, knowledgeably and with empathy. (George Spaeth, Philadelphia, USA)

2. New Associations of an Old Flame: The Role of Inflammation in the Optic Nerve and Retina

Helen concluded that inflammation is a universal response to injury. Gap junction proteins are integral for cell to cell communication in the response to injury. Connexin 43 both on astrocytes and blood vessels are involved in this response to injury and have been shown to be unregulated both in the retina and optic nerve following retinal ischemia, partial transection, and glaucoma. Blocking of hemichannels with Cx 43 blockers shows neuroprotection in acute injury models. (Helen Danesh-Meyer, Auckland, New Zealand)

3. Axon initial segment (AIS) plasticity of RGCs following an acute IOP injury

Clinical and pre-clinical studies have demonstrated that RGCs are capable of functional recovery following a prolonged period of dysfunction. In a highly reproducible injury model, RGC function and excitability is impaired at a week following an acute IOP injury in 12-month-old C57BL/6 mice but recovers by one month following injury. No loss of function or excitability is seen in 3-month-old mice. In this study, the authors demonstrate an age-related reversible loss of length of the axon initial segment of RGCs correlated to the reversible loss of RGC function and excitability in this model. This finding may suggest a role for AIS plasticity in the injury and recovery of retinal ganglion cells, and that this process is impacted by age. (Lewis Fry, Melbourne, with Jonathan Crowston and colleagues)

4. The Visual Function Questionnaire-Utility Index: does it measure glaucoma-related preference-based status?

As health budgets tighten globally, evaluating the cost-effectiveness of glaucoma services is vital; however, there is a lack of validated instruments that measure utility specific to glaucoma patients. The Visual Function Questionnaire–Utility Index (VFQ-UI) shows potential to measure preference-based status in a cohort of glaucoma patients, with the means to calculate utility. To the best of our knowledge, this is the first time that the VFQ-UI has been evaluated in glaucoma patients, which is of significance as it is a vision-related quality of life questionnaire specifically designed to measure utility. Although the VFQ-UI displayed reasonable fit to the Rasch model overall and had reasonable criterion, convergent and divergent validity, its lack of precision is a limitation. The difficulty of the VFQ-UI in discriminating among patients with varying glaucoma severity may be improved by including items specific to glaucomatous visual dysfunction. (Rachel Goh, Melbourne, with Eva Fenwick and Simon Skalicky)

5. Reflections On Complex Surgery

Professor Peter Shah discussed pre-, intra- and post-operative strategies to enhance safety in complex surgery. He focused on anticipating potentially blinding complications, covering: infection, bleeding, wipe-out, decompression retinopathy, hypotony, malignant glaucoma, tissue shortage and uveal effusion. He presented data from the ReGAE project (Research into Glaucoma And Ethnicity) and highlighted methods for increasing patient involvement in care. Throughout the lecture he emphasised the principle of aggregation of marginal gain as a strategy for managing risk. (Peter Shah, Birmingham, UK)

Top-Five of the Spanish Glaucoma Society Meeting Toledo, Spain, March 10–12, 2016



Francisco J. Muñoz-Negrete

1. Evaluation of the RETICS Glaucoma Diagnostic Calculator for Detecting Pre-Perimetric Glaucoma

The RETICS Glaucoma Diagnostic Calculator (RGDC) from Cirrus-OCT demonstrated that RGDC improves glaucoma detection. An analysis was performed in 149 eyes with ocular hypertension. The RGDC showed higher values in PPG than in non-PPG. The AUCs was only 0.66. In cases with PPG and 1-2 red values in the last scan from Cirrus, the AUC increased to 0.88.

(Javier Moreno-Montañés, Pamplona, Spain)

2. Glia-Neuron Interactions in the Mammalian Retina

The glia from the retina, and in particular Müller cells, are the first sensors of damage in glaucoma. Thus, we propose in our paper to pay attention to the glia-neuron interactions to be able to protect the retinal ganglion cells (RGCs) affected by glaucoma. To know the glial surroundings of RGCs is crucial and the neuroprotective treatment could depend on that. (Elena Vecino, Bilbao, Spain)

3. Lamina Cribrosa and Optic Disc Head in Primary Open-Angle Glaucoma

We evaluated factors associated with morphological characteristics of the optic nerve head and lamina cribrosa in 60 primary open-angle glaucomas. Older age, thinner retinal nerve fiber layer, thinner ganglion cell-inner plexiform layer and worse visual field status were significantly correlated with thinner prelaminar tissue thickness, demonstrating that both lamina cribrosa and prelaminar tissue are involved in the physiopathology of glaucoma. (Laura Díez-Álvarez, Madrid, Spain)

4. Contrast Sensitivity And The Impact Of Glaucoma In Quality Of Vision

The aim of this transversal study was to evaluate the relationship between contrast sensitivity tests, which assess visual quality (Pelli-Robson and CSV1000), and perimetric glaucoma severity (mild, moderate, severe), in 140 eyes. The mild glaucoma group showed better visual quality, with statistically better results in Pelli-Robson and CSV1000 under lighting conditions photopic, and mesopic+glare+filter (except highest frequencies: 12-18 cycles/degree). (Noemí Güerri, Zaragoza, Spain)

5. Corneal Hysteresis and Central Corneal Thickness in Patients with Congenital Glaucoma and Health Controls

ORA and Pentacam were used in 66 childhood glaucoma patients and 94 age-matched controls to perform a multivariate binary logistic model to discriminate between both groups. The best model presents a sensitivity of 86.67%, a specificity of 86.89%, an AUC of 93.16%, and as predictors: hysteresis, corneal resistance factor, posterior and anterior maximum elevations, and central corneal thickness. (Lucía Perucho González, Madrid, Spain)

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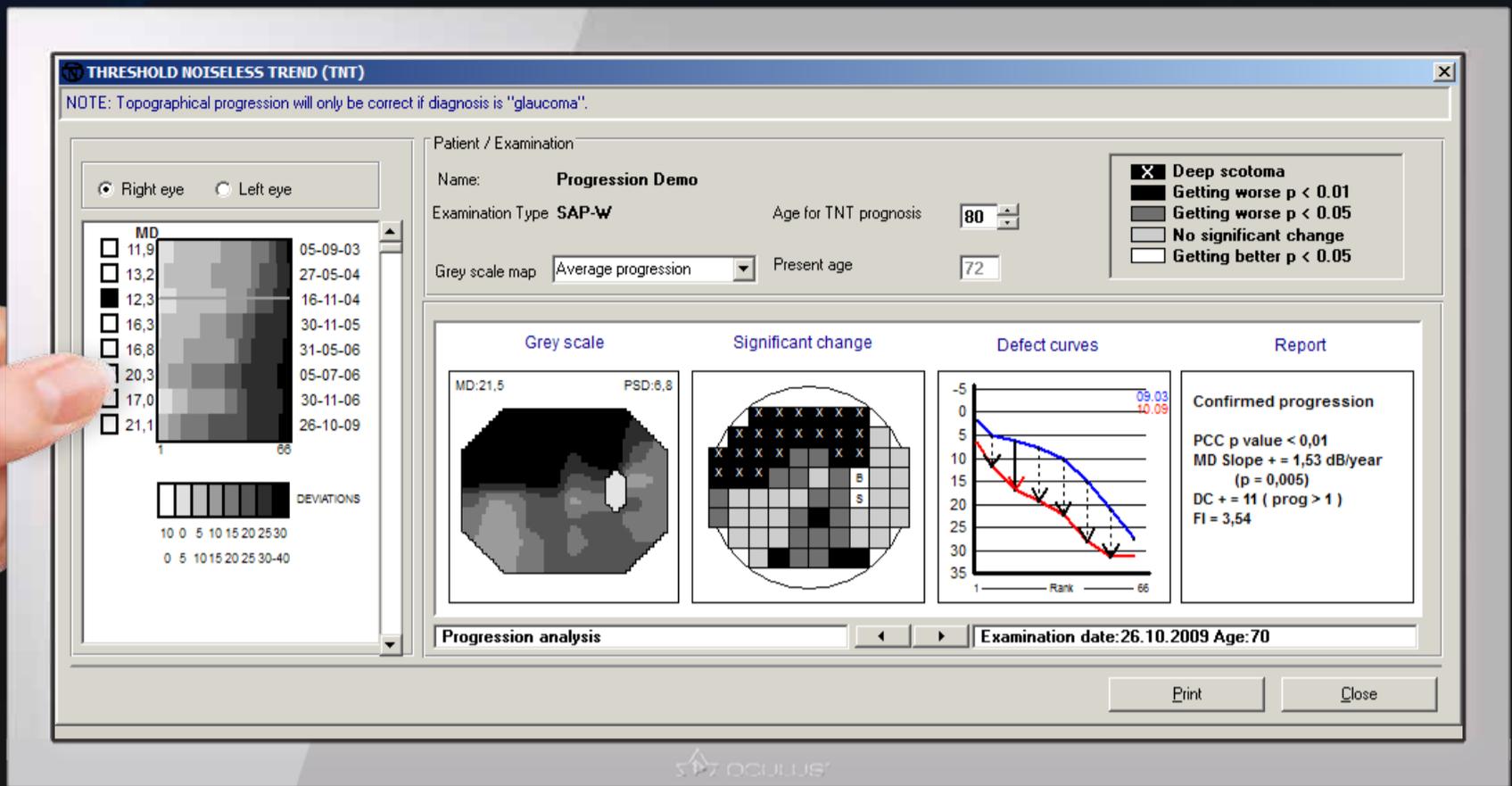
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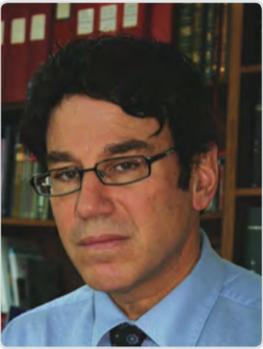


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Editor's Selection

With the multitude and variety of publications it seems almost impossible for the ophthalmologist to intelligently read all the relevant subspecialty literature. Even the dedicated glaucomatologist may have difficulty to absorb 1200+ yearly publications concerning his/her favorite subject. An approach to this confusing situation may be a critical selection and review of the world literature.



Robert N. Weinreb, Chief Editor

Anatomical Structures

Optic disc



Comment by **Andrew Tatham**, Edinburgh, UK

65418 Structural characteristics of the acquired optic disc pit and the rate of progressive retinal nerve fiber layer thinning in primary open-angle glaucoma, Lee SH, Lee EJ, Kim TW, JAMA ophthalmology 2015;133:1151-1158

Acquired optic disc pits (ODPs) are localized defects of the lamina cribrosa (LC), which may be a manifestation of, or perhaps, contribute to, glaucomatous structural change. Although recognized as an important clinical sign, there is poor understanding of the relationship between ODPs and glaucomatous neural loss.

This longitudinal study sought to examine rates of change in retinal nerve fiber layer (RNFL) over time in eyes with and without ODPs.

One hundred sixty-three glaucomatous eyes were included, comprising 83 eyes with ODPs and 80 without, followed for an average of just over three years. There were strict criteria for identification of ODPs, which were required to be visible on baseline stereoscopic disc photographs and confirmed at the final visit by the presence of an alteration of the LC at the corresponding

location on swept source OCT. Only ODPs involving the temporal LC were included due to the difficulty of imaging the nasal LC. Eyes in the non-ODP group were required to have no focal abnormality of the LC on OCT as this may represent a 'microscopic ODP'.

Eyes with ODPs experienced faster rates of RNFL loss, with comparatively faster rates in regions corresponding to the location of the ODP. The average rate of RNFL loss in eyes with ODPs was $0.51 \mu\text{m}$ per year faster than in eyes without an ODP (-1.44 versus $-0.93 \mu\text{m}$ per year, $P = 0.008$). This result suggests that detection of ODPs may help better predict the rate and location of future structural change.

Interestingly, RNFL loss also appeared to be faster in eyes with partial thickness compared to full thickness LC defects. It was proposed that retinal ganglion cell axons in eyes with partial thickness defects might be subject to greater mechanical stress and strain due to a steeper translaminal pressure gradient, whereas the pressure gradient may be decreased where LC is nonexistent.

Lamina cribrosa



Comment by **Marcello Nicolela**, Halifax, Nova Scotia, Canada

65772 Lamina cribrosa depth variation measured by spectral-domain optical coherence tomography within and between four glaucomatous optic disc phenotypes, Sawada Y, Hangai M, Murata K, Ishikawa M, Yoshitomi T, Investigative Ophthalmology and Visual Science 2015;56:5777-5784

Several previous studies have uncovered clinical, demographical and functional characteristics associated with different optic disc phenotypes seen in glaucoma (particularly focal, generalized enlargement, myopic and senile sclerotic optic disc appearances), although with some conflicting results from different groups.

In this manuscript, Sawada *et al.* reported data on mean and maximal lamina cribrosa (LC) depth in eyes from normal controls and from individuals with glaucoma, further sub-classified according to their optic disc phenotypes. The authors expanded on the body of knowledge related to optic disc phenotypes by showing that the LC depth differs between the groups: eyes with generalized enlargement of the cup had greater mean and maximal LC depths and eyes with senile sclerotic appearance had smallest LC depths, not different than controls. Eyes with focal and myopic appearances had intermediate LC depths.

These results suggest that the mechanisms of glaucomatous damage in these different optic disc phenotypes might vary, with the typical posterior displacement of the LC that is thought to occur in glaucoma, being absent in eyes with senile sclerotic appearance. Unfortunately, in the current study, the authors could not offer a more detailed analysis of the LC in these eyes,

particularly related to LC thickness, presence and location of LC focal defects and longitudinal changes in the LC position and structure. With the advancement on OCT imaging of deeper structures within the optic nerve head, our ability to study in greater detail the LC in glaucoma might help us further understand the mechanisms associated with the development of glaucomatous optic neuropathy in these different optic disc phenotypes.



Comment by **Linda Zangwill** and **Min Hee Suh**, La Jolla, CA, USA

65369 Defects of the lamina cribrosa in high myopia and glaucoma, Miki A, Ikuno Y, Asai T, Usui S, Nishida K, PLoS ONE 2015;10:e0137909

Focal LC defect is known to be an important biomarker in the development and progression of the glaucomatous optic neuropathy. Recent studies reported that structural changes of the optic nerve head (ONH) such as neuroretinal rim loss and retinal nerve fiber layer defect were related with the focal LC defect. However, little is known about the correlation between the myopic morphologic changes of the ONH and the LC defect. Miki *et al.* assessed the prevalence and characteristics of the focal LC defects in four subgroups; high myopic eyes with (67 eyes) and without open-angle glaucoma (OAG) (35 eyes), non-myopic eyes with OAG (22 eyes), and healthy normal non-myopic eyes (35 eyes). This study is in line with previous studies that LC defects were commonly found in glaucomatous eyes. Moreover, prevalence of LC defect was significantly higher in myopic eyes without OAG (8/35, 22.9 %) than non-myopic healthy eyes (1/35, 0.03 %) ($P = 0.0304$). These findings suggest that alternation of the biomechanical environments induced by myopia may be related with the development of focal LC damage. However, it is still unclear whether focal LC defect associated with myopia would be pathologically related to the glaucomatous damage. In this study, myopia-related morphologic factors such as axial length, β -zone parapapillary atrophy, ovality index, or disc area were not significantly different between eyes with and without LC defects. This study is also limited by the cross-sectional nature of the study design and small sample size. Further longitudinal studies are warranted to elucidate whether LC defects detected in the high myopic eyes would play a causative role in the development and progression of the glaucomatous optic neuropathy.

Basic Science

Neuroprotection



Comment by **Makoto Araie**, Tokyo, Japan

65574 Losartan treatment protects retinal ganglion cells and alters scleral remodeling in experimental glaucoma, Quigley HA, Pitha IF, Welsbie DS, Nguyen C, Steinhart MR, Nguyen TD, Pease ME, Oglesby EN, Berlinicke CA, Mitchell KL, Kim J, Jefferys JJ, Kimball EC, PLoS ONE 2015;10:e0141137

Many previous studies have reported that pharmacological agents could demonstrate in vivo neuroprotective effects by directly exerting their pharmacological actions onto the retinal ganglion cell (RGC) bodies or their axons. Using a mice experimental glaucoma model, Quigley and his associates reported that systemic administration of a selective angiotensin 1 receptor (AT1R) inhibitor, losartan, demonstrated neuroprotective effects on RGCs not through its direct pharmacological actions on RGCs, but through modification of glaucoma-related changes in peripapillary sclera (PPS).

According to engineering models, PPS behavior is important in determining the effect of intraocular pressure (IOP) on the optic nerve head (ONH), and it has been known that biomechanical characteristics of PPS are substantially altered in human glaucoma eyes and experimental glaucoma eyes.¹⁻³ Among the drugs tested including enalapril, an ACE inhibitor (ATR1- and ATR2-inhibiting actions), only systemic losartan showed pressure-independent neuroprotective effects in the mice experimental glaucoma model. Results of supplementary experiments suggested that the observed effects of losartan were not attributable to losartan's direct pharmacological actions on RGCs, whereas morphological and biomechanical studies of PPS indicated that the losartan-pretreated mice with normal IOP had PPS's features similar to those in non-losartan-treated mice after induction of experimental glaucoma, and showed little further changes after exposure to high IOP. Losartan-treatment altered biomechanical responses of PPS so that it maintained its creep rate in the normal range. A molecular biological finding which might be related to the above mentioned losartan's effects on PPA was that losartan inhibited TGF- β -mediated activation of pERK and modified extracellular matrix remodeling, leaving signaling through ATR2 little affected.

Glaucomatous damage of RGC axons are at least partly mediated through alteration of PPS including lamina cribrosa (LC). Although the current losartan-induced effects on PPS and RGCs in mice experimental glaucoma model need to be further confirmed in other species, especially non-human primates, the result reported by the authors suggest a possibility of medical treatment of PPS including LC to ameliorate glaucoma-induced damage of RGCs. Several previous studies suggested that topically instilled drugs may reach posterior retina at pharmacologically

active concentrations by local diffusion,^{4,5} but it should be much easier for a topically administered drug to reach PPS, since it is directly exposed to retrobulbar space.⁶ Further, PPS has no blood-retinal barrier which limits penetration of systemically administered drugs to RGCs. If PPS could be pharmacologically modified so that it is more resistant to further biomechanical changes caused by glaucomatous mechanical stress, beneficial effects on axons which pass through it would be also expected.

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Mitochondrial function



Comment by **Miriam Kolko**, Copenhagen, Denmark

65591 Measurement of systemic mitochondrial function in advanced primary open-angle glaucoma and leber hereditary optic neuropathy, Van Bergen NJ, Crowston JG, Craig JE, Burdon KP, Kearns LS, Sharma S, Hewitt AW, Mackey DA, Trounce IA, *PLoS ONE* 2015;10:e0140919

Recent evidence exists on reduced mitochondrial capacity in patients with primary open-angle glaucoma (POAG). In particular, attention has been directed towards impaired complex-I enzyme activity as a potential target to prevent glaucomatous damage. The present study compares complex-1 enzyme activity in lymphoblasts from POAG patients and patients suffering from Leber hereditary optic neuropathy (LHON). While Complex-1 enzyme activity is reduced by 29

% in LHON patients, the same activity in lymphoblasts from patients with POAG is decreased by 18 %. In addition to enzyme activity, the authors demonstrate impaired complex-1 and II ATP synthesis as well as reduced proliferation in lymphoblasts from patients with POAG when grown in galactose media, a condition that forces cells to rely on mitochondrial oxidative phosphorylation. All over, the results strengthen the evidence of reduced mitochondrial capacity as a causative factor for POAG. A limitation of the study is the restricted uniformity of the included subjects. In this matter, it is known that smoking affects mitochondrial function. Furthermore, it is highly probable that mitochondrial implications vary among subjects with low-tension glaucoma compared to patients with high-tension glaucoma. Future studies would benefit from a lesser degree of heterogeneity, which will increase the likelihood of an even more evident involvement of mitochondrial dysfunction in the pathogenesis of POAG. Nevertheless, the authors present very important evidence of impaired mitochondrial respiration in POAG patients. The results are extremely interesting and opens up for new strategies to understand, treat and prevent glaucoma.

Stem cells



Comment by **Keith Martin**, Cambridge, UK

65351 Intraocular pressure reduction and neuroprotection conferred by bone marrow-derived mesenchymal stem cells in an animal model of glaucoma, Roubéix C, Godefroy D, Mias C, Sapienza A, Riancho L, Degardin J, Fradot V, Ivkovic I, Picaud S, Sennlaub F, Denoyer A, Rostene W, Sahel JA, Parsadaniantz SM, Brignole-Baudouin F, Baudouin C, *Stem Cell Research & Therapy* 2015;6:177

The therapeutic potential of bone marrow-derived mesenchymal stem cells (MSCs) is being investigated in many different diseases across the whole of medicine. Intravitreally delivered MSCs have previously been shown to protect against retinal ganglion cell (RGC) loss in rats with trabecular laser induced ocular hypertension. Intracamerally delivered MSC have also been shown to lower IOP in mice, again with trabecular laser induced IOP elevation.

In the current study, Roubéix and co-workers administered MSC intracamerally to mice with IOP elevation induced by episcleral vein cautery. They reported IOP lowering after three days in the MSC group, but not control groups which sensibly included dead MSC controls. Interestingly, they also demonstrated that the medium in which MSC were cultured contained soluble factors that could aid the survival and contractility of cultured trabecular meshwork cells.

Perhaps a surprising finding was that intracamerally delivered MSC administered as late as 20 days after IOP elevation seemed to protect peripheral (not central) RGC from degeneration when assessed 25 days after injection. It would be unusual for a neuroprotective therapy to be effective so late after IOP elevation in a glaucoma model and so the authors' suggestion that the effect could be mediated by IOP lowering appears more likely.

Despite some reservations with regard to the episcleral vein cauterization model of ocular hypertension which has some potential issues with ischemia, although of course all current glaucoma models have their own flaws, this is nevertheless a valuable and interesting study which adds further support to the potential use of MSC as a possible future treatment for glaucoma.

Proteomics



Comment by **Derek Welsbie**, Baltimore, MD, USA

65753 Proteomics analysis of molecular risk factors in the ocular hypertensive human retina, Yang X, Hondur G, Li M, Cai J, Klein JB, Kuehn MH, Tezel G, *Investigative Ophthalmology and Visual Science* 2015;56:5816-5830

Rodent models of ocular hypertension have been useful in elucidating the molecular pathways responsible for retinal ganglion cell (RGC) axon degeneration and cell death. In most cases, however, the relevance of these studies to human pathophysiology has yet to be determined. Moreover, the nature of the *initial* injury to RGC axons is even less clearly understood. Thus, in order to gain insight into the mechanism by which elevated intraocular pressure injures human RGCs, Yang *et al.* used a proteomic approach and compared six retinas isolated from patients with longstanding ocular hypertension (without any evidence of glaucomatous optic neuropathy) to six retinas isolated from normotensive age- and gender-matched controls. Protein was extracted from each of the matched retinas, differentially labeled with either ^{16}O (normal oxygen) or ^{18}O (heavy oxygen), and then each pair was analyzed by liquid chromatography mass spectrometry (LC-MS). Six pairwise comparisons were then made, looking for proteins whose expression consistently changed in the setting of ocular hypertension.

The results showed that certain signaling pathways had a clear overrepresentation of protein level changes, including including those that regulate elongation initiation factor 2 (eIF2), eIF4, mammalian target of rapamycin (mTOR), clathrin-mediated endocytosis, protein ubiquitination and mitochondrial function. Somewhat less significant associations were found with mitogen-activated protein kinases and proteins that mediate signaling in response to endoplasmic reticulum (ER) stress, calcium overload, oxidative stress and endothelin-1, all of which have been shown to play a role in RGC injury in rodents.

While it is important to avoid over-interpreting the results, there does seem to be a suggestion that ocular hypertension causes a mismatch in energy supply and demand. Since the retinas were obtained from patients without obvious RGC loss, future studies will almost certainly examine how the spectrum of changes would differ if active RGC loss were occurring.

Clinical Examination Methods

RNFL and macular damage



Comment by **Don Budenz**, Chapel Hill, NC, USA

65487 Central glaucomatous damage of the macula can be overlooked by conventional OCT retinal nerve fiber layer thickness analyses, Wang DL, Raza AS, de Moraes CG, Chen M, Alhadeff P, Jarukatsetphorn R, Ritch R, Hood DC, *Translational Vision Science & Technology* 2015;4:4

In the article by Wang *et al.*, the investigators performed 10-2 visual fields, RNFL, and macular OCT scans on 143 eyes of 143 glaucoma patients or suspects. All subjects had mild visual field loss by 24-2 MD better than -6 dB. They found that of the 61 eyes had abnormal macular and 10-2 visual fields, 77% showed no abnormality on RNFL scans. In 41 eyes, the macular OCT and 10-2 visual field did not agree. The authors state that the research supports performing macular OCT scans and/or 10-2 visual fields to detect macular abnormalities since these may be missed on conventional 24-2 and optic disc cube scans. The conclusions are supported by the data and this adds to the mounting evidence that we are missing detection of defects in the RNFL and visual field near fixation, where defects may have more of an effect on function. This is an important finding since clinicians are not routinely testing near the fovea and, when defects are not found more peripherally, testing should be done centrally using these two techniques. Otherwise, the diagnosis or severe nature of the glaucoma damage may be missed. So, the take home message is that, if the clinician is evaluating a patient for glaucoma and suspects that peripheral testing using visual fields and OCT do not reveal defects or one or the other alone is seeing a defect, it may be beneficial to test the central area with these tests and even follow them for progression once detected.

Perimetry



Comment by **Donald Hood**, New York, USA

65611 Clinical clues to predict the presence of parafoveal scotoma on Humphrey 10-2 visual field using a Humphrey 24-2 visual field, Park HL, Hwang BE, Shin HY, Park CK, *American Journal of Ophthalmology* 2016;161:150-159

Park *et al.* address an important clinical question: When should the clinician perform a 10-2 visual field (VF) test? As they point out, this question is timely as recent evidence suggests that macular damage occurs in early glaucoma.^{1,2} Further, this damage can be missed by the 24-2 VF test.¹⁻⁴ To determine possible predictors of an abnormal 10-2 VF, they examined the abnormal points on the pattern standard deviation (PSD) plot of the 24-2 VF report. All eyes in their study had an abnormal appearing disc, and a 24-2 VF with a MD better than -6 dB. An abnormal 10-2 was defined based upon cluster criteria. It is worth noting that 74.7% of the eyes had abnormal 10-2 VFs, suggesting that macular damage was common in these eyes with early glaucoma.¹⁻³

Park *et al.* concluded that a 10-2 test should be performed if any of the central 12 points of the 24-2 VF (*i.e.*, those within $\pm 10^\circ$) are abnormal with a $p < 0.5\%$, or with a $p < 5\%$ if located in an abnormal region of the retinal ganglion plus inner plexiform (RGC+) layer thickness map obtained from an OCT macular cube scan.

While their advice concerning 24-2 VF points with $p < 0.5\%$ is supported by their data, it is wedded to the implicit assumption that the 24-2 VF should be the gold standard for functional testing. There are alternatives. Some specialists alternate 24-2 and 10-2 VFs, even in eyes without apparent 10-2 abnormalities. Others have suggested adding some of the 10-2 VF points to the 24-2 pattern.⁵

Further, we agree that comparing RGC+ and VF probability plots can aid in detecting macular damage.⁶ However, local arcuate abnormalities and/or diffuse damage seen on RGC+ maps, and confirmed on 10-2 VFs, can be present in eyes without abnormal points on the 24-2 VF.^{1,2} Thus, as Park *et al.* imply, an OCT macular cube scan should be part of the standard OCT protocol for detecting glaucomatous damage.

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Blood flow



Comment by **Tae-Woo Kim**, Bundang-gu, Seongnam, Korea

65739 Quantitative analysis of fundus-image sequences reveals phase of spontaneous venous pulsations, Moret F, Reiff CM, Lagrèze WA, Bach M, *Translational Vision Science & Technology* 2015;4:3

Spontaneous venous pulsation (SVP) is a rhythmic variation in vein diameter. Recent reports have suggested that it may have relevance with the development of glaucomatous optic neuropathy. However, the etiology of SVP remains to be better understood. To understand the SVP etiology, it is important to know when venous collapses occur within the cardiac cycle. While it has long been considered that the collapse coincides with the systole, recent reports demonstrated that the vein collapses at diastole. Moret *et al.* revisited this issue by observing the SVP in 12 healthy subjects using video recording. Instead of detecting the time frame when the collapse was observed, they measured the diameter of the veins near the optic disc (not within the optic disc), then determined the peaks and the troughs of the diameter. At this location, they did not find collapse of the vein in any eyes. Thus, they examined the wave forms and determined the timing of venous-diameter minima. According to their observation, there was inter-individual variation in the venous wave form: some had venous-diameter minima at systole and others had at the end of diastole. The data reconciles the previous data which reported only one type or the other. There is no clear answer for the discrepancy between the observation in this study and that in previous studies, but one possibility is that they have not measured the venous-diameter minima at the location of venous collapse but a location a bit away from that location. It is likely that the intraluminal pressure dynamics is different from that at the site of collapse. Probably the elasticity of the venous wall differs among individuals, thus the intraluminal pressure dynamics at the site of venous collapse may be transferred to the site examined in the present study in a variable way among individuals. While the study approach was novel and the result was intriguing, it is noteworthy to consider that the wave form measured in this study was not based on the collapse of the vein.

Clinical Forms of Glaucoma

Primary angle closure



Comment by **Shan Lin** and **Marissé Masís**, San Francisco, CA, USA

64938 Anterior segment morphology after acute primary angle closure treatment: a randomised study comparing iridoplasty and medical therapy, Sng CC, Aquino MC, Liao J, Zheng C, Ang M, Chew PT, *British Journal of Ophthalmology* 2015; 0:

In this prospective study, the authors compared the effectiveness of argon laser peripheral iridoplasty (ALPI) versus a fixed protocol of medical treatment in patients with acute primary angle closure (APAC). Each group consisted of 15 subjects randomized to each group. Anterior segment optical coherence tomography (ASOCT) was performed before and one hour after the procedure or after medical treatment. Traditional laser peripheral iridotomy was performed when a clear media was achieved in both groups.

A greater increase in angle width was reported in the group treated with ALPI compared to the medical treatment group. Treatment modality (laser vs medical) and iris curvature were the main predictor factors influencing the anatomical change.

Acute angle closure glaucoma is a multifactorial disease given the dynamic relationship between the fluidics and the anterior segment anatomy of the eye. Several studies have been published regarding the role of ALPI as the first approach to the disease. In 2002, Lam *et al.*¹ published a prospective, randomized, controlled trial in which they found that ALPI is significantly more effective than conventional systemic medications in rapidly reducing IOP levels in APAC, mainly in eyes not suitable for immediate laser peripheral iridotomy within the first two hours from the initiation of treatment.

In 2012, a Cochrane-based review² summarized that there is insufficient evidence to support using iridoplasty as an adjunct to iridotomy in any form of angle closure glaucoma. Furthermore, there is not enough data related to the anterior segment effects of ALPI in APAC eyes with unclear media, a topic that is addressed by the current authors.

An important issue that needs to be taken into account is the fact that among all the anterior chamber parameters measured by ASOCT, lens vault is one of strongest predictors and causative factors for angle closure.³ In these cases a change on the anterior surface of the iris from ALPI may not be beneficial to the patient in the long term.

The presence of peripheral anterior synechiae and the amount of persistent appositional angle closure can also contribute to the long-term failure of ALPI or may determine the need for secondary treatment in a longer follow-up period.

Naravanaswamy *et al.* published in 2016 a study that supported that after a one-year follow-up, ALPI was associated with higher failure rates and lower IOP reduction compared with medical therapy in chronic angle closure.⁴ The clinical benefit of ALPI for APAC is still being determined.

Causal influence should be taken into account when deciding a therapeutic approach. In acute angle closure with no clear media, the treatment options are initially limited. This novel study may lead to further clinical investigations of ALPI as an adjunctive therapy, mainly in patients with systemic contraindications to the use of medical treatment.

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Primary angle closure and plateau iris



Comment by **Tin Aung** and **Monisha Esther Nongpiur**, Singapore

65361 To study the efficacy of laser peripheral iridoplasty in the treatment of eyes with primary angle closure and plateau iris syndrome, unresponsive to laser peripheral iridotomy, using anterior-segment OCT as a tool, Ramakrishnan R, Mitra A, Abdul Kader M, Das S, *Journal of Glaucoma* 2015; 0:

Laser peripheral iridotomy (LPI) is the established first line treatment in the management of primary angle closure as it alleviates pupillary block, resulting in widening of the angle and flattening of iris convexity. However, LPI does not open the angles in all cases of angle closure. Persistence of angle closure in the presence of a patent iridotomy has been attributed to non-pupillary block mechanisms such as plateau iris, and lens-related factors.

In this paper, Ramakrishnan and colleagues used anterior segment optical coherence tomography (ASOCT) to assess the effect of iridoplasty in eyes that were unresponsive to LPI. Out of 252 eyes (126 patients) that underwent LPI, 24 eyes of 12 patients were found to be clinically unresponsive to LPI and were subjected to iridoplasty. Eight of the eyes were subsequently

categorized as plateau iris syndrome and the remaining 16 eyes as primary angle closure. The iridoplasty procedure resulted in a significant lowering in IOP, and widening of the angles (as documented by ASOCT). Surprisingly, the authors also found reduction in the extent of PAS, which commonly does not occur after iridoplasty.

The authors should be commended for using imaging instruments such as ASOCT to evaluate response to LPI and iridoplasty. However, while ASOCT can image the anterior segment and angles, it cannot image structures posterior to the iris such as the ciliary body. Ultrasound biomicroscopy should be used for this purpose. One of the limitations of the study was the failure to specifically define 'unresponsiveness to LPI' in quantitative terms. It was not clear how the authors identified the 24 eyes that required further intervention.

The study emphasizes the need to evaluate the angle opening response after LPI, and in eyes with persistent closure, there is a need to consider other approaches to widen the angle such as iridoplasty in order to prevent progression of the disease.

Primary angle closure and myopia



Comment by **Ki Ho Park**, Seoul, South Korea

64904 Does myopia affect angle closure prevalence, Jin G, Ding X, Guo X, Chang BH, Odouard C, He M, *Investigative Ophthalmology and Visual Science* 2015;56:5714-5719

The authors performed a simulation study on age-specific prevalence of occludable angle (OA) by different rates of myopia (from 10% to 60%) in a Chinese population based on data collected in the Liwan Eye Study. The purpose of the authors' study was to determine whether the increasing prevalence of myopia in the East Asian population would lead a reduction in the prevalence of OA.

The results of the study were not what were generally expected. The projected prevalence of OA in the cohorts with myopia prevalence of 10, 20, 40, 50, and 60% was 11.1, 10.7, 9.9, 9.3, and 9.6%, respectively, which indicate that the increasing prevalence of myopia has minimal impact on the prevalence of OA.

The increasing prevalence of myopia has minimal impact on the prevalence of occludable angle

The results are in line with a previous report by a Singapore group, Yong *et al.* according to which, among 427 angle-closure cases, a quarter of them manifested myopia, although these myopic angle closure cases tended to have longer axial and vitreous cavity lengths in comparison with emmetropic and hyperopic angle closure cases.

These two papers might explain the phenomenon that although the Chinese population has a much higher prevalence of myopia compared with European populations, they also have a higher prevalence of angle closure.

So even though the prevalence of myopia is increasing in the East Asian region, (e.g., among teenagers between 16 and 18 years, myopic prevalence in Taiwan increased from 74% in 1983 to 84% in 2000), primary angle-closure glaucoma might deserve the same level of public health attention in the future.

The limitation of this study is that as seen in the simulation groups, the ranges of average spherical equivalent and the average axial length were relatively small: from 0.62 D to -0.81 D and from 23.1 to 23.6 mm, respectively, in which cases, lenticular myopia rather than axial myopia might have contributed in part. In addition it would have been better to include a group or groups representing a higher rate of myopia (e.g., 70% and/or 80%) in the simulation.

Glaucoma and Systemic Diseases

Systemic levels of trace metals



Comment by **Louis Pasquale**, Boston, MA, USA

65417 Association between body levels of trace metals and glaucoma prevalence, Lin SC, Singh K, Lin SC, JAMA Ophthalmology 2015;133:1144-1150

Lin *et al.* performed a cross-sectional study using the Korean National Health and Nutritional Exam Survey to assess the relation between body levels of trace metals (manganese, mercury, lead, cadmium and arsenic) and glaucoma. These metals might effect a variety of physiologic processes but a compelling prior hypothesis specific to glaucoma cannot be articulated based on prior literature. All included patients (n = 2680) had a standardized eye exam although not every participant completed all aspect of that exam. Nonetheless, a standard definition of glaucoma was employed and 36 cases were identified. The specific type of glaucoma was not determined. The authors found a robust, inverse and concentration dependent relation between serum manganese levels and glaucoma in multivariable analysis. If other investigators confirm this result, it is intriguing to consider that manganese could be a therapeutic target for glaucoma. A relation between elevated mercury levels and glaucoma was also found but this result was not concentration dependent. Lin and coworkers did not confirm a prior report of the relation between higher lead levels and primary open-angle glaucoma.¹ No other trace metal was found to be associated with glaucoma but the number of cases was low and power may have been inadequate to see any relations. As there is scant prior data on trace metal exposure and glaucoma, more research is needed, particularly analyses performed on specific glaucoma subtypes.

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Telemedicine

Cost-effectiveness of a screening device



Comment by **Kaweh Mansouri**, Geneva, Switzerland

65343 The cost-effectiveness analysis of teleglaucoma screening device, Thomas S, Hodge W, Malvankar-Mehta M, PLoS ONE 2015;10:e0137913

Teleglaucoma is the application of electronic technologies to ophthalmic devices to remotely identify glaucoma patients. It is increasingly used as a triage tool for rural areas where patients are likely to have to travel greater distances to obtain an ophthalmology consultation.

Previous studies have demonstrated the feasibility of electronic stereoscopic fundus photograph analysis for glaucoma assessment¹ and patient satisfaction with the related time and cost savings of teleglaucoma.² Sensitivity and specificity of teleglaucoma has been reported to be at 86.5% and 78.6%, respectively.³

Thomas *et al.* conducted the first cost-effectiveness analysis of teleglaucoma, using data from rural populations of Alberta, Canada. Their study included patients at-risk of glaucoma over the age of 50. Markov modeling was used to model disease stages and cost-effectiveness ratio (ICER) for teleglaucoma was established. They found teleglaucoma to be more cost-effective than in-person care for detecting glaucoma, with an ICER of \$46.7/QALY. This means that a spending of an additional \$46.7 for each patient screened with teleglaucoma will give an additional QALY in comparison to in-person screening.

For people who were initially screened positive, the Markov model gave a total reward of 15.7 QALYs over 30 years, 1.1 less than for in-person care. However, the cumulative costs for the latter were 3.5 times higher (\$4035 vs. \$1155). The direct financial benefits to patients was a cost saving of \$2474 with teleglaucoma. Importantly, teleglaucoma enabled earlier detection of glaucoma, reducing the probability of blindness by 24%.

Improving access to cost-effective health services is an important public health goal. Currently, teleglaucoma is usually discussed in the context of rural communities. In some countries, such as the UK, however, it is already reality in urban areas underserved by ophthalmologists. With ageing demographics and squeezed health budgets, teleglaucoma may soon become part everyday clinical life.

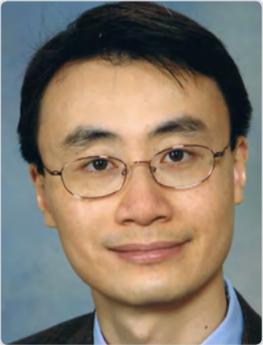
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Medical Treatment

Prostaglandins and blood flow



Comment by **Arthur Sit**, Rochester, MN, USA

65391 Comparison of ocular pulse amplitude-lowering effects of tafluprost and latanoprost by dynamic contour tonometry, Park SH, Yoo SH, Ha SJ, *Journal of Ocular Pharmacology and Therapeutics* 2015;31:617-622

Impaired ocular blood flow has long been implicated in the pathogenesis of glaucoma, and enhancement of ocular perfusion is an attractive potential treatment target. Ocular pulse amplitude (OPA), which is calculated as the difference between systolic and diastolic IOP, has been suggested as a possible, easily measured, marker for ocular perfusion. Using OPA, Park *et al.* performed a study to compare the effects of tafluprost and latanoprost on ocular perfusion.

The study population consisted of 27 normal-tension glaucoma (NTG) and 14 primary open-angle glaucoma (POAG) patients divided into two groups: one treated with tafluprost, and the other treated with latanoprost. OPA was measured using the dynamic contour tonometer (DCT) and IOP measured using Goldmann applanation tonometry. Baseline IOP was 17.1 ± 3.8 mmHg in the taftuprost group, and 17.5 ± 2.9 mmHg in the latanoprost group. Baseline OPA measured by DCT was 2.3 ± 0.6 mmHg in the taftuprost group and 2.6 ± 0.4 mmHg in the latanoprost group. After three months of treatment, the mean decrease in IOP from baseline was 4.1 mmHg in the taftuprost group compared with 2.1 mmHg in the latanoprost group. Although there was a significant difference between the two groups in mean OPA at one week and three months, there was no significant difference in the reduction of OPA from baseline ($P = 0.17$).

Reduction of OPA may be an indication of improved ocular blood flow. However, contrary to the conclusion in this study, the results in this study were largely inconclusive with no clear difference between tafluprost and latanoprost. A significant difference between the two groups in mean OPA was only found at some time points, and no significant difference in OPA reduction from baseline detected. Even if OPA were clearly different between the two groups, extrapolation to a difference in ocular blood flow would be difficult since it is not a specific marker for ocular perfusion. OPA is strongly influenced by IOP, and in this study, the tafluprost group had a greater IOP lowering effect than the latanoprost group. The authors also calculated a corrected OPA, which supposedly compensates for the effect of IOP, but it is not clear how this model was

validated. As well, OPA is strongly influenced by ocular rigidity (which itself is strongly affected by IOP).¹ Ocular rigidity was not assessed in this study, and a difference between the two groups may result in a difference in OPA.

Despite these limitations, the results are interesting and warrant further investigation using more objective methods for assessing ocular perfusion. If a therapy were identified as having a superior beneficial effect on ocular blood flow, it may be particularly useful for NTG patients, in whom impaired ocular blood flow may be especially important.

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New drugs



Comment by **Ivan Goldberg**, Sydney, NSW, Australia

65405 One-year clinical evaluation of 0.4% ripasudil (K-115) in patients with open-angle glaucoma and ocular hypertension, Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Fukushima A, Suganami H, Araie M, *Acta Ophthalmologica* 2016;94:e26-e34

It has been almost 20 years since ophthalmologists have had access for our patients to a new class of topical ocular hypotensive agents. As we have been anticipating the arrival of the Rho-kinase inhibitors, which reduce intraocular pressure (IOP) by modulating conventional trabecular aqueous outflow, it is gratifying to see peer-reviewed publications like this one analyzing the potential for these agents; this allows us to consider how we might be able to include them into our treatment paradigms.

Even though it is an open-label study, this prospective assessment of efficacy and safety in a Japanese population over 52 weeks, compares monotherapy with 0.4% ripasudil (K-115) twice daily with its additive effects to commonly used agents: prostaglandins, beta-blockers and finally fixed combinations where the ripasudil was agent number three. Helpfully, the study also sub-divided patients into those with primary open-angle glaucoma (POAG), exfoliative glaucoma and ocular hypertension (OHT) as well as those with lead-in IOPs greater than or less than 21 mmHg.

Not only for the overall group, but for every sub-group as well, the results demonstrated clinically-relevant IOP reduction. For the monotherapy group, IOP reduction was 2.6 (trough) to 3.7 (peak) mmHg; as expected this was somewhat less when ripasudil was added to a beta-blocker (2.2 to 3.0), less when added to a prostaglandin (1.4 to 2.4), but when added to a fixed

combination, notably 1.7 trough and 1.7 peak. As indicated, these would be helpful add-ons for patient management. Also unsurprisingly, efficacy was greater when baseline IOP was higher and less for exfoliative glaucoma than for OHT or POAG.

What about side effects? Conjunctival hyperemia was common (97%) but usually transient and relatively mild. A greater potential limitation was allergic blepharitis and allergic conjunctivitis (mechanism not yet determined) that lead to almost 15% discontinuation, with onset most frequently some 12-36 weeks after initiation.

Given these results, mirroring data for sibling rho-kinase inhibitors under assessment, it seems unlikely these agents will become first-line hypotensives. Their role as add-on agents seems more promising. Congratulations to the authors for pursuing this research.

New drugs



Comment by **Robert Feldman**, Houston, TX, USA

65509 Evaluation of the effect of latanoprostene bunod ophthalmic solution, 0.024% in lowering intraocular pressure over 24h in healthy Japanese subjects, Araie M, Sforzolini BS, Vittitow J, Weinreb RN, *Advances in Therapy* 2015;32:1128-1139

Latanoprostene bunod (LBN) is a nitric oxide-donating prostaglandin F_{2α} receptor antagonist that has been shown to lower intraocular pressure (IOP) in open-angle glaucoma and ocular hypertension. The purpose of this study was to evaluate LBN 0.024% in reducing IOP over a 24-hour period in normal eyes with normal IOP.

In this single-center, single-arm study, 24 Japanese males (mean age 26.8 ± 6.3 years) used LBN QD at 8 p.m. for 14 days. IOP measurements were taken at 8 p.m., 10 p.m., 12 a.m., 2 a.m., 4 a.m., 8 a.m., 10 a.m., 12 p.m., and 4 p.m. at baseline and 14 days after start of treatment. The authors found a significant reduction in IOP over the entire 24-hour period and at each time point.

However, there are several problems with this study. IOP measurements were taken at time points throughout the night, but the authors used a Goldmann applanation tonometer, meaning measurements were not taken in a habitual position without waking subjects during the night (which can alter the pressure, inducing significant study artifacts). Additionally, this study lacks a control group, and we do not know what effect the protocol would have on untreated eyes. Overall it is helpful to see that the medication lowers IOP over 24 hours while upright and awake, but it would be more useful to see that effect in the habitual state of supine and low light low activity unstimulated conditions.

Surgical Treatment

Trabeculectomy vs. Drainage Devices



Comment by **Angelo Tanna**, Chicago, IL, USA

64915 Trabeculectomy versus Ex-Press shunt versus Ahmed valve implant: short-term effects on corneal endothelial cells, Casini G, Loiudice P, Pellegrini M, Sframeli AT, Martinelli P, Passani A, Nardi M, American Journal of Ophthalmology 2015;160:1185-1190.e1

Casini *et al.* used specular microscopy to prospectively investigate the impact of trabeculectomy (n = 22), the ExPress Shunt procedure (n = 24) and Ahmed drainage device surgery (n = 18) on corneal endothelial cell number, density and morphology at one and three months after surgery compared to of 32 fellow eyes that were on medical therapy and had no prior incisional glaucoma surgery. The authors found small but statistically significant reductions in corneal endothelial cell density at three months in the trabeculectomy group (4.2%, p = 0.007) and in the Ahmed drainage device group (3.5%, p = 0.04); however, there was no significant change in the ExPress group.

Although performed prospectively, eyes were not randomized to the different surgical interventions. A confounding factor may lie in the fact eyes that had deep anterior chambers underwent ExPress Shunt implantation and other eyes (presumably with shallow anterior chamber angles) underwent trabeculectomy.

Eyes that undergo ExPress shunt implantation usually do not experience flattening of the anterior chamber during surgery. With trabeculectomy, however, the anterior chamber is likely to be flat at some point during creation of the fistula if measures to avoid this are not undertaken, including use of an anterior chamber maintainer or intracameral viscoelastic, the use of pre-placed scleral flap sutures, and the creation of a small, valved corneosclerostomy. The authors do not specify the details of their surgical techniques nor do they specify whether the anterior chamber was flat in any of the study eyes during the procedure.

Wagschal *et al.* previously reported the results of a prospective clinical trial that studied endothelial cell density in 64 eyes that randomized to trabeculectomy or the ExPress Shunt procedure and found no significant difference from baseline or between groups at one year.¹ Controversy remains as to whether there is a difference in the impact on the corneal endothelium with the ExPress Shunt versus trabeculectomy, therefore, further studies are needed.

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Trabectome



Comment by **Murray Johnstone**, Seattle, WA, USA

65609 Episcleral Venous Fluid Wave Correlates with Trabectome Outcomes: Intraoperative Evaluation of the Trabecular Outflow Pathway, Fellman RL, Feuer WJ, Grover DS, *Ophthalmology* 2015;122:2385-2391.e1

The authors set out to determine whether an intraoperative episcleral vein fluid wave (EVFW) can act as a potential indicator of the outcome of trabectome surgery. An underlying premise was that the fluid wave was reflective of the patency of the distal outflow system.

The EVFW outcome measures were fluid wave intensity and clock hours of blanching using a masked observer approach. The study demonstrated a statistically significant correlation between wave extent in clock hours and postoperative IOP at one month and three months but not at six or 12 months. At 12 months, the mean IOP in the extensive EVFW group (4,5 or 6 clock hours) was 13.3 ± 2.7 mmHg on 1.4 ± 1.2 medications compared with an IOP of 18.4 ± 3.1 mmHg on 2.9 ± 0.9 medications in the poorly defined group (both $P = 0.001$).

The authors conclude that the EVFW can provide a gauge for the patency of the distal outflow pathway and that the technique may be able to predict surgery outcomes after trabectome surgery. The paper points out that a spectrum of findings was present; the technique was particularly valuable when there was either a definitive intense fluid wave and/or extent of blanching or when fluid wave findings were very minimal.

Predictive value was less for those in the middle of the spectrum of EVFW findings. Both fluid wave intensity and the extent of the fluid wave are subjective observer-dependent criteria, a limitation that is regularly shared by studies of this type and is mitigated by the author's use of a masked approach.

The authors are to be congratulated on their development of a test to predict surgical outcomes that becomes predictive immediately following the operating room procedure. Their insights suggest that in-office imaging techniques might one day be used to identify inappropriate candidates for MIGS surgery even before they reach the operating room.

Deep sclerectomy



Comment by **Philippe Denis**, Lyon, France

65406 Outcomes of combined phacoemulsification and deep sclerectomy: a 10-year UK single-centre study, Mercieca K, Shevade B, Anand N, *Eye* 2015;29:1495-1503

Mercieca *et al.* report the long-term outcomes of combined phacoemulsification and deep sclerectomy (DS). This retrospective review was comprised of 296 eyes from 282 consecutive glaucoma patients (mainly, with POAG) which were identified from a surgery database over a ten-year period and underwent a combined surgery with phaco-DS. Two levels of IOP success criteria were defined: (A) IOP < 19 mmHg and/or 20% decrease from baseline and, a more stringent level, (B) IOP < 16 mmHg and/or 30% decrease from baseline.

Mean age at time of surgery was 80.3 ± 6.6 years and mean follow-up was 63.5 ± 35.3 months. It is noteworthy that nearly half of the patients (45.7%) died during the observation period, and this result may simply reflect the increased population age of patients in this retrospective study. Kaplan-Meier success rates in all eyes for criteria A were 89.1% and 80% with glaucoma medications (qualified success) and 81.2% and 68.3% without medications (unqualified success) at two and five years, respectively. Qualified success for criteria B was 72.4 and 61.4% and unqualified rates were 67.2 and 55.2% for the same time periods. At last follow-up, 20% of eyes were on glaucoma medications.

Mitomycin C was applied in 49% of patients, but the decision of use MMC was not clearly investigated (similar age, similar number of drops at inclusion). Furthermore, univariate and multivariate actuarial analyses failed to demonstrate a significant effect of MMC application on long-term IOP control. Hypotony was observed in only 3% of the cohort, mainly in MMC-treated eyes. Laser goniopuncture, which was performed in nearly 55% of patients, was associated with a better clinical outcome. Conversely, the absence of implantation/injection of a spacer device (mainly SK-Gel and viscoelastics) during the procedure was negatively associated with long-term success.

In summary, with the limitations of a retrospective study, the authors have collected information on long-term IOP results of phaco-DS. Phacoemulsification with non-penetrating glaucoma surgery appears to be an effective and safe technique to lower IOP in patients with coexisting glaucoma and cataract, with few postoperative complications and significant IOP-lowering efficacy. The long-term outcomes also suggest that phaco-DS is a valid option when compared to trabeculectomy, or to combined phaco-trabeculectomy. It would be interesting to compare phaco-DS surgery with MIGS procedures, which can also offer IOP reduction, decrease in dependence on glaucoma medications and a good safety profile when combined to cataract surgery.

Surgical treatment complications



Comment by **Steven Gedde**, Miami, FL, USA

65306 Intraocular pressure outcomes and risk factors for failure in the Collaborative Bleb-Related Infection Incidence and Treatment Study, Sugimoto Y, Mochizuki H, Ohkubo S, Higashide T, Sugiyama K, Kiuchi Y, *Ophthalmology* 2015;122:2223-2233

Sugimoto and colleagues report the intraocular pressure (IOP) outcomes and risk factors for failure in the Collaborative Bleb-Related Infection Incidence and Treatment Study. A total of 829 eyes of 829 patients who underwent trabeculectomy with mitomycin C (MMC) alone or in combination with phacoemulsification were evaluated in this multicenter, prospective study. Mean IOP was reduced from 24.9 ± 9.0 mmHg to 12.6 ± 5.2 mmHg after five years of follow-up, and the mean number of medications decreased from 2.8 ± 1.0 medications to 1.2 ± 1.3 medications. Multiple different success criteria were used to present study results, in accordance with recommendations from the World Glaucoma Association. Preoperative factors predicting failure in a multivariate analysis included previous cataract surgery, more than one prior glaucoma surgery, and higher IOP. Needling procedures and cataract surgery were postoperative factors associated with an increased risk of failure. Choroidal detachment, wound leak, anterior chamber shallowing, hypotony maculopathy, hyphema, and bleb leak were among the most common postoperative complications observed after trabeculectomy.

This national collaborative study offers a large database for examining the safety and efficacy of trabeculectomy with MMC. The results are consistent with other prospective clinical trials involving glaucoma filtering surgery. It is interesting that combined phacoemulsification and trabeculectomy with MMC achieved a similar success rate as trabeculectomy with MMC alone, and subsequent cataract surgery was a risk factor for trabeculectomy failure. This suggests that combined surgery may be preferable to the frequently recommended staged procedure in which glaucoma surgery is followed by cataract extraction.

Although the racial characteristics of the study population are not provided, they are expected to be fairly homogeneous in this Japanese study. The results may not be generalizable to other areas of the world with different racial composition. Trabeculectomy technique was not standardized and left to the discretion of the surgeon. Data are presented for needling procedures and resuturing the conjunctiva, but it is lacking for other interventions such as laser suture lysis and subconjunctival injection of 5-fluorouracil. Despite these limitations, the authors are to be congratulated for sharing valuable information about the long-term outcomes of trabeculectomy with MMC in a large cohort of patients.

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