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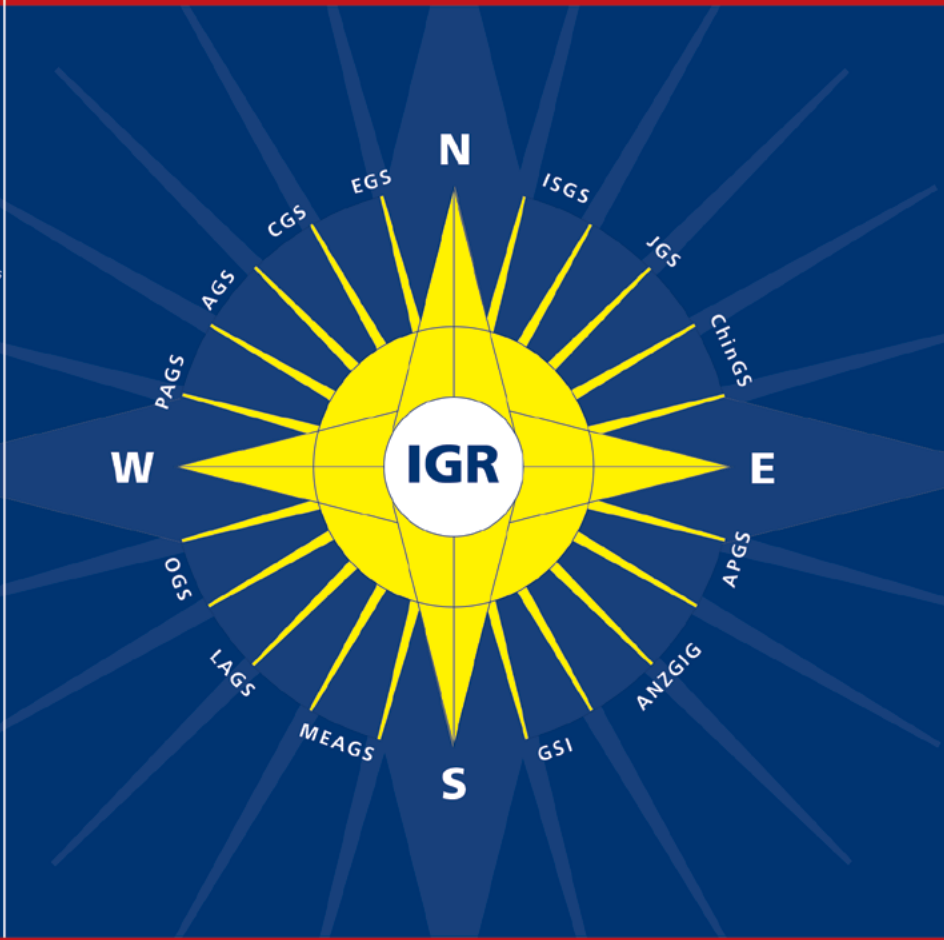

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All abstracts are available online in the classified IGR searchable glaucoma database

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The affiliations of the contributors to this issue can be found on www.e-IGR.com.

The 8th World Glaucoma Congress was held from March 27–30, 2019 in Melbourne, Australia

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We welcomed over **2000 ophthalmologists** and allied health professionals from more than **90 different countries**.

The scientific program was a stimulating mix of symposiums, courses, workshops, wetlabs, rapid fire sessions and poster walks covering topics from the basic science and genetics of glaucoma, to the **latest developments** in medical and surgical management of glaucoma.

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We look forward to welcoming you for the next edition, taking place March 24-27, 2021 in Kyoto Japan!

WGA

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From the WGA Executive Office

Dear IGR readers,

The World Glaucoma Association is proud to welcome Dr. Fabian Lerner as our President of the WGA. Fabian has recently completed his tenure as the Education Committee Chair. Under his leadership, the Education Committee developed the Online Basic Course in Glaucoma which was taken by more than 1400 ophthalmologists and were made available in English, Spanish, Portuguese and Chinese. In addition, the Education Committee has created the Patient Education Website with educational materials written for the patient and their family members. This is available in English and Spanish and soon for additional languages.

The World Glaucoma Association is proud to sponsor and coordinate the global events of the World Glaucoma Week. Last year we had 626 participating events organized in various countries around the globe. This year, as World Glaucoma Week took place in the midst of a surge of COVID-19 in many areas of the world, there was the expected reduction in the number of participating centers. However, there was still an excellent turnout of 399 activities worldwide. Also, we were able to reach out to hundreds of thousands through our online and social media campaigns including Facebook, Twitter and Instagram. Please let us know if we missed your activity for World Glaucoma Week so that we may add it to the WGW Worldmap and include your efforts in our website. Thanks to all who were able to participate this year!

Dr. Neeru Gupta is the immediate Past-Chair and Dr. Vijaya Lingham is the present Chair of the Global Outreach Committee. The committee has expanded our joint ICO-World Glaucoma Association Fellowship program to 10 glaucoma fellowships for 2021. We have received numerous applications and are in the process of selecting our fellows from amongst the many high-quality applicants. Also, the Global Outreach Committee has established additional fellowships programs for qualified applicants to train at sites in India and Nepal.

We welcome Dr. Pradeep Ramulu as the new Chair of the Education Committee. Dr. Ramulu and his committee will continue to expand the number of learning modules in the Online Courses in Glaucoma as well as coordinate with the World Glaucoma Patient Committee to produce patient education materials.

The World Glaucoma Patient Committee, under the leadership of Drs. Ivan Goldberg, Robert Ritch, and Ki Ho Park, had a very productive inaugural meeting during the annual American Academy of Ophthalmology meeting in San Francisco last year. Several initiatives have already begun with the goal of greater education of and advocacy for our patients with glaucoma.

Our Program Planning Committee (co-chaired by Drs. Tina Wong and Arthur Sit) for the 2021 World Glaucoma Congress in Kyoto convened at the AAO to start creating the scientific and clinical programs for the meeting. The committee has continued to develop the program via email communications and conference calls. A planned meeting at ARVO (cancelled due COVID-19) will take place virtually as a teleconference.

We hope you had a chance to visit the WGA booth at the American Glaucoma Society.

We look forward to your continued participation in WGA activities and at future World Glaucoma Congress meetings. The COVID-19 pandemic has demonstrated the value of community, including on a global level, and the WGA is glad to be able to serve as your resource for education and connection to the international glaucoma community. Take care and stay healthy as we continue our fight to save the sight of our patients, even through these challenging times.

World Glaucoma Association
The Global Glaucoma Network

Get to know us!

Fabian Lerner – WGA President 2020-2021

I was involved with the WGA since the consensus meeting in 2007. Since then I participated in several consensus meetings up to the last one on Glaucoma Surgery.

I joined the Board of Governors in 2012 and was co-director of the scientific program for WGC-2013 and 2015. I co-chaired the Education Committee, where a series of online courses were developed as well as a website for glaucoma patients, relatives and the general public. I was President-Elect in the last two years and have now the privilege and honor to serve as President of the WGA for 2020-2021.

Working at the WGA was (and still is) a very stimulating and inspiring activity as there are so many talented people involved to help. This happened in all the positions I had in the past and is still the case at the Executive Committee. The WGA has grown so much during the last years with many committees and activities aimed at reducing visual disability due to glaucoma around the world!

After doing my residency in Buenos Aires, I did a glaucoma fellowship with Professor Jorge Alvarado at UCSF, after which I returned to Buenos Aires. I served as President of the Argentina Glaucoma Association, the Pan American Glaucoma Society and the Argentina Society of Ophthalmology. I am now Professor and Head at the Department of Ophthalmology, University Favaloro School of Medical Sciences in Buenos Aires, Argentina.

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World Glaucoma Week

#glaucomaweek was a success!

Throwback to World Glaucoma Week

Thank you to all who showed their support during World Glaucoma Week. With your continuous collaborative efforts, we have confidence that we will improve the current state of glaucoma diagnosis and early treatment worldwide. Have a look at some of the best moments captured on social media by browsing the official hashtag #glaucomaweek on Facebook, Twitter or Instagram.

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World Glaucoma Week

World Glaucoma Week is a global joint initiative between the World Glaucoma Association (WGA) and the World Glaucoma Patient Committee (WGPC), in order to raise awareness on glaucoma. Through a series of engaging worldwide activities patients, eye-care providers, health officials and the general public are invited to contribute to sight preservation. The goal is to alert everyone to have regular eye (and optic nerve) checks in order to detect glaucoma as early as possible.

Each year, the World Glaucoma Week adopts a common theme, which is adapted to local conditions, and yet unifies our efforts. To be effective, community awareness projects need to be relevant for the general population. That means they need to be based locally and thus, rely on individuals in each location to be actively involved, adopting the unifying global message into local culture.

To eliminate glaucoma blindness, there are several issues that need to be addressed. Glaucoma usually gives no warning until it is advanced, but the damage it causes to vision is ongoing and could become irreversible. Fortunately, for many patients treatment can halt the damage. That means the earlier the diagnosis, the more vision there is to save and the less likely the person is to become blind. Therefore, the World Glaucoma Week aims at alerting members of the broader community to the need for regular simple eye checks, which allow earlier detection and, hence, saved sight.

Newsletters and social media posts (Facebook, Twitter, Instagram) can inspire you and give you some ideas to arrange a project in your own area or neighborhood. This will create a network in which we are all able to motivate and guide one another as we share our goals and strategies. By sharing successes, as well as less successful ventures, we are able to learn from one another and be even more effective in reaching our goal; the elimination of glaucoma blindness.

For further details about who is at risk, what are the symptoms, and how glaucoma can be treated, both patients and the general public may visit glaucomapatients.org.

This year marks a decade of raising awareness on glaucoma through the World Glaucoma Week campaign. What are the key lessons of the last ten years?

Ivan Goldberg

Co-Chair World Glaucoma Week Committee

Fabian Lerner

President World Glaucoma Association

I.G. Public awareness programs need to be on message and patiently repeated over and over again. It's like water dripping onto a rock; it takes many drops to see an indent.

F.L. In the last ten years we have also seen many changes in the association, relating to the campaigns and education opportunities both for eye-care providers and patients. The World Glaucoma Association developed a workplace for patients and the general population, and the education Committee of WGA has developed a series of courses for ophthalmologists and other eye-care providers that are free of charge and provided in many languages. Of course, the rise of social media has been a powerful tool to get people around the world involved, and has played a key part in our mission towards raising awareness. Whether successful or unsuccessful, stories promoted through Twitter, Facebook and Instagram can have a big impact on general awareness about glaucoma prevention and treatment.

When it comes to glaucoma, the 'sneak thief of sight', lack of awareness may cause severe issues, that could even lead to permanent vision loss. And as glaucoma isn't always under the radar of health officials worldwide, the World Glaucoma Week activities are crucial. How can people contribute?

I.G. By organizing imaginative, publicity-attractive awareness projects locally, such as pamphlets and posters, screening stations and talks; all have their value. As do marches with banners and illuminating buildings in green, glaucoma's logo color, or green lapel ribbons.

F.L. The overarching goal of this campaign is for everyone to know about the disease called 'glaucoma' and encourage the general public to go and get tested. Glaucoma is one of the leading causes of irreversible blindness, but with early treatment, the damage may get limited and sight may be saved. By promoting regular testing, we also want glaucoma patients to get their relatives involved, as the chances of them getting glaucoma are 10

times higher than someone with no glaucoma history in their close family environment. Therefore, the World Glaucoma Week is a great opportunity to raise awareness through word of mouth.

How do you foresee the prevention and treatment of glaucoma in the next decade, and what does this mean for the World Glaucoma Week?

I.G. Same as in the last decade, we will be seeing a lot of advances in glaucoma. Genetics knowledge will contribute to earlier glaucoma detection, and therefore damage prevention may also start earlier. We might also see monitors developed through AI, which will help ophthalmologists in the follow-up of patients, and also see drugs administered through delivery devices.

F.L. Artificial intelligence driven interpretations of images of a person's optic nerve promises to revolutionize early detection on a large scale. This is most exciting, allowing as it will more accurate diagnosis and earlier onset of effective treatment.

GREEN = Go get your eyes tested for Glaucoma Save Your Sight!

Your Special Attention For

Swept-Source OCT for evaluating the lamina cribrosa: A report by the American Academy of Ophthalmology
Takusagawa HL, Hoguet A, Junk AK, Nouri-Mahdavi K, Radhakrishnan S, Chen TC
Ophthalmology 2019; 126: 1315-1323
abstract no. 80823

Aqueous shunts with mitomycin C versus aqueous shunts alone for glaucoma
Foo VHX, Htoon HM, Welsbie DS, Perera SA
Cochrane Database of Systematic Reviews 2019; 4: CD011875
abstract no. 80885

Twelve-year incidence and baseline risk factors for pseudoexfoliation: The Thessaloniki Eye Study (An American Ophthalmological Society Thesis)
Topouzis F, Founti P, Yu F, Wilson MR, Coleman AL
American Journal of Ophthalmology 2019; 206: 192-214
abstract no. 81051

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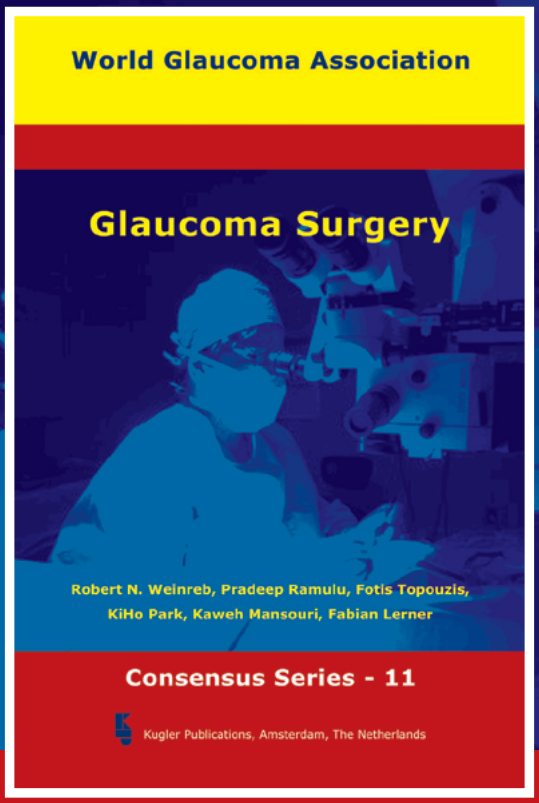

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Editor's Selection

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

Pathogenesis

IOP and Posture

Comment by John Liu, La Jolla, CA, USA

81419 Posture-Dependent 24-Hour Intraocular Pressure Fluctuation Patterns in an Intraocular Hypertension Monkey Model; Tu S, Li K, Hu D, Li K, Ge J; Translational vision science & technology 2019; 8: 63

Non-human primates are superior to any other animal species to study anatomical characteristics related to human glaucoma. Since elevated intraocular pressure (IOP) is the most important risk factor for glaucoma and a laser induced glaucoma model using rhesus monkeys is available, an important issue is the timing and the magnitude of IOP elevation in this model. While a snapshot measurement of IOP does not represent the dynamic nature of IOP, periodical IOP measurements during a 24-hour period may determine daily timing of IOP peak. The current report is a comprehensive study on the posture-related IOP changes during a 24-hour period using this experimental model. Measurements of IOP were taken immediately and ten-minute after changing to the supine position as well as immediately and ten-minute after changing to the sitting position. Comparisons were made between glaucomatous monkeys and carefully matched healthy monkeys. The authors reported that IOP levels in the glaucomatous monkeys were always higher than

those in healthy monkeys in all study parameters. Short-term and long-term IOP fluctuations during the 24-hour period were also larger in the glaucomatous monkeys. Critically, results showed that **24-hour IOP pattern had its highest IOP during the diurnal/wake period in these glaucomatous monkeys.** Timing for the largest postural-dependent IOP changes also occurred during the diurnal/wake period. As the authors acknowledged, all the IOP measurements in this study were under anesthesia following intramuscular injections of ketamine and chlorpromazine. These agents probably eliminated normal posture-related responses in the cardiovascular and neuronal systems in conscious monkeys. In this regard, how significant is the gap between real life and the experimental conditions affecting IOP fluctuation is unclear. Therefore, **it is important to verify the observations in the current report using conscious monkeys with implanted pressure transducers to monitor IOP.** In addition, one should not forget the difference in natural sleeping postures for rhesus monkeys (usually sitting) and humans (recumbent) when considering the real-life 24-hour IOP patterns in habitual body positions.

Oxygen Delivery and Function Loss

Comment by Leopold Schmetterer, Singapore

80900 Relating glaucomatous visual field loss to retinal oxygen delivery and metabolism; Aref AA, Maleki S, Tan O, Huang D, Varma R, Shahidi M; Acta Ophthalmologica 2019; 0:

Glaucoma is associated with reduced ocular blood flow and changes in retinal vascular oxygen saturation. To fully understand alterations in oxygen metabolism associated with the disease concomitant measurements of blood flow and oxygen saturation are required. This is the approach taken by Aref and co-workers who **measured total retinal blood flow using Doppler Optical Coherence Tomography (OCT) and oxygen saturation using a dual wavelength Scanning Laser Ophthalmoscope (SLO) in a small group of patients with primary open angle glaucoma (20 eyes of 14 patients).** The authors showed that increasing glaucomatous visual field loss was associated with reduced total retinal blood flow and reduced oxygen delivery.

There is a long-standing discussion whether changes in blood flow and oxygen metabolism are primary or secondary in glaucoma. Since this small-scale study was cross-sectional it does not contribute to the solution of this fundamental question

The strength of the study is related to the use of sophisticated technology that allows for quantitative assessment of oxygen metabolism. Limitations are the small sample size and the lack of a control group, which would be required to understand the potential of the technique in discriminating healthy from diseased eyes. There is a long-standing discussion whether changes in blood flow and oxygen metabolism are primary or secondary in glaucoma. Since this small-scale study was cross-sectional it does not contribute to the solution of this fundamental question. Do the techniques used by the authors have potential to be established as a diagnostic tool in glaucoma? Most likely not, because they do not provide localized tissue oxygenation. Technologies that do provide high lateral resolution for quantification of tissue oxygen may, however, be promising because they could identify areas of reduced metabolic demand due to neural loss.

Demyelination and Neurodegeneration

Comment by Kevin Chan, New York, NY, USA

79922 Demyelination precedes axonal loss in the transneuronal spread of human neurodegenerative disease; You Y, Joseph C, Wang C, Gupta V, Liu S, Yiannikas C, Chua BE, Chitranshi N, Shen T, Dheer Y, Invernizzi A, Borotkanics R, Barnett M, Graham SL, Klistorner A; Brain 2019; 142: 426-442

Increasing evidence indicates that glaucoma involves transneuronal degeneration in the brain's visual system and beyond.[1,2] However, the underlying mechanisms remain unclear.[3] In this cross-sectional, case-control study, You *et al.* used diffusion tensor imaging (DTI) and multifocal visual evoked potential (VEP) recordings on 25 and 16 glaucoma patients respectively, and suggested that demyelination precedes axonal loss in the transneuronal spread of human neurodegenerative diseases including glaucoma. Specifically, they showed that radial diffusivity in the optic radiation of glaucoma patients increased with visual field deficits and cortical thinning in a retinotopic manner.

> Radial diffusivity in the optic radiation of glaucoma patients increased with visual field deficits and cortical thinning in a retinotopic manner

In addition, the extent of radial diffusivity increase appeared more widespread throughout the optic radiation than that of axial diffusivity decrease. They also observed significant associations between increased radial diffusivity in optic radiation and delay of VEP latency, which is a potential functional measure of demyelination as authors demonstrated

previously in a rat model of optic neuritis.[4] To confirm histologically their hypothesis, authors used a mouse model of optic nerve axotomy and observed early glial activation and demyelination in the posterior visual projections prior to amyloid precursor protein accumulation in the axons.

While glaucoma is often considered not a demyelinating disease, the **hypothesis of early demyelination in glaucoma, if proven to be true, may be impactful to improving strategies for glaucoma neuroprotective treatment.** However, cautions should be taken when interpreting the findings of this study. In particular, *in vivo* directional diffusivities in conventional DTI are known to be sensitive but not specific to individual pathophysiological events. For example, while axonal injury and demyelination are demonstrated to be associated with axial and radial diffusivities, observations of axial and radial diffusivity changes do not necessarily imply axonal and myelin damages, as other events such as cell infiltration, vasogenic edema, and tissue loss can also contribute to directional diffusivity changes concurrently.[5] To improve the specificity of biophysical measurements, higher-order diffusion MRI such as diffusion basis spectrum imaging, diffusion kurtosis imaging and the standard model of white matter tract integrity may be used[5,6] and are now available at clinically feasible scanning durations. Since diffusion-based measurements cannot directly assess myelin content, more extensive imaging modalities such as magnetization transfer imaging and myelin water imaging may also be employed with diffusion MRI alongside longitudinal investigations and larger samples to validate these claims in terms of myelin integrity. As the optic nerve axotomy model is typically regarded as an acute, severe traumatic optic neuropathy model, more relevant mild chronic glaucoma models may also be considered for histopathology in parallel with *in vivo* preclinical multiparametric MRI.[7,8] Cautions may also be noted when deriving regional visual field sensitivity thresholds given the log units used in standard automated perimetry test reports.[9]

More detailed comments on glaucoma imaging and other aspects of this paper: *see* ref. 10.

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Prevention and Screening

Health Economics of Screening in China

Comment by Steve Mansberger and Seth Bricel, Portland, OR, USA

81123 Cost-effectiveness and cost-utility of population-based glaucoma screening in China: a decision-analytic Markov model; Tang J, Liang Y, O'Neill C, Kee F, Jiang J, Congdon N; The Lancet. Global health 2019; 7: e968-e978

Glaucoma seems a disease well-suited for screening: it is relatively common, often asymptomatic, easily screened-for, and treatable. However, several review articles suggest that population-wide screening is not cost-effective when studied in high-income countries. Tang *et al.* examined whether this holds true in China, where the costs of screening are lower and prevalence of PACG in particular is far higher than in European-derived populations such as the UK and Finland where prior, similar studies had focused. Overall, screening is more effective when it occurs in locations and groups with high prevalence of disease with high risk of morbidity.

The authors used Markov modeling simulations using the following data sources: 1) a meta-analysis of glaucoma prevalence studies in China; 2) inferred probability of transition to blindness from studies on closely-related populations such as in Mongolia; and 3) cost data from the Wenzhou Medical University Hospital. These data were used to model a proposed screening examination of Van Herrick testing for PACG and fundus photos to screen for POAG. The authors used a cost utility analysis using the World Health Organization established thresholds for cost effectiveness of an intervention based on the incidental cost-utility ratio (ICUR) compared to per-capita GDP. ICUR was defined as the cost difference between screened and unscreened populations divided by the difference in number of quality-adjusted life-years attributable to the intervention.

We applaud the authors for their important study. Several caveats include that the Van Herick method, while non-invasive and inexpensive, lacks sensitivity. It is unclear how the results would be altered with newer methods such as anterior segment OCT or digital

gonioscopy. **Several previous studies suggest that the follow-up proportion after a glaucoma screening is poor (from 40-60% with follow-up), when conducted in urban areas.** It is unclear whether the Markov model includes lack of follow-up after screening and how this would impact the ICUR results especially in rural areas. The large confidence intervals of ICUR estimates may suggest variable results. **The current manuscript found screening for PACG and POAG to meet cost effectiveness criteria in China.** Their findings could be used to support public health policy changes.

Anatomical structures

Peripapillary Vessel Density

Comment by Zia Pradhan and Harsha Rao, Narayana Nethralaya, Bangalore, India

81323 Systemic Determinants of Peripapillary Vessel Density in Healthy African Americans: the African American Eye Disease Study; Chang R, Nelson AJ, LeTran V, Vu B, Burkemper B, Chu Z, Fard A, Kashani AH, Xu BY, Wang RK, Varma R, Richter GM; American Journal of Ophthalmology 2019; 0:

Chang and colleagues **examined the associations between peripapillary vessel density (VD) measurements of OCT angiography (OCTA) and multiple systemic factors** (age, sex, diagnosis of hypertension, presence and duration of diabetes mellitus, haemoglobin A1c, body mass index, blood pressure, use of antihypertensive medication, history of heart failure or stroke and smoking status) in 1029 eyes of 1029 healthy African American subjects from a population-based cross-sectional study.

Only 1556 OCTA scans of 4135 scans acquired (37.6%) were of acceptable quality and could be included in the analysis. This highlights that image quality continues to be a limitation of the OCTA technology. The strongest influence on VD measurements was the signal strength (SS) of the scans; VD measurements increased significantly with increase in SS.

> The magnitude of effect of the systemic factors on the peripapillary VD measurements become clinically insignificant

Using multivariate analysis and controlling for the SS of OCTA scans, they found that **older age, male sex and longer duration of diabetes were associated with a statistically significant reduction in peripapillary VD** ($p < 0.05$). Peripapillary VD decreased by 1.2% per decade of increasing age and by 0.2% per five years of increasing duration of diabetes.

Peripapillary VD was on an average 0.7% lesser in men compared to women. The study concluded that these systemic factors should be considered while interpreting peripapillary VD changes in glaucoma.

However, one should note that **although the associations between peripapillary VD and these three systemic factors were statistically significant, the magnitude of associations were small.** Additionally, a previous study using OCTA system from a different manufacturer, has shown that coefficient of repeatability of average peripapillary VD measurements is as high as 3%; thus, a change in peripapillary VD of 3% is within the test-retest variability of OCTA.[1] If the result of the study by Chang *et al.* is interpreted in the background of the test-retest variability of VD measurements, the magnitude of effect of the systemic factors on the peripapillary VD measurements become clinically insignificant.

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Peripapillary Choroid and RNFL

Comment by Linda Zangwill, La Jolla, CA, USA

81115 Evaluation of Parapapillary Choroidal Microvasculature Dropout and Progressive Retinal Nerve Fiber Layer Thinning in Patients With Glaucoma; Kim JA, Lee EJ, Kim TW; JAMA ophthalmology 2019; 137: 810-816

Optical coherence tomography angiography (OCTA) has facilitated the three-dimensional visualization of retinal vasculature architecture of the optic nerve head and macula. Most glaucoma studies to date have focused on the microvasculature of the radial peripapillary capillaries layer of optic nerve head and the superficial vascular complex of the macula, as these layers have been shown to be associated with severity of glaucomatous visual field damage. Given that the short posterior ciliary arteries that perfuse the optic nerve head are located in the choroid, assessing the microvasculature in the choroid may be of particular importance for improving of understanding of the pathophysiology of the disease, and for developing predictive models of POAG progression. **In the first longitudinal study quantifying parapalliary choroidal vascular dropout (MvD) over time, Kim and colleagues[1] report that an enlargement in choroidal MvD area measured from enface Triton swept-source OCT angiogrpahy images is associated with progressive RNFL thinning** in 68 POAG patients. In contrast, baseline and follow-up MvD area by itself

was not associated with the rate of RNFL loss over time. Global and sectoral MvD changes were also documented. Other factors associated with faster RNFL thinning include larger beta zone parapapillary atrophy, and disc hemorrhage during follow-up.

This study adds to the growing literature suggesting that vascular insufficiency is associated with faster glaucomatous progression

The study is well designed, with appropriate masking, good interobserver agreement in the manual assessment of MvD area, and appropriate statistical analysis. This study adds to the growing literature suggesting that vascular insufficiency is associated with faster glaucomatous progression by measuring microvascular dropout in the parapapillary choroid. As the authors mention, caution should be exercised when evaluating the microvascular of the deeper layers as projection artifacts from the superficial layers are often not completely removed. Moreover, as only patients with MvD at baseline were included, the relative importance of MvD area enlargement in terms its prevalence and role in glaucoma pathophysiology remains to be determined. Further investigation is also necessary to assess the temporal relationship between MvD and the development of glaucoma to determine whether MvD enlargement is a cause or result of glaucomatous progression.

Basic Science

Effects of ROCK Inhibitors

Comment by Douglas Rhee and Rahul Raghu, Boston, MA, USA

79411 RKI-1447, a Rho kinase inhibitor, causes ocular hypotension, actin stress fiber disruption, and increased phagocytosis; Dang Y, Wang C, Shah P, Waxman S, Loewen RT, Loewen NA; Graefe's Archive for Clinical and Experimental Ophthalmology 2019; 257: 101-109

Rho-associated protein kinase (ROCK) inhibitors have been an area of active investigation, particularly for their ocular hypotensive effects in the treatment of glaucoma. **Dang *et al.* investigated the hypotensive effect of RKI-1447, a ROCK 1/2 inhibitor previously used in breast cancer treatment, in a porcine *ex vivo* pigmentary glaucoma model.** In the study, 28 of 40 total porcine anterior chambers were infused with medium contained pigment particles for 48 hours. Sixteen of the 28 pigment infused chambers subsequently received treatment with RKI-1447, versus the 12 chambers which remained untreated after pigment infusion and served as the vehicle control group.

As intended, after 48 hours of infusion with pigment, TM outflow facility (microliter/min-mmHg) decreased from 0.27 ± 0.03 to 0.18 ± 0.02, p = 0.003. Treatment with RKI-1447 appeared to reverse the decreased outflow facility, and when compared to the 12 chambers not infused with pigment, there was no statistically significant difference (0.230 ± 0.010 and 0.287 ± 0.017, p = 0.209). IOP in the RKI-1447 group also decreased significantly from 20.14 ± 2.59 to 13.38 ± 0.91 mmHg, while the untreated pigment group IOP remained significantly higher than its baseline (all P < 0.05).

Based on their immunostaining analysis, the authors posit that the most likely mechanisms by which RKI-1447 lowers IOP and increases outflow facility, are via its roles in disrupting formation of actin stress fibers and increasing TM phagocytosis, as well the TM cell morphologic changes induced by other ROCK inhibitors (cell rounding, contraction, and decreased adhesion). Interestingly, changes in TM cell motility were not observed between groups.

The authors acknowledge the established limitations of *in-vitro* and animal model studies, and their work provides compelling evidence for the potential therapeutic applications of RKI-1447, particularly for pigmentary glaucoma The authors also briefly mention a potentially increased safety profile of RKI-1447, 'due to lack of cross-reactivity with AKT, MEK, PKA, and PKG even at high concentrations'. With the known importance of ROCK in virtually all tissues, minimizing systemic side effects must remain a high priority, particularly in a glaucoma population who may be on treatment for decades. Ongoing surveillance for cumulative ROCK inhibitor exposure should be an important area of investigation.

Clinical Examination Methods

Contact lens IOP sensor

Comment by Luciano Quaranta, Pavia, Italy

80490 Fluctuations of the Intraocular Pressure in Medically Versus Surgically Treated Glaucoma Patients by a Contact Lens Sensor; Muniesa MJ, Ezpeleta J, Benítez I; American Journal of Ophthalmology 2019; 203: 1-11

This is a relevant study that reports results obtained with a relatively new technology (Contact lens Sensor; CLS) on IOP related fluctuations during 24 hours, in a sample of medically and surgically treated glaucoma patients. IOP-related fluctuations were larger in the medically treated group, and a larger fraction of the surgical group exhibited an absence of nocturnal acrophase when compared to the medically treated group.

Similarly, Konstas and associates[1] evidenced that **glaucoma patients with well-functioning trabeculectomies had lower mean IOP, but also lower peaks and ranges of IOP over 24 hours when compared with glaucoma patients on maximum tolerated medical therapy.**

Furthermore, we have also demonstrated that trabeculectomy is able to reduce but not to avoid IOP elevation due to changing posture from sitting to supine position.[2]

Some considerations should be done either about technology, and the significance of nighttime fluctuations. CLS have been demonstrated to have a good correlation with 24 IOP fluctuation profile in glaucoma patients.[3]

In the study of Muniesa and associates there was a significant difference in IOP levels between the two groups, nevertheless after adjustment for IOP as measured by applanation tonometry, surgical patients had less IOP related fluctuations in 24-hours than the medical group. In order to better analyze the results, it would be interesting to know if there were any difference in 24-hour blood pressure profile between the studied groups. Pulsatile ocular blood flow, the volume of blood entering the eye for each cardiac cycle, is part of IOP related fluctuations, and thus CLS measurements could reflects modifications of ocular perfusion pressure. For this reason, it should be interesting to analyze the results also after adjusting for blood pressure, and possibly for blood pressure medicines between the two groups.

The role of nighttime IOP fluctuations in glaucoma progression is not completely understood and investigated

It is important to consider that the role of nighttime IOP fluctuations in glaucoma progression is not completely understood and investigated, even if it is logical to believe that stable and low 24-hours IOP is a desirable target for glaucoma patients. More convincing literature exists that correlates progression of glaucoma in patients with larger 24-hours fluctuation of ocular perfusion pressure.[4] For this reason, it is possible to speculate that the use of CLS associated with 24-hour blood pressure assessment should be an integrated method to evaluate the risk of progression of the disease.

I applaud the authors for their effort making a substantial contribution to glaucoma research.

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Contact lens IOP sensor

Comment by Tony Realini, Morgantown, WV, USA

80490 Fluctuations of the Intraocular Pressure in Medically Versus Surgically Treated Glaucoma Patients by a Contact Lens Sensor; Muniesa MJ, Ezpeleta J, Benítez I; American Journal of Ophthalmology 2019; 203: 1-11

Muniesa and colleagues have conducted **a prospective comparison of 24-hour fluctuations in intraocular pressure (IOP) in eyes with open-angle glaucoma (OAG) treated either with medical therapy (and no history of glaucoma surgery) or surgical therapy (one-third of whom were also receiving medical therapy). IOP fluctuations were measured with Sensimed Triggerfish contact lens sensor,** which infers IOP changes based on changes in ocular shape at the limbus over time and reports its output in units referred to as millivolt equivalents (mv Eq). The group found significantly higher fluctuations (the outcome measure being amplitude of the mathematically-smoothed 24-hour mv Eq tracing) in the medically-treated group compared to the surgically-treated group (131 versus 100 mv Eq, respectively; p = 0.01). The implication is that surgery more effectively reduces IOP variability than medical therapy in eyes with OAG. There are, however, several important caveats to this conclusion. The true relationship between mv Eq and IOP is undefined. It may not be linear. Thus, the equivalent 24-hour IOP fluctuations may be greater or less than the mv Eq fluctuations, and the clinical significance of these findings cannot be known. More importantly, the very significance of IOP variability is incompletely characterized. The investigators reported that significantly fewer surgically-treated eyes than medically-treated eyes manifested nighttime peaks in mv Eq (14% versus 43%, p = 0.011). Unfortunately, the relevance of nighttime IOP peaks is unclear. Even healthy subjects have higher IOP at night. Until we better understand the specific characteristics of IOP variation over time that confer risk of the development and/or progression of glaucoma, studies such as these are challenging to discuss in the context of clinical implications.

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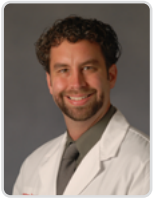
Retinal Blood Flow



Comment by Alon Harris and Brent Siesky, New York, NY, USA

80928 Diurnal change of retinal vessel density and mean ocular perfusion pressure in patients with open-angle glaucoma; Baek SU, Kim YK, Ha A, Kim YW, Lee J, Kim JS, Jeoung JW, Park KH; PLoS ONE 2019; 14: e0215684

The paradigm of calculating risk for the development and progression of glaucomatous optic neuropathy has undergone a significant evolution over the past several decades. While reduction of intraocular pressure (IOP) remains the only current therapeutic approach, the disease has been shown to be multifactorial with highly varied progression patterns and risk clusters. Ocular hemodynamic contributions to the disease process have been identified as a significant consideration in many individuals, with higher vascular involvement in certain populations including persons of African descent and patients with normal-tension glaucoma. Determining total risk is additionally complicated by diurnal variations in physiological biomarkers, including fluctuations in IOP, blood pressure (BP), ocular perfusion pressures (estimated by BP and IOP) and blood flow. In consideration of this, Baek and coauthors utilized swept-source optical coherence tomography angiography (OCTA) to assess retinal vessel density (RVD) variation between 8:00 AM and 8:00 PM in primary open-angle glaucoma and healthy subjects. **The authors found diurnal changes of IOP, mean ocular-perfusion pressure and RVD were significantly greater in glaucoma patients compared to healthy controls.** The authors identified the largest difference between groups at **8:00 PM where macular RVD increased to the highest level in the healthy group while glaucoma patients conversely demonstrated their lowest levels.** These findings highlight the difficulty in estimating risk from biomarkers assessed only during normal clinical office hours. The study utilizes OCTA which allows for visualization of RVD at levels of specificity not previously possible and the authors demonstrated high levels of intra-visit repeatability (0.755-0.943) and inter-visit reproducibility (0.843-0.986). One **significant limitation is the inclusion of patients taking ocular hypotensive medication which both influence IOP variation and possibly ocular hemodynamics.** Additionally, other vascular beds not assessed with OCTA in this study may be important to consider, such as those seen within the retrobulbar blood vessels. Nocturnal variation was also not assessed, and the authors correctly suggest targeting nocturnal variation as a needed follow up for future research. Moving forward, the use of mathematical modeling and artificial intelligence (AI) in understanding the complex interactions of risk biomarkers and their variation both within and across individuals may improve risk calculation and lead to individually tailored approaches for precision medicine.

OCT and OCT-A

Comment by Kouros Nouri-Mahdavi, Los Angeles, CA, USA

80613 Measurement Floors and Dynamic Ranges of OCT and OCT Angiography in Glaucoma; Moghimi S, Bowd C, Zangwill LM, Penteado RC, Hasenstab K, Hou H, Ghahari E, Manalastas PIC, Proudfoot J, Weinreb RN; Ophthalmology 2019; 126: 980-988

Moghimi *et al.* explored the measurement floor and dynamic range of measurements for circumpapillary RNFL and macular GCC thickness and compared those to perifoveal and circumpapillary capillary vessel densities (cpCD and pfVD, respectively) derived from OCTA in a group of normal eyes and eyes with suspected or established glaucoma. They hypothesized that OCTA parameters may provide additional information in later stages of the disease when thickness measurements have reached their floor.

They reported that the change point, i.e., the point where any given OCT parameter reaches its measurement floor, occurred either later (cpCD) or could not be detected (pfVD) with OCTA parameters as compared to thickness measures. However, when the number of potential steps of change within the dynamic range of thickness and OCTA parameters were compared, there was actually a smaller number of steps with OCTA measures compared to OCT parameters. **The investigators concluded that OCTA measures may be useful for detection of change in advanced glaucoma.**

Can OCTA parameters predict functional deterioration with high enough accuracy to be clinically useful for confirmation or forecasting of functional glaucoma progression?

The findings are promising but should be considered preliminary. One issue is that the number of eyes with advanced glaucoma (i.e., beyond -15 dB of MD) was small; under such circumstances the 95% CI for the change point can be quite wide or a change point may not be detectable and therefore, it is difficult to prove a later change point for any outcomes of interest. A direct comparison of the performance of macular measures to RNFL measures may have been affected by the composition of the study sample and the proportion of glaucoma eyes with early central damage; only a small number of test locations (12 or less) within the 24-2 VF actually correspond to the central macula. A smaller number of steps within the dynamic range for the OCTA parameters could potentially limit their utility. On the other hand, one might argue that with newer iterations of OCTA hardware

and software, there would be less variability and the rates of change of OCTA measures may become more accurate or the number of step changes detectable within the dynamic range may increase.

Further confirmation of these findings is needed. If confirmed, additional questions will need to be addressed before the findings can be clinically applied. **The main question is whether a change in OCTA parameters can predict functional deterioration with high enough accuracy to be clinically useful for confirmation or forecasting of functional glaucoma progression?** We will be looking forward to additional studies on this cohort.

Disease Progression

Comment by Jost Jonas, Heidelberg, Germany

80958 Optic Disc Microhemorrhage in Primary Open-Angle Glaucoma: Clinical Implications for Visual Field Progression; Ha A, Kim YK, Baek SU, Park KH, Jeoung JW; Investigative Ophthalmology and Visual Science 2019; 60: 1824-1832

Glaucomatous optic neuropathy (GON) is morphologically characterized by an almost pathognomonic loss of neuroretinal rim, a deepening of the optic cup, thinning of the peripapillary retinal nerve fiber layer, development and enlargement of parapapillary beta zone, focal and diffuse thinning of the retinal arterioles, and optic disc hemorrhages (DHs). After Stephan Drance had alerted the scientific community to the association of DHs with GON, numerous studies have examined the prevalence and incidence of disc hemorrhages in eyes with GON and their associations with other morphological and psychophysical parameters. These investigations revealed that the DHs, although being highly significantly associated with the presence and progression of GON, are not pathognomonic for GON but can occur in a variety of disorders and diseases including posterior vitreous detachment from the optic nerve head, that the number and size of detected DHs is significantly higher in so-called normal-pressure glaucoma than in high-pressure glaucoma, that they remain ophthalmoscopically visible for about one to three months, and that they indicate with a high probability a progression of the glaucomatous process at the site of the DH in eyes with GON, to mention only few of the findings. All these studies were limited in the sense that they assessed the ophthalmoscopically visible DHs. DHs smaller than the spatial resolution of their ophthalmoscopical detectability remained undetected. Since however the event leading to the hemorrhage, such as a vessel break, may be more important than the size of the bleeding, the limitation of the ophthalmoscopical detectability of the DHs might have led to a marked bias in the whole discussion of the pathogenesis of glaucomatous DHs and their importance for GON. To cite an example, the lower intraocular pressure in eyes with normal-pressure glaucoma as compared to eyes with high-pressure

glaucoma leads to an higher transmural pressure difference in the retinal arterioles of eyes with normal-pressure glaucoma, so that a vessel break leads to a larger DH in eyes with normal-pressure glaucoma. Due to their larger size, the DHs in eyes with normal-pressure glaucoma remain longer detectable so that the frequency of their ophthalmoscopical detection is higher.

To overcome these limitations of the preceding studies, Ahnul Ha and colleagues used a customized image-compensation software to enhance stereo disc photographs to detect micro-DHs defined by a size of less than 0.01-mm2 and being undetectable on conventional stereo disc photographs. Among 107 eyes with primary open-angle glaucoma and with macro-DHs, the authors found micro-DHs prior to the macro-DHs in 37% of the eyes, with a median time lag between both hemorrhages of 13.6 months. During a follow-up of 7.1 ± 0.8 years, a perimetric progression of GON was detected in 54% of the eyes with micro-DHs and in 28% of the 68 eyes without micro-DHs ($P = 0.008$).

During a follow-up of 7.1 ± 0.8 years, a perimetric progression of GON was detected in 54% of the eyes with micro-DHs and in 28% of the 68 eyes without micro-DHs ($P = 0.008$)

The differences between the micro-DHs positive group and the micro-DH-negative group in the cumulative perimetric progression probability ($P = 0.001$) and in the overall visual field deterioration rate (−1.01 ± 0.58 vs. −0.78 ± 0.49 dB/year; $P = 0.029$) were significant.

The technique applied by Ha and colleagues and the findings may open a new avenue for a more precise detectability of DHs in eyes with glaucoma, for a better understanding of the etiology of DHs in the process of GON, and for a better clinical diagnosis of the presence and progression of GON.

Forms of Glaucoma

Systemic Risk Factors

Comment by Shan Lin, San Francisco, CA, USA

80969 Association of Statin Use and High Serum Cholesterol Levels With Risk of Primary Open-Angle Glaucoma; Kang JH, Boumenna T, Stein JD, Khawaja A, Rosner BA, Wiggs JL, Pasquale LR; JAMA ophthalmology 2019; 137: 756-765

Kang *et al.* evaluated the association of cholesterol levels and statin use with risk for developing primary open-angle glaucoma (POAG), using data from three population-based cohorts (the Nurses' Health Study, the Nurses' Health Study 2, and the Health Professionals' Follow-up Study).[1] These studies had followed nurses and other health professionals for four years or more and employed health questionnaires for data gathering. In addition, reported incident cases of glaucoma – and more specifically for POAG – were verified by expert review of the clinical data from their eye care professionals, including slit-lamp examination, visual field testing, maximal intraocular pressure, and optic nerve information.

There were 136,782 participants among the cohorts and 886 incident cases of POAG during the study periods. Self-report of high cholesterol was associated with 17% increased risk for POAG (RR, 1.17 [95% CI, 1.00-1.37]). It was also found that for every increase of 20 mg/dL of total serum cholesterol, there was a 7% increase in risk for POAG (RR, 1.07 [95% CI, 1.02-1.11]). In terms of statins, participants with any history of statin use had a 15% lower risk for POAG (RR, 0.85 [95% CI, 0.73-0.99]). When duration of statin use was evaluated, there was statistically significantly lower risk (21% lower risk) for POAG at five years or greater duration (RR, 0.79 [95% CI, 0.65-0.97]), when compared to no use of statin drugs.

The authors have found within the same population cohorts that **lower cholesterol and statin use are associated with lower risk for incident glaucoma.** These results are overall consistent with prior studies. Strengths of the current study include a large population sample, incidence data from a prospective observational study design, and expert review of clinical data related to glaucoma diagnosis. Weaknesses include non-population-based subjects, a predominantly white cohort of subjects, and potential selection bias for getting more timely eye examinations among those who have high cholesterol and/or are being treated for high cholesterol. What would be interesting to study in the future is whether use of statin drugs can be helpful for glaucoma prevention or treatment even among those within the normal range of cholesterol levels.

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Pseudo-exfoliation

Comment by Miriam Kolko, Copenhagen, Denmark

80844 Nailfold Capillaroscopy of Resting Peripheral Blood Flow in Exfoliation Glaucoma and Primary Open-Angle Glaucoma; Philip S, Najafi A, Tantraworasin A, Pasquale LR, Ritch R; JAMA ophthalmology 2019; 137: 618-625

In the present study, the authors investigate the measure of peripheral blood flow as a surrogate marker of systemic vascular involvement in patients with exfoliation glaucoma (XFG), high-tension glaucoma (HTG), and normal-tension glaucoma (NTG) compared to controls. More studies have previously related systemic vascular dysfunction to glaucoma. In particular, decreased peripheral capillary blood flow at the nailfold has been found in patients with NTG, whereas it has previously been reported that patients with XFG have high degree of nailfold microvascular tortuosity. Here, the authors report a decreased resting peripheral capillary blood flow in patients with XFG and NTG compared to controls by means of a nailfold capillaroscopy (NFC). A similar, but not significant tendency is found in HTG patients. Findings concerning XFG are highlighted and it is discussed that exfoliation material may lead to alterations in elastosis, levels of oxidative stress, and endothelial function, followed by vascular stiffness. **Thus, the peripheral capillary blood flow in XFG may be particularly decreased related to the systemic nature of exfoliation material.** While the results are interesting and supporting a systemic nature of XFG and NTG, the relatively large age difference among individuals in the glaucoma subgroups and controls as well as the lack of temperature control during NFC measurements should be considered. Moreover, significant inter-individual variations within all groups exists and future studies are needed to confirm the significance of the present study. In summary, the study is, however, well performed and the authors are highlighting the limitations of the study and adjusting for multiple co-variables. In conclusion, the findings provide supportive evidence of decreased peripheral capillary blood flow as a part of the XFG and NTG phenotypes and contribute to increasing evidence of a systemic nature of glaucoma.

Medical Treatment

ROCK Inhibitors

Comment by Karim El-Assal and Gus Gazzard,

80619 Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients With Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study; Khouri AS, Serle JB, Bacharach J, Usner DW, Lewis RA, Braswell P, Kopczynski CC, Heah T; American Journal of Ophthalmology 2019; 204: 97-104

The Rho kinase (ROCK) inhibitors, a new class of topical ocular hypotensive drugs, are a recent addition to the glaucoma treatment family. Netarsudil ophthalmic solution 0.02%, was approved by the FDA in 2017, over 20 years since the introduction of Latanoprost in 1996. ROCK inhibitors reduce the intraocular pressure (IOP) in a unique way by modulating the cytoskeleton of the trabecular meshwork, reducing its resistance and increasing trabecular outflow facility.

> One concern is that almost 20% of patients in the Netarsudil arm discontinued treatment due to adverse events (AEs) compared to just over 2% in the timolol group

In this article, Khouri and colleagues compared the safety and efficacy of Netarsudil versus timolol in a multi-centre, double-masked, randomized, non-inferiority study. Patients with open-angle glaucoma or ocular hypertension having unmedicated baseline IOP > 20 to < 30 mmHg were included. The primary endpoint was mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM week 2, week 6, and month 3 (a total of nine time points) in patients with baseline IOP < 25 mmHg. Secondary end points were mean IOP at the same time points in patients with IOP < 27 mmHg and in the overall study population. Safety analysis covered six months. In total 708 patients were randomized to either drug. One hundred eighty-six patients were included in each arm for the primary efficacy analysis.

Non-inferiority was defined as mean IOP within 1.5mmHg for all time points and within 1.0 mmHg at the majority of time points. **It was encouraging to find that Netarsudil met the criteria for non-inferiority to timolol** for both the primary and secondary efficacy analysis. Most common ocular AEs in the Netarsudil group were conjunctival hyperaemia (47.9%), cornea verticillate (vortex keratopathy) (24.4%) and conjunctival haemorrhage (16%). The majority of AEs were reported as mild and there was a good systemic safety profile.

One concern is that almost 20% of patients in the Netarsudil arm discontinued treatment due to adverse events (AEs) compared to just over 2% in the timolol group. The authors gave no explanation why that was the case. Based on this study Netarsudil is non-inferior to timolol in IOP lowering in patients with ocular hypertension and open angle glaucoma. The once daily dosing may make it a convenient choice for patients.

Surgical Treatment

What if it were you?

Comment by Rupert Bourne and Sokratis Zormpas, Cambridge, UK

80960 Glaucoma surgery preferences when the surgeon adopts the role of the patient; Chang TC, Vanner EA, Parrish RK; Eye 2019; 33: 1577-1583

This paper reports the results of a survey in 2018 of 27% of American Glaucoma Society (AGS) members (n = 289) which asked them to imagine they were a glaucoma patient and then their preference of glaucoma procedure. The clinical scenario presented was that of a primary open-angle glaucoma patient with normal visual acuity, adherent taking all commercially available glaucoma medications, but with inadequate intraocular pressure (IOP) control and progressive visual field loss. The members were asked to choose one procedure from a list of 15 surgical options under each of three preoperative IOP levels.

> Ab interno trabeculotomy was the most frequently chosen procedure (20%), followed by the Xen gel stent (19%)

Overall, ab interno trabeculotomy (gonioscopy-assisted transluminal trabeculotomy [GATT] or Trab360) was the most frequently chosen procedure (20%), followed by the Xen gel stent (19%), iStent with two devices (14%), traditional trabeculectomy augmented with mitomycin C (14%), and glaucoma drainage devices (GDD; Ahmed/Baerveldt; 7%). **The authors were able to compare these findings to a survey of AGS members in 2016,**[1] **who were asked which procedure they would choose to offer to a hypothetical patient with glaucoma, where 59% had chosen a traditional trabeculectomy** with MMC and 23% a GDD. The authors suggest that the decreased preference of either procedure in the most recent survey may be due an increase in the perceived risks (potential loss) when the AGS participants adopted the patient role, which would support the notion that loss aversion can alter the perceived risk/benefit ratio when an individual's perspective is shifted from that of a surgeon (expected utility theory) to that of a patient (prospect theory).[2]

This approach is intriguing as other studies have shown that doctors' recommendations are affected by cognitive biases, for example among retina specialists who select different age-related macular degeneration treatments for themselves than for hypothetical patients.[3] At lower preoperative IOP levels, more participants preferred non-bleb forming and/or conjunctiva-sparing procedures, which is also interesting as it suggests that the **perceived risk associated with bleb-forming or conjunctiva-violating procedures outweighed concerns over relative lack of efficacy.** Although there are several limitations of this study which the authors give due consideration, it does make one reflect on one's own biases in making surgical decisions – perhaps we all need to read Kahneman![2]

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Selective Laser Trabeculoplasty

Comment by Tony Realini, Morgantown, WV, USA

80933 Primary Selective Laser Trabeculoplasty for Open-Angle Glaucoma and Ocular Hypertension: Clinical Outcomes, Predictors of Success, and Safety from the Laser in Glaucoma and Ocular Hypertension Trial; Garg A, Vickerstaff V, Nathwani N, Garway-Heath D, Konstantakopoulou E, Ambler G, Bunce C, Wormald R, Barton K, Gazzard G; Ophthalmology 2019; 126: 1238-1248

Garg and colleagues have recently presented **a post hoc analysis of data from the landmark LiGHT study, which compared primary medical therapy to primary selective laser trabeculoplasty (SLT) in newly diagnosed and treatment-naïve patients with primary open-angle glaucoma (POAG) or high-risk ocular hypertension (OHT),** in which clinical outcomes following SLT are described in greater detail. The topline results are as follows. Through three years of follow-up, 75% of eyes were medication-free while achieving their disease- and severity-specific target IOP with one or two SLT treatments; considering initial SLT only, the 3-year success rate was nearly 60%. Mean IOP reductions among these three-year survivors were on the order of 8 mmHg (31%). Of note, **no sight-threatening complications were observed in 776 SLT treatments.** Interestingly,

only a single IOP spike warranted medical management, suggesting that the incidence of IOP spikes in treatment-naïve eyes is substantially lower than in treated eyes in prior studies. The implications of these findings are enormous. SLT offers many advantages over medical therapy, including elimination of the nonadherence issue, the avoidance of medication-related side effects, and favorable cost-effectiveness. Why SLT has not supplanted medical therapy as the preferred first-line therapy before now is puzzling. Now, with the outcomes from LiGHT continuing to demonstrate the favorability of SLT, we are due an evidence-based paradigm shift. Interestingly, some of the impetus for this paradigm shift is derived from the surgical arena and the growing utilization of minimally invasive glaucoma surgeries (MIGS) in combination with cataract surgery to reduce the medication burden of our patients with glaucoma. As we embrace the positive impact on our patients' quality of life in living a drop-free lifestyle post-MIGS, we should ask ourselves why we are still starting with drops in the first place.

With the outcomes from LiGHT continuing to demonstrate the favorability of SLT, we are due an evidence-based paradigm shift

Drainage Devices I

Comment by Frederick R. Burgess and Andrew Tatham, Edinburgh, UK

80503 Optical coherence tomography analysis of filtering blebs after long-term, functioning trabeculectomy and XEN®; stent implant; Teus MA, Paz Moreno-Arrones J, Castaño B, Castejon MA, Bolivar G; Graefe's Archive for Clinical and Experimental Ophthalmology 2019; 257: 1005-1011

The success of subconjunctival glaucoma surgery depends on the formation of an adequate filtering bleb. Post-operatively, blebs can be categorized by macroscopic appearance or by internal morphology using anterior segment optical coherence tomography (ASOCT). Important parameters include bleb height, bleb wall thickness, tissue reflectivity and the presence of epithelial microcysts. **This study compared bleb morphology in 15 eyes treated with trabeculectomy and ten eyes treated with the Xen Gel Stent.**[1]

Trabeculectomies were performed using a fornix-based conjunctival flap, triangular scleral flap and 0.02% mitomycin C (MMC) for two minutes. Xen Gel Stents were implanted into the superonasal quadrant using an ab interno approach in eyes pre-treated (15 mins before surgery) with a 0.1 ml injection of 0.02% MMC. **Bleb morphology was examined using Swept-Source OCT and using the Indiana Bleb Appearance Grading Scale (IBAGS) at least one year after surgery.**

Using the IBAGS, Xen blebs tended to be flatter than trabeculectomy blebs, however both procedures produced blebs of similar horizontal extent. Twenty percent of eyes in each group had avascular cystic blebs. Using ASOCT, Xen blebs were significantly flatter than trabeculectomy blebs (417±183 µm versus 618±256 µm) but in both cases the conjunctiva was significantly thicker than in a control group (244±45 µm). Although Xen blebs were flatter than those seen with trabeculectomy, both groups had a similar average reduction in intraocular pressure (IOP), suggesting effective conjunctival filtration.

Interestingly, the conjunctival epithelium was thicker in Xen than trabeculectomy blebs (65±18.5 µm versus 60±17.7 µm) but Xen blebs seemed to be associated with less subconjunctival fibrosis. None of the Xen eyes compared to six out of nine trabeculectomy eyes were noted to have subepithelial fibrosis on ASOCT.

> There is likely to be wide variation in bleb morphology produced with both procedures and it is not clear whether any patients had bleb needling which will inevitably affect morphology

Bleb evaluation is important to determine functionality and this study demonstrates the different characteristics of blebs produced following Xen and trabeculectomy surgery. However, there is likely to be wide variation in bleb morphology produced with both procedures and it is not clear whether any patients had bleb needling which will inevitably affect morphology. The study is also limited by a small sample size and high risk of inclusion bias as the case selection process was not described. In addition, it is not clear whether the Xen Gel Stents were placed under the conjunctiva or Tenon's. The finding of an absence of fibrosis in eyes treated with Xen is also surprising given the high needling rate reported with this device.[1]

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Drainage Devices II

Comment by Kimberly A. Mankiewicz and Robert Feldman, Houston, TX, USA

80976 Initial Clinical Results of the eyeWatch: a New Adjustable Glaucoma Drainage Device Used in Refractory Glaucoma Surgery; Roy S, Villamarin A, Stergiopulos C, Bigler S, Guidotti J, Stergiopulos N, Kniestedt C, Mermoud A; Journal of Glaucoma 2019; 28: 452-458

The goal of glaucoma surgery is to control intraocular pressure (IOP) to prevent progression of vision loss. One way to achieve this, after exhaustion of medication options, is by use of glaucoma drainage devices. The Baerveldt Glaucoma Implant (BGI; Abbott Medical Optics, Inc., Santa Ana, CA) is one of the more commonly used devices. The BGI does not have a valve restricting aqueous flow in the early period after implantation. Thus, either an obturator that is removed postoperatively or tube ligature must be used to prevent hypotony until an adequate bleb has formed. However, during flow restriction, IOP control is difficult, potentially resulting in IOP spikes above target and necessitating the use of IOP-lowering medications. Also, an additional step is required to remove flow restriction, increasing risk to the patient and cost.

> The eyeWatch is a potentially useful device for patients with refractory glaucoma who require a nonvalved glaucoma implant for glaucoma control

Roy *et al.* analyzed the use of the eyeWatch device, a device implanted with the BGI that allows for adjustable flow resistance. The eyeWatch allows variable compression of the tube draining aqueous from the anterior chamber using a magnetic rotor and is adjusted with an external control unit, the eyeWatch Pen, containing a magnet and compass to read the rotor position. Fifteen eyes from 15 patients were included in this study. Patients included were 18 years or older with refractory glaucoma after previous filtering surgeries, with an IOP > 20 mmHg on maximally tolerated medical therapy. Patients with secondary glaucomas or related previous eye surgeries were excluded. BGIs with surface areas of either 250 or 350 mm^2 were implanted. Complete success was defined as IOP ≤ 18 or ≥ 6 mmHg and IOP reduction of 20% with no IOP-lowering medications at last visit. Overall success was the same except with or without IOP-lowering medications. Additional surgery requiring a trip to the operating room was defined as a failure, but procedures at the slit lamp were not considered reoperation (e.g., bleb needling, paracentesis, etc.).

IOP decreased from 26.2 ± 6.8 mmHg at baseline to 11.9 ± 2.8 mmHg at 12 months, a 54% decrease ($P < 0.001$). Mean number of glaucoma medications also decreased from 3.0 ± 0.7 at baseline to 0.8 ± 0.9 at last visit, a 73% reduction ($P < 0.001$). Mean endothelial cell count and central corneal thickness were not different at baseline and last visit. Best-corrected visual acuity also remained stable. **The failure rate was 7%,** and four eyes had complications, two conjunctival wound leaks and two choroidal detachments. Three resolved spontaneously, with one wound leak requiring surgical revision. No slit-lamp interventions were required. Five patients with the device underwent magnetic resonance imaging (MRI) with no complications during or after imaging, but this may vary depending on the size of the MRI magnet.

The eyeWatch is a potentially useful device for patients with refractory glaucoma who require a nonvalved glaucoma implant for glaucoma control. Further and larger studies will be necessary to investigate efficacy and safety fully.

Drainage Devices III

Comment by Nils Loewen, Pittsburgh and Yousef Al Yousef, PA, USA

80996 A Prospective Analysis of iStent Inject Microstent Positioning: Schlemm Canal Dilatation and Intraocular Pressure Correlations; Gillmann K, Bravetti GE, Mermoud A, Mansouri K; Journal of Glaucoma 2019; 28: 613-621

The iStent and iStent inject are trabecular meshwork (TM) bypass devices used in an add-on procedure with cataract surgery,[1,2] and this use pattern continues to be the most common one. This elegant prospective study by Gillmann *et al.* examines the anatomic changes caused by the iStent inject by anterior segment optical coherence tomography (ASOCT) and attempts to correlate them to IOP and glaucoma medications. The authors enrolled 25 eyes from 19 patients with open-angle glaucoma or PEX glaucoma and compared them to 13 control eyes. The authors found that **device protrusion and larger Schlemm's canal (SC) diameters were associated with lower postoperative IOP** (rs = −0.54;P=0.005 and rs = −0.43;P=0.04, respectively), whereas the distance between the devices' heads and SC was inversely correlated with SC dilatation (rs = −0.41;P=0.04).

> How difficult it is to place TM bypass stents in a consistent and effective manner, even in expert hands

Interestingly, the average major and minor diameter of the temporal SC of implanted eyes was larger than in controls. However, similar effects were described following standalone cataract surgery[3] possibly from a trabeculoplasty-like effect from TM stretch or ultrasound exposure during phacoemulsification[4] that is absent when TM is removed comprehensively.[5] The authors discuss shortcomings, including a relatively low patient number and the fact that two iStents inject are implanted, which limits a device-specific assessment.

This study highlights how difficult it is to place TM bypass stents in a consistent and effective manner, even in expert hands. The authors do not mention that fibrosis[6] or biofilm deposition[7] can likely not be seen due to the limited resolution of ASOCT that might be responsible for the waning effect observed in larger studies.[8,9]

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Miscellaneous

Glaucoma and Driving

Comment by Andrew Tatham, Edinburgh, UK

81404 Eye Movements of Drivers with Glaucoma on a Visual Recognition Slide Test; Lee SS, Black AA, Wood JM; Optometry and Vision Science 2019; 96: 484-491

Drivers with glaucoma are reported to have reduced ability to detect traffic hazards and higher rates of motor vehicle collisions, though the underlying mechanisms are poorly understood.[1] Visual field loss is undoubtedly a major contributor, but previous studies have suggested that scanning behavior, as explored by observing eye movement patterns, is also altered in glaucoma and that changes to visual field and eye movement patterns are inextricably linked. For example, Crabb *et al.* observed older drivers with glaucoma to have a higher rate of saccades when performing a hazard perception test, perhaps as a strategy to compensate for glaucomatous visual loss.[2] **The aim of Lee and colleagues' work was to evaluate eye movement patterns and performance of drivers with glaucoma compared to age-matched controls.**

Visual search behavior was evaluated in 31 drivers with glaucoma and 25 controls, while performing DriveSafe, a slide recognition test purported to predict fitness to drive. The DriveSafe consists of 11 images of driving scenes presented on a computer screen. Participants are required to report the type, position and direction of travel of different road users shown in the scene. A score was assigned for the total number of correctly reported items and visual search during testing examined using an eye tracker.

> Patients with glaucoma may have less effective visual scanning strategies, reducing their ability to identify potential hazards

Drivers with glaucoma were found to have significantly worse DriveSafe scores compared to controls, indicating greater difficulty in identifying and locating relevant objects. Differences in eye movement measures were also noted, including smaller amplitude saccades and the observation that those with glaucoma spent less time fixating on road users, with the rest of the time spent looking at less relevant objects. Longer fixation on road users was associated with better DriveSafe scores. According to the developer's recommended cut off score, only one participant failed the DriveSafe test, but this likely reflects the relatively mild visual field loss in the better eyes of participants (average mean deviation of -2.88 ± 3.17 dB).

Although it seems intuitive that drivers with glaucoma would spend more time fixating on road users, in order to maximize identification of potential obstacles, the opposite was true. The shorter time spent fixating on road users may have been due to the shorter saccadic amplitudes and short task time. This suggests that patients with glaucoma may have less effective visual scanning strategies, reducing their ability to identify potential hazards.

Although the DriveSafe test has not been validated for the evaluation of patients with visual impairment this study provides an important starting point and adds to the important work examining how glaucoma affects activities of daily living.

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News Flashes

- How difficult it is to place TM bypass stents in a consistent and effective manner, even in expert hands
- Can OCTA parameters predict functional deterioration with high enough accuracy to be clinically useful for confirmation or forecasting of functional glaucoma progression?
- The role of nighttime IOP fluctuations in glaucoma progression is not completely understood and investigated"
- Ab interno trabeculotomy was the most frequently chosen procedure (20%), followed by the Xen gel stent (19%)
- Radial diffusivity in the optic radiation of glaucoma patients increased with visual field deficits and cortical thinning in a retinotopic manner
- The eyeWatch is a potentially useful device for patients with refractory glaucoma who require a nonvalved glaucoma implant for glaucoma control
- One concern is that almost 20% of patients in the Netarsudil arm discontinued treatment due to adverse events (AEs) compared to just over 2% in the timolol group
- During a follow-up of 7.1 ± 0.8 years, a perimetric progression of GON was detected in 54% of the eyes with micro-DHs and in 28% of the 68 eyes without micro-DHs (P = 0.008).
- The magnitude of effect of the systemic factors on the peripapillary VD measurements become clinically insignificant.
- Until we better understand the specific characteristics of IOP variation over time that confer risk of the development and/or progression of glaucoma, studies such as these are challenging to discuss in the context of clinical implications.
- With the outcomes from LiGHT continuing to demonstrate the favorability of SLT, we are due an evidence-based paradigm shift
- There is a long-standing discussion whether changes in blood flow and oxygen metabolism are primary or secondary in glaucoma. Since this small-scale study was cross-sectional it does not contribute to the solution of this fundamental question
- Patients with glaucoma may have less effective visual scanning strategies, reducing their ability to identify potential hazards
- There is likely to be wide variation in bleb morphology produced with both procedures and it is not clear whether any patients had bleb needling which will inevitably affect morphology
- This study adds to the growing literature suggesting that vascular insufficiency is associated with faster glaucomatous progression

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