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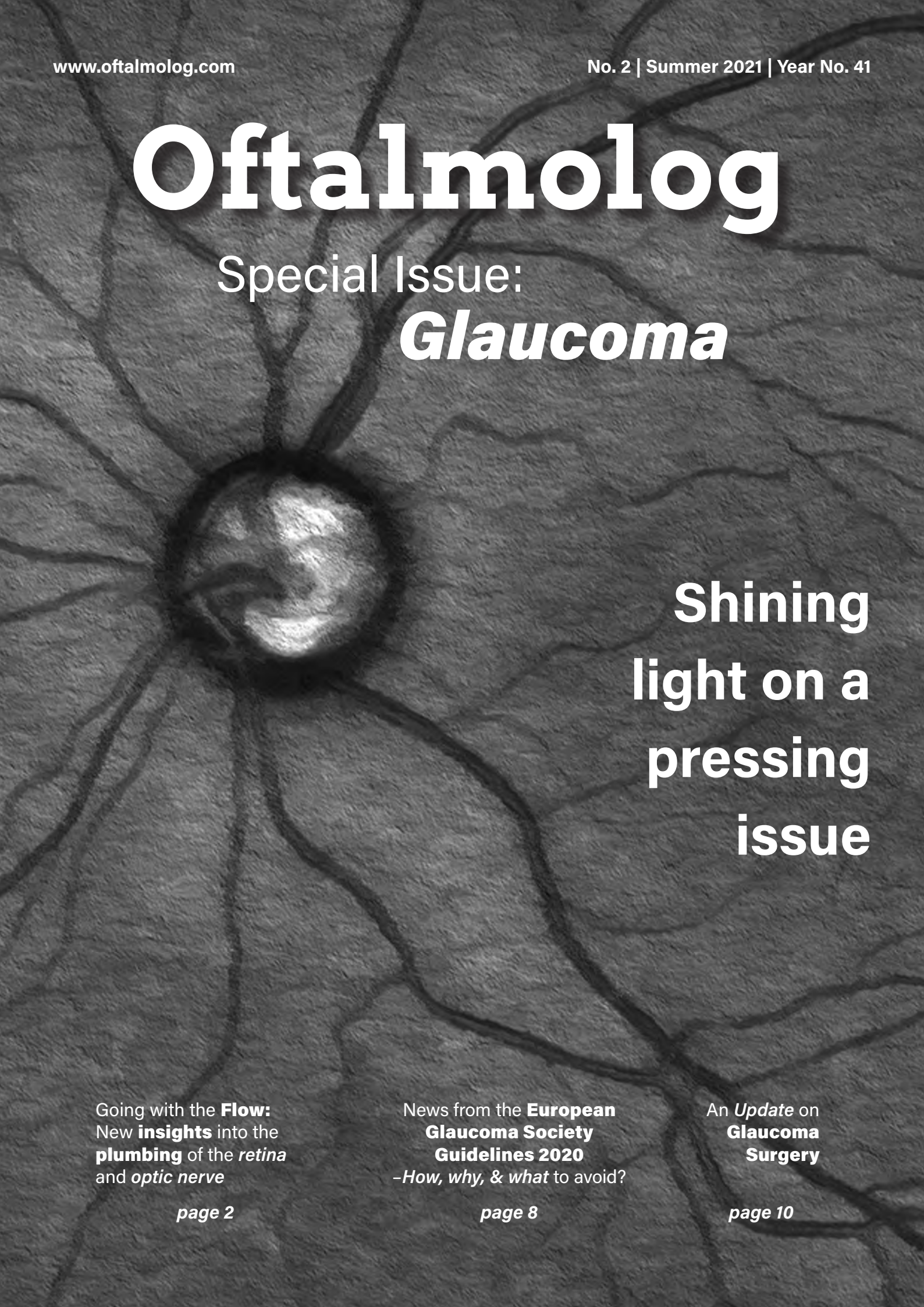
Special Issue: *Glaucoma*



Shining light on a pressing issue



Leif Hynnekleiv | Alexander S. Thrane | Vinita Rangroo Thrane

Going with the **Flow:**

New **insights** into the **plumbing** of the ***retina*** and ***optic nerve***

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Abstract

Fluid and solute movement in the posterior segment of the eye is not fully understood. Much like the brain, the retina has high fluidic demands, and yet, is completely devoid of conventional lymphatics. In a recently published study, we present evidence of a novel fluid clearance pathway through the retina and optic nerve that involves perivascular spaces and lymphatics, much like the glymphatic system of the brain. These discoveries bring new insights into diseases like glaucoma with new opportunities for treatment.

Water is the universal solvent of life but does not flow completely freely through our body. Ever since the Nobel Prize-winning discovery of aquaporins by Peter Agre, our eyes have been opened to the molecular machinery governing where and how water and solutes move at the microscopic level - our subcellular plumbing.[1] Directional fluid and solute movement driven by hydrostatic and electrochemical gradients, known as advection, is notoriously difficult to study. This is because advection is easily drowned out by the much larger amounts of random fluid movements, or diffusion. However, on a tissue or organ level, advective preferential pathways for fluid movement reveal themselves.[2]

The importance of this dichotomy between the macro- and microscopic functions of our subcellular plumbing was recently highlighted by the discovery of a novel "lymphatic-like" system for fluid and waste clearance in the brain. Although aquaporin water channels were known to be densely expressed by supporting astroglial cells plastering the cerebrovasculature, their exact role was not understood. That is, until imaging of solute transport in the brain was done on a larger organ-wide scale.[3]

In 2012, Iliff et al. showed that in our crowded brains, a quasi-lymphatic system facilitated by water channels in glial-cells allowed for rapid movement of solutes and fluid through doughnut shaped paravascular spaces surrounding the blood vessels.[4] This fluid moves through the brain tissues, is collected in the peri-venous spaces, and is dumped in the meningeal lymphatics (**Figure 1**). The system was described as the *glymphatic system* (combining the words glia- and lymphatics), sometimes also termed the *brainphatic system.* These findings sparked a revolution in research and understanding of glial-cells and their function. Further research has shown that the brain's glymphatic system is critical for the elimination of amyloid-beta plaques linked to Alzheimer's disease, and seems to hold clues to the importance of sleep for "washing" our brains.[5] The drive and mechanism underlying this flow is not quite understood, though the pulsatility of the brain and cerebral vessels is postulated to serve a role in the movement of this fluid.[6]

How is this relevant to ophthalmologists?

The neural tissue of the eye is developmentally a direct protrusion of the forebrain. For this reason, the optic nerve is physiologically like a white matter tract, and therefore vulnerable to diseases like multiple sclerosis. The optic nerve is ensheathed by the meninges, which contains lymphatic vessels in the dura mater layer.[7]

By some estimates, the eye contains more than 98% water. In the anterior part of the eye, production and drainage routes for water and solutes via trabecular and uveoscleral pathways are well described (**Figure 2**).[8,9] However, the posterior neural tissues of the eye have some of the highest metabolic rates and fluidic demands per gram of any tissues in the body. And yet, similar to the brain parenchyma, the eye is devoid of lymphatics to facilitate fluid and solute transport.[10]

In 2017, Mathieu et al. demonstrated the movement of small cerebrospinal fluid tracers

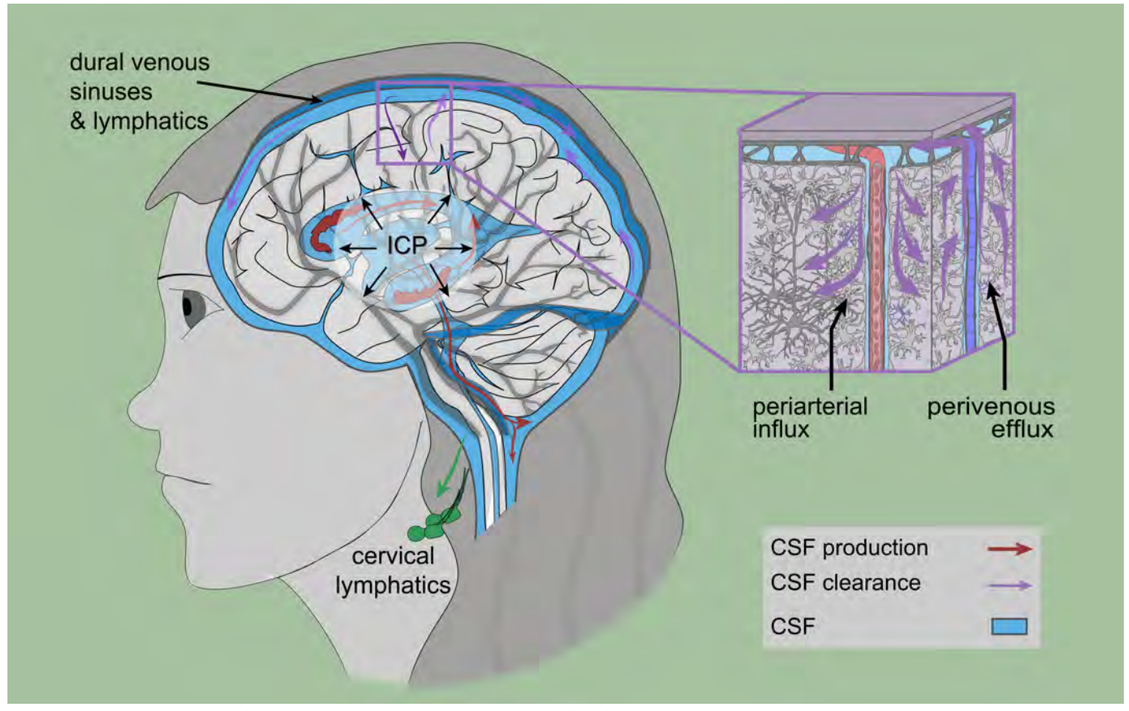

Figure 1. Proposed function of the brain glymphatic system. Periarterial fluid flows through interstitial brain tissue, to the perivenous-spaces, and is cleared by dural lymphatics. Adapted from Thrane et al. Trends Neurosci 2014 (https://pubmed.ncbi.nlm.nih.gov/25236348/, Fig 1)

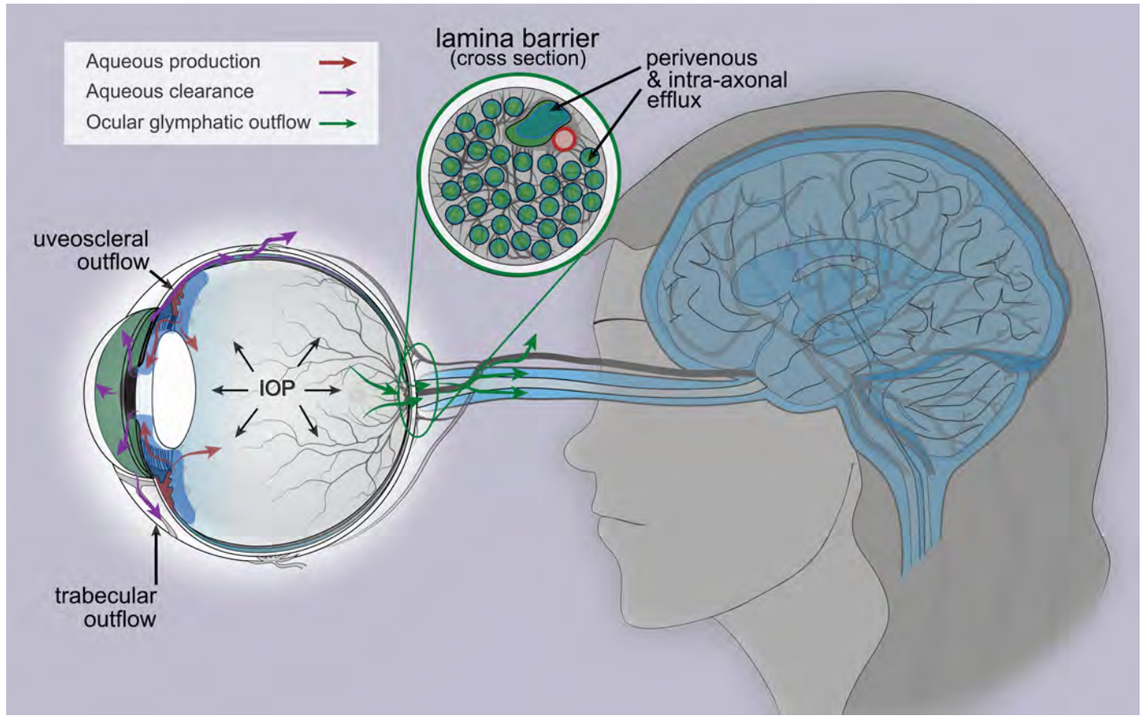

Figure 2. Known fluid transport systems of the eye. Aqueous fluid produced in the ciliary body (red arrows). Aqueous drained by the trabecular meshwork in the anterior chamber angle and through the uveoscleral outflow pathway (purple arrows). The newly discovered ocular glymphatic flow moving from the intravitreal and suprachoroidal spaces, though the lamina cribrosa, to the perivenous spaces, to the dural lymphatics surrounding the optic nerve (green arrows). Adapted from Rangroo Thrane et al. Acta Ophthalmol 2021 (https://pubmed.ncbi.nlm.nih.gov/32706172/, Fig 1)

from the brain into the optic nerve, consistent with glymphatic transport in the *retrograde direction*, from the brain towards the eye.[11] In collaboration with several laboratories, we recently published a study outlining the existence and basic function of a two-way ocular glymphatic system (**Figures 3 & 4**). This system shares similarities with the brain glymphatic system, with some local adaptations.[12]

Following various tracer infusions into the vitreous, suprachoroidal space, intravascularly and intra-cisternally, imaging of transparent rodent heads showed a bidirectional glymphatic transport between the eye and the optic nerve (**Figure 4**).[13] This fluid system was directly dependent on the high-to-low pressure gradient between the intraocular- and intracranial pressures (**Figure 5**). The system was also affected by the status of the lamina cribrosa, a fibrous connective tissue structure perforated by axon bundles and vessels. It acts as a supporting structure and barrier between the eye and the optic nerve and is essentially a gateway between the eye and the brain. In our study, when intracranial pressure was raised, the glymphatic drainage through the lamina was completely halted. Conversely, lowering the intracranial pressure *increased* the glymphatic flow (**Figure 5**).

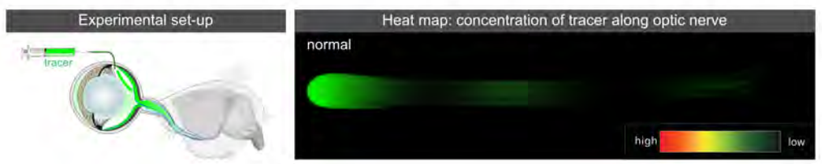

Figure 3. Heat-map of intravitreal tracer (green) found in optic nerve showing baseline glymphatic flow. Tracer has moved from the vitreous, through the neuro-retina and lamina cribrosa, to the optic nerve. Adapted from Wang et al. Sci Transl Med 2020 (https://pubmed.ncbi.nlm.nih.gov/32213628/, Fig 4A)

Small tracer molecules like amyloid-beta and radio-labelled potassium enter retinal axons and the perivenous spaces of both the retina and optic nerve, before being cleared by dural lymphatics around the optic nerve, and eventually, cervical lymph nodes.[12] Interestingly, larger molecules like dextrans were blocked by the lamina in rats and mice. This indicates that under physiological conditions, the glympathic outflow pathway exhibits selectivity, allowing some, but not all, molecules to pass. The lamina has the anatomical function of not only supporting axon bundles but also acts as a hydrostatic barrier by redirecting fluid and solute movement into axons and the perivenous spaces at the optic nerve head.[14]

Simultaneous injections of different tracers into the vitreous of the eye and the cisterna magna of the brain demonstrated that the forward and backward glymphatic flow are spatially separated (**Figure 4**). Cisterna magna tracers were transported along periarterial and pericapillary spaces in the optic nerve, stopping several hundred micrometres from the globe itself. Meanwhile, the intravitreal tracers were transported along peri*venous* spaces in the optic nerve (**Figure 4**).

Müller glial cells of the retina express large amounts of the water channel aquaporin-4 (AQP4).[15,16] In the brain, AQP4 is heavily expressed by astroglia end-feet, and line virtually all of the central nervous system vasculature.[17] Comparing control mice with knock-out mice, in which the AQP4 gene was deleted, we found a significant reduction in amyloid-beta clearance. This supports existing evidence that AQP4 facilitates water movement into and out of paravascular spaces in the brain. AQP4 thus seems to act in the eye and brain much like catch basins and grates of city streets that direct water into larger sewage pipes.

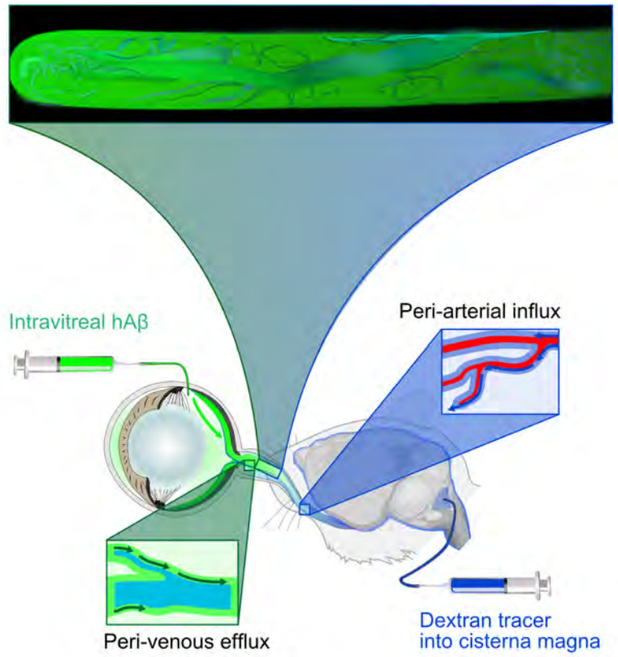

Figure 4. Illustration of mouse with dextran tracer (blue) injected into the CSF of the cisterna magna, which moves into peri-arterial spaces, while intravitreal human amyloid-beta (green) tracer moves through to the optic nerve and is found peri-venously. Proof of spatially and functionally separated bi-directional glymphatic flow. Adapted from Wang et al. Sci Transl Med 2020 (https://pubmed.ncbi.nlm.nih.gov/32213628/, Fig 1H)

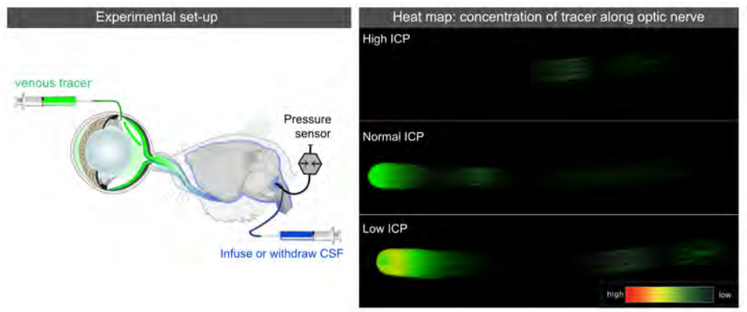

Figure 5. Changing glymphatic flow by manipulating intracranial pressure (ICP). Increased ICP reduced flow, while lowering ICP encouraged flow. Adapted from Wang et al. Sci Transl Med 2020 (https://pubmed.ncbi.nlm.nih.gov/32213628/, Fig 3A)

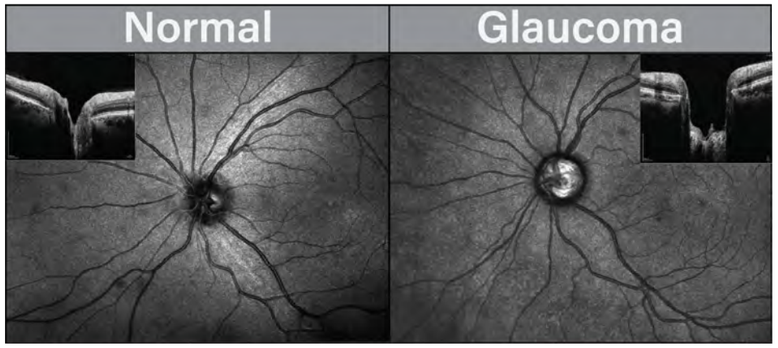

Figure 6. Confocal scanning laser ophthalmoscopy (C-SLO) and spectral domain optical coherence tomography (OCT, inset) images of normal and glaucomatous optic nerve head from Canon HS100. Glaucoma is associated with thinning of the retinal nerve fiber layer (RNFL) and optic disc rim tissues increasing the cup/disc ratio and causing a loss of the striated RNFL fundus reflex. With advancing glaucoma, we also see a posterior deflection and damage to the lamina cribrosa with increased pore size and sometimes acquired optic pits, resulting in pathological glymphatic flow.

Glymphatics & Glaucoma

Glaucoma is a neurodegenerative eye disease characterized by a recognized pattern of retinal ganglion cell death, optic disc excavation, and visual field loss. Increased intraocular pressure is one of the main risk factors of glaucoma.[18] Amyloid-beta has been shown to accumulate in the retina of glaucomatous eyes and to induce apoptosis of retinal ganglion cells.[19] Alzheimer's disease, the most common cause of dementia, is a neurodegenerative disease hallmarked by the accumulation of amyloid-beta in extracellular brain tissue. The brain glymphatic system has been tightly implicated in the pathophysiology of dementia.

Our initial hypothesis was that a reduction in glymphatic flow might contribute to glaucoma. However, using two distinct animal models of glaucoma, we found an *increase* in glymphatic tracer clearance, even *after* normalization of the intraocular pressure. Excessive outflow during high intraocular pressure could be explained by an increase in the translaminar pressure gradient. However, the increased flow after normalization of intraocular pressure, suggested that damage to the lamina cribrosa had occurred.

Destruction and outward deflection of the lamina cribrosa is a well-known feature of glaucoma (**Figure 6**), but its role in the disease development is not established.[14]

By examining the microscopic distribution of tracer clearance in glaucomatous and age-matched healthy controls, we found that clearance no longer was intra-axonal and perivascular, but primarily *extracellular*. When comparing the lamina barrier of glaucomatous and healthy mice by electron microscopy, we found obvious structural defects in the lamina. Functionally, these defects allowed passage of large dextrans out of the eye. The lamina no longer re-directed fluid into axons, and instead allowed free passage via large defects.

We hypothesize that excessive and unfiltered glymphatic outflow across the eye-brain hydrostatic gradient may cause wash-out of important metabolites and nutrients. Slowing of intra-axonal tracer clearance might lead to build-up of metabolic waste products, like amyloid-beta, leading to neurotoxicity, dysfunction, inflammation, and cell death.[20]

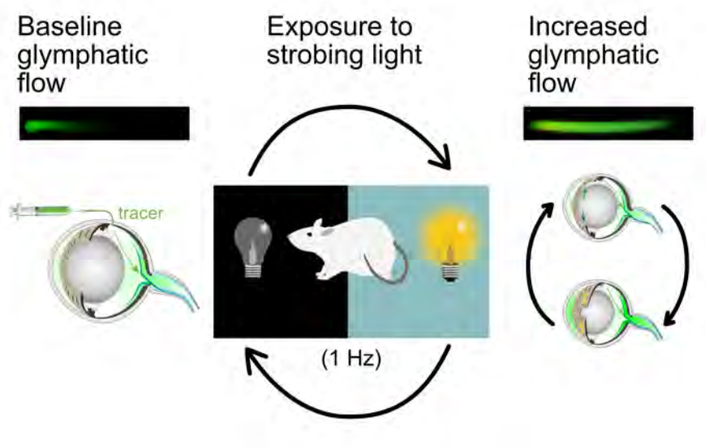

Figure 7. Significantly increased glymphatic flow through the optic nerve compared to baseline after flickering-light exposure. Adapted from Wang et al. Sci Transl Med 2020 (https://pubmed.ncbi.nlm.nih.gov/32213628/, Fig 4)

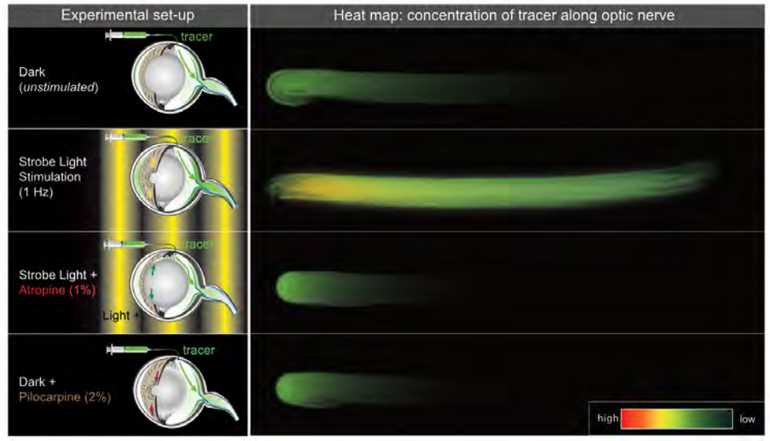

Figure 8. Heat-map showing basal glymphatic flow through the optic nerve and a significant increase in flow after unhindered repeated pupillary constriction/dilation induced by flickering light. In mice after first administering atropine or pilocarpine eye drops (which paralyzed pupillary constriction/dilation) flow did not increase from baseline, suggesting a link between pupillary movement and glymphatic flow. Adapted from Wang et al. Sci Transl Med 2020 (https://pubmed.ncbi.nlm.nih.gov/32213628/, Fig 4)

Another intriguing and puzzling finding in our study was that tracer outflow via the glymphatic pathway could be accelerated by the pupillary light response using flickering light (**Figure 7**). Rodents that were exposed to a flickering light once per second had a marked increase in glymphatic flow. This enhancement was blocked by topical atropine and pilocarpine, indicating that the movement of the pupil itself contributed to the increased glymphatic flow (**Figure 8**). Rodents have a rather rudimentary ciliary muscle compared to humans, so an even stronger functional link between glymphatic drainage, pupillary movement, and accommodation may exist in humans. When we injected tracers into the suprachoroidal space of rodents, a portion could be found in the optic nerve. Is it possible that an explanation could be found in an interplay between the glymphatic and uveoscleral outflow systems?

The net amount of fluid that exits through this novel glymphatic clearance route at the posterior pole of the eye is unknown and difficult to quantify. Large fluid and solute movement across the optic nerve head is physically impossible due to space constraints. It is likely to be orders of magnitude lower than intraocular fluid clearance from the anterior segment. Our findings indicate that the net amount of fluid clearance is not as important as the delicate balance of fluid and solute management.

REMAINING QUESTIONS:

- What other molecules are transported by the ocular glymphatic clearance pathway?
- What other eye diseases could be linked to glymphatic impairment?
- Can we develop diagnostic tracers to study this pathway in a clinical setting?
- Can we develop treatments that modulate transport or prevent damage to the glymphatic system?

Conclusion

To summarize, we have described a novel ocular glymphatic system characterized by selective fluid and solute transport from the retina along axons, across the lamina cribrosa, and via perivenous spaces to "classical" lymphatics. This system is dependent on the pressure gradient between the eye and the brain, and the clearance is stimulated by pupil movement. Glaucomatous damage to the lamina barrier greatly disturbs glymphatic function which impairs intra-axonal clearance of potentially neurotoxic solutes. Several important questions remain. Further characterization and knowledge of the ocular glymphatic system could be vital in the understanding of various eye diseases, and in the development of new diagnostics and treatments.

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KEY POINTS:

- ***We discovered a novel ocular glymphatic system***, which selectively transports solutes and fluids from the retina, along axons, across the lamina cribrosa, to the lymphatic system.
- ***The pressure gradient between the eyes and the brain is key*** to this transport and clearance is stimulated by pupil movement.
- ***Damage caused by glaucoma can impact this system***, potentially preventing proper clearance of neurotoxic solutes.

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News from the **European Glaucoma Society Guidelines 2020** – *How, why, & what* to avoid?

Miriam Kolko

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EGS guidelines: History

In December 2020, the 5th edition of the European Glaucoma Society (EGS) Guidelines became available. Since the first edition of the EGS guidelines was published in 1998, the EGS has been continuously working to update the evidence-based guidelines for dealing with the increasing number of glaucoma patients. The Danish Glaucoma Guidelines from 1997 greatly inspired the first edition, especially regarding classification and terminology.

5th edition EGS guidelines: How?

For the 5th edition, the process began by identifying important clinical questions within treatments and diagnostic technologies (Figure 1). Following the identification of these critical questions, the best available evidence was identified and evaluated by invited experts. All evidence was then assessed according to the strength of evidence and the level of recommendation. Relevant evidence was collected in 2019 in cooperation with the US-Cochrane Eyes and Vision Group (CEV-US) by conducting an overview of systematic reviews of glaucoma interventions and diagnostic technologies. Unlike previous editions of the EGS guidelines, the 5th edition contains only references to high-quality systematic reviews, landmark glaucoma trials, and population-based studies. The reason for the stringent restriction is to avoid biased selection of publications.

A large group of international glaucoma experts, methodologists, and evidence-based experts from CEV-US, patient representatives and external reviewers from the Latin American Glaucoma Society, the American Glaucoma Society, and the World Glaucoma Association were involved in the completion of the EGS guidelines, 5th edition. From the Nordic countries, Anders Heijl, Gauti Jóhannesson, Anja Tuulonen, Miriam Kolko and John Thygesen were invited by the guideline committee.

The mission statement of the EGS guidelines is to provide a guideline for "the best care for people with, or at risk of, glaucoma and to promote their well-being and quality of life within a sustainable health care system." The guidelines are financed by an unrestricted grant from the EGS Foundation.

5th edition EGS guidelines: Why?

The purpose of the EGS Guidelines is to support ophthalmologists in the management of people with or at risk of glaucoma. The guidelines highlight that they should be considered as a guide rather than strict decision-making procedures! Decision-making should always be individualized according to patients' needs and circumstances, ideally guided by the best available documentation.

5th edition EGS guidelines: What's new?

The 5th edition is dived into two parts. Part one consists of the key questions and evidence-based recommendation. For all key questions the level of evidence is reported as very low, low, moderate, or high, and the strength of recommendation is provided as "strong" or "weak." If a recommendation is "strong," it can be translated into that most patients should receive the intervention, whereas if a recommendation is "weak" the limited evidence of the intervention should be discussed with the patients and their values and preferences considered. In addition to the key questions, things to avoid are highlighted as a new feature in the 5th edition (Figure 1). Moreover, patients' major concerns are summarized, e.g., the importance of taking the anxiety of glaucoma patients into consideration and remembering the potential information gaps when consulting glaucoma patients. Finally, part one includes glaucoma epidemiology, landmark randomized clinical trials, and considerations of cost-effectiveness when managing glaucoma.

Part two consists of patient examination, classification, and terminology, as well as treatment options. Some examples of changes since the latest edition of EGS guidelines include phasing out the use of cup-disc ratio, the removal of the classification "normal tension glaucoma," and introducing rho kinase inhibitors.

5th edition EGS guidelines: How to get them?

The 5th edition of the EGS guideline can be downloaded from the EGS website: www.eugs.org/eng/guidelines.asp. Hard copies will be available from some of the EGS congress sponsors.

Santen has given support to the authors Miriam Kolko and John Thygesen. No company has had influence on the content of the present article.

EGS Guideline Recommendations:	Things to avoid*:
• SLT can be offered as first choice treatment for early primary or moderate open angle glaucoma or OH • Iridotomy in PAC suspects has a weak recommendation • Iridotomy in PAC and PACG of patients below 50 years has a strong recommendation • Iridotomy or lens extraction in PAC and PACG of patients above 50 years has a strong recommendation	• IOP correction algorithms based on OCT • Glaucoma diagnosis based on OCT alone • Glaucoma progression based on OCT alone • Replacement of gonioscopy with anterior chamber imaging *EGS guidelines for the full list*

Figure 1. Selected guidelines updates in the 5th edition. Abbreviations: *EGS: European Glaucoma Society, SLT: Selective Laser Trabeculoplasty, PAC: Primary Angle Closure, PACG: Primary Angle Closure Glaucoma, IOP: Intraocular Pressure, OCT: Optical Coherence Tomography, OH: Ocular Hypertension*

An Update on Glaucoma Surgery

Every glaucoma patient is different, yet all must cope with their disease (and its treatment) for the rest of their lives. Early surgery may be the best option for some patients – but which procedure to choose, for which patients, and when?

Ike K. Ahmed, Ophthalmologist at Prism Eye Institute; Assistant Professor, Fellowship Director, Kensington Eye Institute, University of Toronto; Clinical Professor, University of Utah; Research Director, Kensington Eye Institute, University of Toronto; Co-Medical Director, TLC Mississauga, CanadaDirector, TLC Mississauga, Canada

Traditionally, glaucoma patients are offered surgery only late in the patient journey; eye drops remain first-, second- and third-line therapy! But this years-old paradigm isn't working; too many glaucoma patients are suffering from quality-of-life issues and vision loss (1), and the impact of topical therapy on patient well-being has made compliance problems ubiquitous. This alone is sufficient reason to replace drops earlier than we typically do. But there is also a cost-effectiveness argument: non-adherence is correlated with disease progression (2), and progression results in more expensive treatments (3). Moreover, drops cannot prevent significant progression in the long-term. Clearly, it's time to drop the drops and adopt a new, more proactive approach – an approach already supported by innovations in glaucoma management.

Interventional glaucoma: a new mindset for a new era

- Be more proactive and aggressive from the start
- Aim to get IOP lower, earlier
- Consider early trabeculoplasty, MIGS, and novel glaucoma drainage devices
- Achieve protection by sustaining IOP reduction
- Consider combination cataract surgery
- Balance compliance and risks with more aggressive therapy
- Address adherence; future options include sustained release drug delivery and MIGS synergy

The era of interventional glaucoma is here

Accumulating evidence suggests glaucoma is best managed when managed proactively: early, aggressive intervention can reduce IOP in a sustainable, predictable way. Remember, each mmHg reduction reduces progression risk by up to 10 percent (4); keeping pressure below 15 mmHg significantly reduces progression risk even in early glaucoma (5), and early control gives better long-term preservation of vision (6). The traditional paradigm should be replaced by a new approach (see Box: Interventional glaucoma).

We must stop judging earlier surgery by the outcomes of late procedures that give less predictable results and more complications than earlier intervention. The data show that for patients with moderate glaucoma it can help control pressure effectively, and sustained low IOP reduces risk of visual field progression (moderate glaucoma, IOP surgically controlled at ~12 mmHg) (7). Patients who maintain pressures of 13 mmHg or less show an improvement in the visual field (8), and primary surgery lowers IOP better than primary medication (9). Overall, early surgery gives better visual field preservation, lower progression risk, lower peak IOPs, reduced pressure fluctuations, elimination of adherence issues, and improved quality of life – and may be less costly, long-term, than drops.

Which intervention to use?

Trabeculectomy is still the gold standard for patients who need very low pressures, but for other patients we have many options. Development-stage products include surface implants, gel-forming drops, punctal plugs, intrascleral implants, intracameral implants, injectable drugs, and subconjunctival implants (10, 11, 12, 13); in addition, we have excellent surgical options available right now. Which one to use? Factors to consider include: safety, efficacy, post-operative management intensity, ease of use, speed of visual recovery, cost, patient age, possibility of combining with cataract surgery, disease severity, target IOP, and medication tolerance. Although no two patients are the same, we can often assign them into provisional categories (see Box How does Ike Ahmed categorize his patients?).

What about outcomes? A comparison of selective laser trabeculoplasty with medical therapy as first-line therapy in early-stage glaucoma patients showed that the surgery achieved good IOP control without medication; note that eleven patients required trabeculectomy in the medication group versus zero in the trabeculoplasty group (14). In many patients, however, a MIGS procedure may be a better choice; these address physiologic outflow safely (and with fast recovery) in early-stage patients, and (even with only ~2 mmHg reduction) reduce medication burden (15). Thus, Schlemm's canal stent plus phaco reduces risk of secondary surgical intervention at two years by 60 percent versus phaco alone (16). Rather than first-line trabeculectomy, we should consider less invasive, more standardized stenting procedures – notably the subconjunctival MIGS – or micro-invasive bleb procedures. For example, XEN® and PRESERFLO™ MicroShunt blend advantages of both MIGS and trabeculectomy, avoiding hypotony while reducing pressure to acceptable levels. Indeed, XEN® has Kaplan-Meier success curves similar to those of trabeculectomy (but requires significantly more needlings and revisions) (17, 18).

PRESERFLO™ MicroShunt (see Box PRESERFLO™ MicroShunt: A material advantage) is particularly potent: it consistently reduces IOP to 12 or 13 mmHg, requires minimal post-operative management, and usually reduces medications to zero (19). These kinds of results are seen even in refractory glaucoma patients who have had previous surgery (20). Overall, PRESERFLO™ MicroShunt patients have a more rapid and more complete visual recovery than is normal for bleb surgery.

The new era starts now

We are now entering the age of interventional glaucoma; we must respond proactively to uncontrolled disease. Escalating topical therapy is not the answer – it achieves little more than increased toxicity and lower adherence (25, 26). We must remember the many years that our patients have to live with glaucoma, intervening aggressively with safe options that do not preclude future options. A variety of procedures are available – not least PRESERFLO™ MicroShunt, which predictably and consistently achieves IOPs of <15 mmHg with minimal post-operative management (27).

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How does Ike Ahmed categorize his patients?

- Those requiring combination with cataract surgery (consider MIGS)
- Those requiring standalone surgery with an IOP target in the mid-high teens (consider a large trabeculotomy ab interno)
- Those requiring standalone surgery with an IOP target of 12 mmHg (typical approach: minimally invasive bleb surgery)
- Those requiring standalone surgery, IOP target <10 mmHg (typical approach: trabeculectomy)

PRESERFLO™ MicroShunt: A material advantage

- Many surgical devices are made from polyurethane or silicone rubber – unstable compounds that can degrade and cause chronic inflammation (21)
- PRESERFLO™ MicroShunt is fabricated from SIBS – poly(styrene-b-isobutylene-b-styrene) – an innovative polymer with a number of advantages (21, 22, 23)
- In particular, when compared with standard devices, ocular implants made from SIBS are associated with less inflammation and with dramatic reductions in myofibroblast numbers and in the thickness of the pseudo capsule surrounding the implant (24)
- Thus, SIBS devices help address one of the biggest challenges in glaucoma surgery – wound and tissue healing

REDUCTION OF INTRAOCULAR PRESSURE IN PATIENTS WITH OPEN-ANGLE GLAUCOMA OR INTRAOCULAR HYPERTENSION
WHO ARE INSUFFICIENTLY RESPONSIVE TO BETA-BLOCKERS OR PROSTAGLANDIN ANALOGUES

LATANOPROST + TIMOLOL

Two molecules in one PRESERVATIVE-FREE DROP

Fixopost®

latanoprost 50 micrograms/ml + **timolol** 5 mg/ml

Effective IOP reduction[1] | Proven safety profile[1*] | Maintains patient's quality of life[2]

* Irritation, burning, stinging, itching. References: 1. SPC Fixopost 2020-10-22 (DK), 2020-04-30 (NO), 2020-05-04 (SE), 2020-06-18 (FI), 2020-05-27 (IS)), 2. J.Thygesen Clinical Opht. 2018:12 707-717.

FIXOPOST (latanoprost and timolol) 50 micrograms/ml + 5 mg/ml eye drops, solution in single-dose container. Ophthal-mological betablocking agents timolol, combinations, ATC code: S01ED51 **Indication:** Fixopost is indicated in adults (including the elderly) for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topical betablockers or prostaglandin analogues. **Posology and method of administration*:** Recommended therapy is one eye drop in the affected eye(s) once daily. If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily. A single-dose contains enough eye drops solution to treat both eyes. For single use only, to be used immediately after opening. Any remaining contents must be discarded immediately after administration. **Contraindications*:** Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease; Sinus bradycardia, sick sinus syndrome, sino atrial block, second or third degree atrioventricular block not controlled with pace maker, overt cardiac failure, cardiogenic shock; Hypersensitivity to the active substances or to any of the excipients. **Special warnings and precautions for use*:** Fixopost is absorbed systemically. Due to the betaadrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic betaadrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. In patients with cardiovascular diseases and hypotension therapy with betablockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and for adverse reactions. Betablockers should only be given with caution to patients with first degree heart block. Cardiac reactions, and rarely, death in association with cardiac failures have been reported following administration of timolol. Patients with severe peripheral circulatory disturbance/disorders should be treated with caution. Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic betablockers. Fixopost should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. Betablockers should be administered with caution in patients subject to spontaneous hypoglycaemia or in patients with labile diabetes, as betablockers may mask the signs and symptoms of acute hypoglycaemia. Betablockers may also mask the signs of hyperthyroidism. Patients with corneal diseases should be treated with caution. The effect on intraocular pressure or the known effects of systemic betablockade may be potentiated when timolol is given to the patients already receiving a systemic betablocking agent. Patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. Choroidal detachment has been reported with administration of aqueous suppressant therapy after filtration procedures. The anaesthetist should be informed when the patient is receiving timolol. Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes. No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent. Patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues. Unilateral treatment can result in permanent heterochromia. Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost. Latanoprost may gradually change eyelashes and vellus hair in the treated eye. Eyelash changes are reversible upon discontinuation of treatment. It is recommended that Fixopost should be used with caution in patients with inflammatory, neovascular or chronic angle closure glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues. Macular oedema has been reported during treatment with latanoprost. Fixopost contains macrogolglycerol hydroxystearate (castor oil polyoxyl hydrogenated) which may cause skin reactions. **Interactions*:** The use of two or more prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended. There is a potential for additive effects resulting in hypotension and/or marked bradycardia when an ophthalmic betablocker solution is administered concomitantly with oral calcium channel blockers, betaadrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine. Potentiated systemic beta blockade has been reported during combined treatment with CYP2D6 inhibitors and timolol. The use of two or more topical betaadrenergic blocking agents is not recommended. Mydriasis resulting from concomitant use of ophthalmic betablockers and adrenaline has been reported occasionally. The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking betablockers. Betablockers may increase the hypoglycaemic effect of antidiabetic agents. Betablockers can mask the signs and symptoms of hypoglycaemia. **Pregnancy and lactation*:** Fixopost should not be used during pregnancy or while breast feeding. **Effects on ability to drive and use machines:** Fixopost has minor influence on the ability to drive and use machines. Instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines. **Undesirable effects*:** Very common: Iris hyperpigmentation. Common: Eye pain, eye irritation (including stinging, burning, itching, foreign body sensation). Uncommon: Headache, corneal disorders, conjunctivitis, blepharitis, eye hyperaemia, vision blurred, lacrimation increased, rash, pruritus. For timolol, the most serious adverse reactions are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospasm and allergic reactions. **Overdose*:** Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm and cardiac arrest. Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are known if latanoprost is overdosed. If symptoms of overdose occur the treatment should be symptomatic and supportive. If accidentally ingested orally: Gastric lavage if needed. **Pack size:** 30 or 90 single-dose containers. **Valid only for Denmark: Dispensing group:** B. **Reimbursement status:** General reimbursement. **Valid only for Norway: Prescription rules**: Prescription group C, prescription drug. **Reimbursement:** Yes (blå resept). **Reimbursement conditions:** Reimbursement indicated for reduction of intraocular pressure with open-angle glaucoma and ocular hypertension, when topical beta-blockers or prostaglandin analogues are not sufficient. **Reimbursement code:** ICPC F93/ICD H40 Glaucoma. Terms: 154 Reimbursement is only granted who cannot use eye drops with preservatives. Price (2021-03-10): 30-pack 254.50 NOK and 90-pack 678.70 NOK . **Valid only for Sweden**: **The status of the product:** Rx. **Reimbursement status:** (F), only for patients who do not tolerate preservatives. **Valid only for Finland: Statutory dispensing conditions:** Prescription drug. **Reimbursement terms and price** (2021-03-10): Special reimbursement (100%), Glaucoma. Basic reimbursement (40%). 30-pack 23.54 €, 90-pack 68.60 €.
The summary of product characteristics (SmPC) has been rewritten/abbreviated compared to the authorized SmPC, versions in local language last revised 2020-10-22 (DK), 2020-04-30 (NO), 2020-05-04 (SE), 2020-06-18 (FI), 2020-05-27 (IS) can be ordered free of charge from the marketing authorisation holder (Laboratoires THEA) or local contact: Théa Nordic AB, Storgatan 55, 703 63 Örebro, Sweden. For actual price and detailed information on this medicinal product, see www.felleskatalogen.no (NO), www.fass.se (SE), www.phrmacafennica.fi (FI), www.medicinpriser.dk (DK) and www.serlyfjaskra.is (IS).

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