Towards Personalised Glaucoma Management

Identification of Specific Factors Influencing Glaucoma Treatment Outcomes

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The corpus of research articles presented in this thesis is only a sample of the research I have carried out with many colleagues over the years. My thanks naturally go to all my co-authors whose names appear through the following pages, but also to all colleagues, assistants, optometrists, orthoptists, nurses, secretaries, administrators, trainees and students, who were not credited by name, and without whom my work could not have been the same.

Finally, I would like to thank my family for their unwavering support through the writing of this thesis.

Abstract

Glaucoma is a group of neurodegenerative diseases resulting in irreversible vision loss through retinal ganglion cell death. A number of treatment options are currently used to treat glaucoma, ranging from pharmaceutical therapies and localized laser treatments, to surgical filtration procedures and a wide variety of novel Minimally Invasive Glaucoma Surgery (MIGS) procedures. All of these options aim at reducing the rate of retinal ganglion cell apoptosis through the lowering of intraocular pressure (IOP).

Yet, two significant limitations impact the choice of glaucoma treatments in clinical practice, and are addressed successively in this thesis. First, while all glaucoma treatments currently target IOP to slow or halt disease progression, a growing body of evidence suggests that static in-clinic tonometry does not provide an accurate representation of IOP. Indeed, the dynamic nature of IOP as well as its out-of-office variations were shown to have a direct impact on glaucoma progression (Article 1). Besides, a number of intrinsic and extrinsic may have influence IOP, causing immediate, short-term and long-term pressure fluctuations (Article 2-4). Second, while the number of therapeutic options for glaucoma is growing with the addition of new MIGS techniques every year, there is, to date, no clear consensus guiding treatment choice. Yet, glaucoma is a multifactorial disease and recent literature abounds with suggestions that specific clinical or demographic characteristics may influence the outcomes of medical or surgical treatments (Article 5-8). Although this implies that tailoring treatment options to individual patients' characteristics may be beneficial, interstudy heterogeneity have so far impaired study comparability and generalisation. Thus, specific clinical recommendations guiding personalized therapeutic choices remain scarce.

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Statement

a. About the author

The author is a medical researcher and an ophthalmologist. After a first career as an architect, he graduated with a Bachelor of Medicine and Surgery (MBBS) from Newcastle University and became a Fellow of the European Board of Ophthalmologists (FEBO) in 2018. Following his ophthalmology training, he subspecialised in the diagnosis and treatment of glaucoma in Switzerland and at the Moorfields Eye Hospital. Since 2017, he has been a principal research coordinator at the Glaucoma Research Centre in Lausanne.

The author has published over 50 peer-reviewed articles in the field of glaucoma, contributed to several book chapters and international guidelines, and lectured at the University of Liverpool and the University of London. In 2019, he was awarded a Medical Doctorate (MD) from the University of Lausanne for his studies on Minimally Invasive Glaucoma Surgery (MIGS). He is also the main editor of Elsevier's upcoming glaucoma textbook: "The Science of Glaucoma Management – From Translational Research to Next-Generation Clinical Practice". At the time of writing, his work had attracted 497 citations, with a h-index of 13.

Aside from his academic and clinical work, the author has devoted some of his research to clinical service improvement through the study of patient experience, for which he was awarded a Master in Business Administration (MBA) with Distinctions and a prize for academic achievement from the University of London. He also holds a Master of Architecture (MArch) from the University of Paris La Villette where he defended a thesis on the interconnections between hospital design, patient perception and society.

b. About the research institution

All the incorporated publications result from research carried out at the Glaucoma Research Centre in Lausanne, Switzerland. The Glaucoma Research Centre is a private research centre supported by the Swiss Glaucoma Research Foundation. Its mission is to improve glaucoma care through clinical research, with a particular emphasis on surgical clinical trials as well as telemetric and imaging technologies. It currently employs two senior clinician-researchers, a research coordinator, a clinical research assistant, and two ophthalmology registrars.

c. About the incorporated publications

Eight key peer-reviewed publications by the author are discussed in the present thesis. This paragraph introduces them and details the author's role and contribution in each project. The author will also refer to some of their other publications, not included in this corpus, to support their arguments.

- ***Article 1:*** *Gillmann K, Young CC, Stanley J, Seibold LK, Hoskens K, Midha N, Kahook MY, Mansouri K. Relationship between contact lens sensor output parameters and visual field progression in open-angle glaucoma: assessment of a practical tool to guide clinical risk-assessment. Journal of glaucoma. 2020 Jun 20;29(6):461-6.*

This article examined the link between intraocular pressure fluctuations and glaucoma progression. It was published in Journal of Glaucoma, a tier 1 peer-reviewed journal part of

Lippincott Williams and Wilkins Ltd. with an impact score of 1.89 - defined as the ratio of the number of journal citations to the number of journal publications over the last two years.

The author was in charge of the execution of the trial at the main investigation site in Switzerland, coordinating with the secondary investigation site, as well as analysing data, interpreting results, and writing the final report. Dr Hoskens and Dr Midha performed a blinded assessment of the risk of progression of participating patients at the Swiss investigation centre. Dr Young and Dr Stanley did the same at the University of Denver, USA, with Dr Seibold computing their data locally under the supervision of Professor Kahook. Professor Mansouri supervised the project and reviewed the manuscript.

The author's estimated contribution represents 70% of the project.

- ***Article 2:*** *Gillmann K, Weinreb RN, Mansouri K. The effect of daily life activities on intraocular pressure related variations in open-angle glaucoma. Scientific reports. 2021 Mar 23;11(1):1-7.*

This article examined the effect of lifestyle and daily activities on intraocular pressure fluctuations. It was published in Scientific Reports, a tier 1 peer-reviewed journal part of Nature Publishing Group with an impact score of 4.54.

The author was in charge of the study design, data collection, analysis and interpretation, as well as the writing of the final report, based on an original concept by Professor Mansouri. The project was supervised by Professor Weinreb.

The author's estimated contribution represents 80% of the project.

- ***Article 3:*** *Mansouri K, Gillmann K, Rao HL, Weinreb RN. Weekly and seasonal changes of intraocular pressure measured with an implanted intraocular telemetry sensor. British Journal of Ophthalmology. 2021 Mar 1;105(3):387-91.*

This article examined the effect of weekdays and seasons on intraocular pressure fluctuations. It was published in British Journal of Ophthalmology, a tier 1 peer-reviewed journal part of BMJ Publishing Group with an impact score of 4.91.

The author was in charge of the study design, the data collection and interpretation, and the writing and illustration of the final report. Professor Mansouri surgically implanted the pressure sensors in the participating patients and oversaw data collection. Dr Rao performed the statistical analysis. The project was supervised by Professor Weinreb.

The author's estimated contribution represents 70% of the project.

- ***Article 4:*** *Gillmann K, Wasilewicz R, Hoskens K, Simon-Zoula S, Mansouri K. Continuous 24-hour measurement of intraocular pressure in millimeters of mercury (mmHg) using a novel contact lens sensor: Comparison with pneumatonometry. PloS one. 2021 Mar 23;16(3):e0248211.*

This article evaluated the safety and accuracy of a novel contact lens sensor to measure intraocular pressure fluctuations. It was published in PLoS ONE, a tier 1 peer-reviewed journal part of Public Library of Science with an impact score of 3.58.

The author was in charge of the study design and execution, data analysis and interpretation, as well as the writing of the final report. Doctor Wasilewicz contributed to the original development of the technology, Doctor Hoskens assisted with the recruitment and follow-up of patients, and Doctor Simon-Zoula from SENSIMED SA assisted with the extraction of the numerical data from the sponsor's proprietary software. The project was supervised by Professor Mansouri.

The author's estimated contribution represents 70% of the project.

- ***Article 5:*** *Gillmann K, Mansouri K. Minimally invasive glaucoma surgery: where is the evidence? Asia-Pacific Journal of Ophthalmology (Philadelphia, Pa.). 2020 May;9(3):203.*

This article reviewed and meta-analysed the current evidence on the safety and efficacy of minimally invasive glaucoma surgery techniques. It was published in Asia-Pacific Journal of Ophthalmology, a tier 1 peer-reviewed journal part of Lippincott Williams and Wilkins Ltd. with an impact score of 3.21.

The author was in charge of the meta-analysis design, literature review, data collection and analysis, as well as the writing and illustration of the final report. The project was supervised by Professor Mansouri who also reviewed the final manuscript.

The author's estimated contribution represents 95% of the project.

- ***Article 6:*** *Gillmann K, Aref A, Niegowski LJ, Baumgartner JM. Combined Ab interno viscocanaloplasty (ABiC) in open-angle glaucoma: 12-month outcomes. International Ophthalmology. 2021 May 20:1-7.*

This article evaluated the safety and the efficacy of ab interno viscocanaloplasty in open-angle glaucoma. It was published in International Ophthalmology, a tier 2 peer-reviewed journal part of Springer Netherlands with an impact score of 2.01.

The author was in charge of the clinical trial design, data analysis and interpretation, as well as the writing and illustration of the final report. Doctor Aref and Doctor Niegowski were in charge of patient recruitment and data collection. Doctor Baumgartner operated all the patients included in this clinical trial and reviewed the final manuscript.

The author's estimated contribution represents 80% of the project.

- ***Article 7:*** *Gillmann K, Bravetti GE, Rao HL, Mermoud A, Mansouri K. Combined and stand-alone XEN 45 gel stent implantation: 3-year outcomes and success predictors. Acta Ophthalmologica. 2021 Jun;99(4):e531-9.*

This article evaluated the safety, efficacy, and success factors of XEN 45 gel stents in open-angle glaucoma. It was published in Acta Ophthalmologica, a tier 1 peer-reviewed journal part of Wiley-Blackwell Publishing Ltd. with an impact score of 3.30.

The author was in charge of the clinical trial design, patient recruitment, data collection, analysis and interpretation, as well as the writing and illustration of the final report. Doctor Bravetti assisted with patient recruitment and data collection. Doctor Rao assisted with data analysis. Professor Mansouri and Professor Mermoud operated all the patients included in this clinical trial and supervised the project.

The author's estimated contribution represents 75% of the project.

- ***Article 8:*** *Gillmann K, Bravetti GE, Mermoud A, Mansouri K. A prospective analysis of iStent inject microstent positioning: Schlemm canal dilatation and intraocular pressure correlations. Journal of glaucoma. 2019 Jul 1;28(7):613-21.*

This article evaluated the safety, efficacy, and anatomical positioning of iStent inject micro-bypass in open-angle glaucoma. It was published in Journal of Glaucoma, a tier 1 peer-reviewed journal part of Lippincott Williams and Wilkins Ltd. with an impact score of 1.89.

The author was in charge of the clinical trial design, patient recruitment, data collection, analysis and interpretation, as well as the writing and illustration of the final report. Doctor Bravetti assisted with data collection. Professor Mansouri and Professor Mermoud operated all the patients included in this clinical trial and reviewed the final manuscript.

The author's estimated contribution represents 90% of the project.

Chapter 1 - Introduction

1.1. Glaucoma

Glaucoma refers to a group of neurodegenerative diseases resulting in irreversible vision loss through retinal ganglion cell (RGC) and optic nerve axons death.[1] These conditions can be further divided into subgroups based on clinical characteristics such as patient's age, iridocorneal angle width, trabecular meshwork appearance and intraocular pressure (IOP).[2]

The exact process by which retinal ganglion cell apoptosis occurs remains misunderstood, and many potential mechanisms have been studied, including direct barometric damage, axoplasmic flow obstruction, oxidative stress, inflammation, vascular dysregulation, and mitochondrial dysfunction.[3] Yet, many of these factors are still hypothetical, and to date, abnormally high IOP is still considered the most determinant factor. Thus, IOP control remains the focus of all glaucoma treatments.[4]

Glaucoma is mostly asymptomatic in its early stages. As it progresses, glaucomatous loss of RGC and nerve fibres leads to gradual peripheral or paracentral loss of vision, eventually resulting in tunnel vision or blindness in terminal disease. Vision loss caused by glaucoma is permanent, and as such, glaucoma is the leading cause of irreversible blindness worldwide.[5]

1.2. Societal context and public health impact

1.2.1. Health burden

Globally, it is estimated that 80 million, or 3.54% of the world population over the age of 40 years, currently have glaucoma, and as many as fifty percent of those who have glaucoma remain undiagnosed.[6] In 2020, an estimated 5.9 million worldwide were bilaterally blind due to glaucoma, and in the United-Kingdom glaucoma accounts for 16% of all registrations for sight impairment.[7] Studies forecast a rapid growth in these numbers, with glaucoma cases predicted to reach approximatively 112 million by 2040.[8] In 2014, Tham and colleagues carried out a meta-analysis based on data from fifty population-based studies.[8] They concluded that male gender, living in urban areas, and being of African descent were all risk factors for developing glaucoma.

Drawing on these figures, glaucoma has become one of the most prevalent neurodegenerative diseases affecting human population globally, ahead of Alzheimer's or Parkinson's diseases.[9,10]

1.2.2 Financial burden

The financial impact of glaucoma is both direct and indirect. Direct costs include medical appointments and medications, while indirect costs include productivity loss, caregivers and disability benefits. In 2006, Lee and colleagues have estimated that glaucoma cost an average USD 2.9 billion a year.[11] Their study also highlighted the importance of effective glaucoma diagnosis and treatment, as they identified clear correlation between the financial burden and disease severity, with a 4-fold increase in the annual cost of treatment increased between early and advanced glaucoma.

1.3. Pathophysiology

1.3.1. Clinical observations

In glaucoma, visual field defect and retinal nerve fibre loss tend to follow distinct recognisable patterns. While some eyes may deviate from the typical peripheral arcuate loss and initially present with paracentral defects, a consistent feature of glaucoma is its respect for the horizontal meridian.[12,13] This results in a characteristic asymmetry between the superior and the inferior hemifield, both in terms of structural defect and functional loss. This pattern closely follows the course of retinal nerve fibres rather than the distribution of inner retinal or choroidal blood vessels, implying that the root cause of glaucoma is neurodegenerative in nature.[14] This also explain another key characteristic of glaucoma: its progressive nature.

Clinical observations have identified a number of risk factors for glaucoma. First, there is a strong correlation between optic disc haemorrhages and glaucoma progression.[14] Second, the architecture of the optic nerve head itself has become a key diagnostic factor in glaucoma, with observable changes to the optic disc rim in the form of a gradual increase in cup-to-disc ratios with disease progression, suggesting that the optic nerve head may be the initial site of damage in glaucoma.[15] This clinical hypothesis was since confirmed by animal model studies,[16,17] and serves as the basis for the current gold standard method in the structural assessment of glaucoma: the measurement of peripapillary retinal nerve fibre layer (RNFL) thickness. Indeed, clinical glaucoma progression was associated with the gradual thinning of retinal ganglion cell and nerve fibre layers, which was in turn correlated with the gradual worsening of visual fields defects.[4] Finally, the direct correlation between IOP and the relative risk of developing glaucoma was evidenced in a number of clinical trials and confirmed in animal models of ocular hypertension.[18,19,20,21,22] This has led to renewed efforts and hypotheses to elucidate the relationships between IOP, optic nerve head damage and RGC loss in the pathophysiology of glaucoma.

1.3.2. Optic nerve head compression

1.3.2.1. Pressure strain on the lamina cribrosa

Within the optic nerve head, the lamina cribrosa (LC) has been a particular focus of research in the study of glaucoma pathophysiology. It is a collagen mesh-like structure through which the optic nerve axons and blood supply run as the exit the eye posteriorly, traveling from a high-pressure to a low-pressure environment.[23] Despite its porous nature, the architecture of the LC ensures that the pressure gradient between the intraocular space and the central nervous system are maintained under normal physiological conditions. Supportive LC glial cells surround the collagen beams of the LC, maintaining its structural integrity and diffusing energy substrates to optic nerve axons.[24]

Owing to its specific role and location, any level of IOP causes a strain on the LC. When IOP exceeds physiological levels, LC cells enter a proliferative phase causing connective tissue remodelling.[25] Chronic intraocular pressure elevation causes thickening, disinsertion, and posterior displacement of the LC.[26] It was speculated that LC displacement may severe local microvasculature, impair supportive LC cells blood supply, and directly compress RGC axons.[27]

There has been, however, some debate over the levels of intraocular pressure at which these structural changes begin to occur.

1.3.2.2. Translaminar pressure gradient

As previously described, the LC separates two compartments: the globe and the central nervous system. While the intraocular space is pressurized by IOP, cerebrospinal fluid pressure in the intracranial space remains comparatively low. Recent studies of the LC have highlighted the potential importance of this translaminar pressure gradient in the pathophysiology of glaucoma.[28] Some clinical trials observed significantly lower intracranial pressures in normal-tension glaucoma, suggesting that elevated translaminar pressure gradients may contribute to the pathogenesis of glaucoma.[29] Yet, this correlation was not confirmed in all studies, and a number of structural and anatomical factors may influence translaminar pressure gradients.

1.3.2.3. The role of intraocular pressure in a unified hypothesis

Many factors have been suspected to play a role in the pathophysiology of glaucoma, including vascular, immune, age-related, oxidative mechanisms, but progressing research suggests that all these mechanisms may result from ocular tissues' reaction to hypertension.[30]

The study of mitochondrial diseases has shown that RGC's function and metabolism is highly energy dependent.[31] The intense anterograde and retrograde transport occurring through RGC axons certainly accounts for their high energy demand.

Novel models therefore suggest the following sequence of events. Ocular hypertension exceeding the physiological adaptability of ocular tissues results in biomechanical strain and compression of the LC and RGC axons.[24] Increased, prolonged or repeated LC strain causes remodelling of the local architecture and microvasculature, and changes in the physiological function of supportive glial cells.[25,26] The combination of impaired blood supply and homeostatic function of these cells may affect their supportive function through reduced nutrient flow.[32] Higher translaminar pressure gradients result in an increased energy costs for RGC to maintain their axonal transport capabilities. The association of heightened energy costs and reduced energy provided by supporting LC cells produce an energy crisis, further impacting axonal transport. This causes both axonal degeneration and reduced flow of essential neurotrophic factors to the RGC, leading to cell apoptosis. Supportive glial cell depletion triggers an increase in the remaining cells' metabolism, which in turn leads to local neurotoxicity through oxidative stress and cytokine release.[33]

The association between aging and increased sensitivity to ocular hypertension may therefore be explained by two factors. The gradual changes in the optic nerve head architecture and LC's collagen fibre adaptability, and the reduced efficacy of RGC mitochondria resulting in a lower threshold for axonal transport breakdown.[34]

To date, this unified hypothesis is the simplest model to explain most observed risk factors and to connect most suspected mechanisms involved in the pathophysiology of glaucoma.

1.3.3. Intraocular pressure

1.3.3.1. Physiology of intraocular pressure

Intraocular pressure results from the equilibrium between the production and the outflow of aqueous humour (AH).[35] AH fills both the anterior and the posterior chambers of the eye and play crucial roles in its normal function, including providing essential nutriments to avascular ocular structures, and maintaining the structural integrity and the optical properties of the globe. Under physiological conditions, normal IOP ranges from 9 to 21 mmHg.

The AH is produced by the ciliary body at a rate of approximatively 2.4 microliters per minute.[36] AH secretion varies according to a circadian rhythm, with reduced flowrates overnight.[37] AH flows around the crystalline lens and through the pupil, where its flow is influenced by convective currents created by the gradient of temperature across the anterior chamber. AH drains out of the eye by passive flow through two main outflow pathways located in the iridocorneal angle. The conventional pathway accounts for approximatively 85% of the outflow.[38] It drains AH through the trabecular meshwork into Schlemm's canal, from where it travels through collector channels, aqueous veins and reaches the episcleral venous system following pressure gradients. It is estimated that 75% of the resistance to AH outflow resulting in elevated IOP is localized in the trabecular meshwork, while 25% is distal.[39] Research suggests that the trabecular meshwork is a complex and dynamic structure, and its role and influence in the pathophysiology of ocular hypertension remain poorly understood.[40,41] AH draining through the non-conventional or uveoscleral pathway enters the connective tissue of the anterior ciliary body, where it drains into the suprachoroidal space. Contrary to the conventional pathway, uveoscleral outflow is not pressure dependent. These features were characterized by Goldmann equation: $F = (P_i - P_e)\,C + U$, where F is the rate of AH production, $P_i - P_e$ is the gradient between intraocular and episcleral venous pressures, C represents outflow capacities, and U illustrates the pressure-independent uveoscleral outflow.[36]

Studies have shown that aging induces a reduction in the secretion of AH by the ciliary body, which is balanced by an equivalent reduction in uveoscleral outflow.[42] Nevertheless, uncompensated impairment of the AH outflow capacity would disturb the secretion-drainage equilibrium, resulting in ocular hypertension. This is one of the central concepts underpinning the pathophysiology of glaucoma.

1.3.3.2. Intraocular pressure variations

Far from being a static measurement, IOP has long been observed to be highly dynamic. Three types of IOP variations have been described: circadian, short-term and long-term variations.

1.3.3.2.1. Circadian variations

Circadian variations are defined as cyclic IOP fluctuations that follow a 24-hour repeatable pattern.[43] IOP follows a circadian rhythm, during which it exhibits a significant nocturnal elevation. This may be explained by the nocturnal shift in the AH production/outflow equilibrium. Indeed, while aqueous production is halved during sleep, both outflow pathways are equally downregulated, leading to an overall rise in IOP.[44] Laboratory studies have suggested that these variations may be triggered by prolonged periods of eyelid closure, as the release of matrix metalloproteinase from trabecular cells appears to be regulated by

physiological temperature oscillations.[45] However, the technical limitations associated with IOP measurement has long prevented the study of IOP during sleep or behind closed eyelids. The magnitude of diurnal IOP variations was observed to be approximatively of 2-6 mmHg in healthy subjects, and even greater in glaucomatous eyes.[46]

Blood pressure (BP) also follows a circadian rhythm, although its trough is during sleep.[47] This difference between IOP and BP cycles results in an increased translaminar gradient overnight.

1.3.3.2.2. Short-term variations

Short-term variations are defined as instantaneous IOP fluctuations that last only seconds or minutes, and are often mediated by external factors. Due to the pressure-dependent nature of the conventional outflow pathway, elevation in central venous pressure was correlated with a rise in IOP. This was confirmed both in animal and human studies.[48] Since this observation, a number of studies have confirmed the IOP-increasing effect of water drinking, supine body position, and neck flexion, extension or compression.[49] Scarce studies involving the direct cannulation of human eyes prior to enucleation also suggested a mechanical effect of blinking, squeezing of the lids and accommodation on IOP, with transient fluctuations as high as 90 mmHg.[50]

This suggests that Goldmann tonometry (GAT), with patients sitting at the slit lamp, with their head in a neutral position and both eyes open, may be measuring IOP at its lowest compared to other body positions.

1.3.3.2.3. Long-term variations

Long-term variations are defined as variations that occur over weeks or months, and are often observed over several clinic appointments. Most data on long-term IOP variations result from secondary analyses of data from large clinical trials demonstrating inter-visit IOP variability. The ad hoc nature of these analyses and the relatively small number of individual measurements does not allow to completely exclude the influence of short-term and circadian factors on the long-term IOP variations observed. Nevertheless, some of these studies suggested that medically treated glaucoma patients may exhibit wider long-term variations than surgically treated patients.[51]

1.4. Clinical considerations

1.4.1. The clinical importance of intraocular pressure

While clinical studies have identified a number of risk factors for glaucoma, IOP remains by far the most important one, both for the development and the progression of the disease. Indeed, the ocular hypertension treatment study (OHTS) showed that treating ocular hypertension can half the risk of developing glaucoma at 5 years.[52] Besides, the Collaborative Initial Glaucoma Treatment Study (CIGTS) has shown that newly diagnosed glaucoma patients whose IOP were aggressively controlled exhibited more stable diseases than those with more conservative treatment.[53] The United Kingdom Glaucoma Treatment Study (UKGTS) confirmed that IOP-lowering treatments achieved measurable and significant visual function preservation compared to placebo eye drops over 24 months in open-angle glaucoma,[18] an observation that was further backed by the Laser in Glaucoma and Ocular Hypertension

(LiGHT) trial.[54] Interestingly, the Collaborative Normal Tension Glaucoma Study (CNTGS) showed that even in normal tension glaucoma, in which glaucomatous changes occur despite physiological IOP levels, reducing IOP was effective in slowing disease progression.[55]

The clinical effect of IOP reduction was further quantified by the Early Manifest Glaucoma Trial (EMGT) in which a 25% IOP reduction was associated with a 27.4% reduction in the number of mild-to-moderate glaucoma patients showing glaucoma progression at 5 years.[56] The Canadian Glaucoma Study suggested that each mmHg increase in IOP may be associated with a 19% increase in the risk of glaucoma progression over 5 years.[57]

This clear clinical association between IOP and glaucoma progression, even at physiological levels, was highlighted by genetic studies that observed that most risk alleles for glaucoma were also associated with IOP regulation mechanisms.[58,59,60,61] This may explain why IOP is currently the only known modifiable risk factor, both for the development and the progression of glaucoma.

1.4.2. The clinical importance of intraocular pressure variations

Difficulties in measuring and quantifying IOP variations has impaired the study of their clinical significance in the pathogenesis of glaucoma, and evidence therefore remains scarce. Despite these limitations, a secondary ad hoc analysis of the Advanced Glaucoma Intervention Study (AGIS) database suggested that a greater inter-visit IOP variability may constitute an independent risk factor for glaucoma progression.[62] This conclusion was supported by the findings of another study evaluating the variability of five daily IOP measurements over two consecutive days, in which patients with higher diurnal IOP variability were more likely to show glaucoma progression despite physiological IOPs.[63] These observations suggest that IOP variations, although they remain understudied, may play an independent role in the pathophysiology of glaucoma, thus highlighting an area for further research.

1.4.3. Current standards of care

1.4.3.1. Intraocular pressure evaluation

While the diagnosis of glaucoma is independent from IOP levels, IOP evaluation remains at the core of glaucoma control and monitoring. Indeed, based on the thresholds recommended by the National Institute for Health and Care Excellence (NICE)[64] and work from the the Canadian Target IOP Workshop,[65] the latest European Glaucoma Society (EGS) Guidelines recommend that the likelihood of loss of quality of life is used to determine a target IOP to guide glaucoma treatment.[66] Based on a combination of pre-treatment IOP and glaucoma severity, they recommend seeking to achieve consistent readings below the 18-20 mmHg range along with a 20% reduction from baseline IOP in early glaucoma, IOP below the 15-17 mmHg range along with a 30% reduction from baseline IOP in moderate glaucoma, and IOP below the 10-12 mmHg range in advanced glaucoma. The guidelines also recommend escalating treatment until the target pressure is achieved, and further lowering the target IOP by 20% if any disease progression is observed despite consistent measures within the target range during follow-up appointments.

The current gold standard technique for IOP measurement is the Goldmann applanation tonometer (GAT). It relies on the Imbert-Fick principle to measure the force required to applanate a set, 7.35 mm^2, corneal area.[67] During the measurement, the patient is sitting at the slit lamp, their cornea is anaesthetized and fluoresceine is instilled on their ocular surface. Under a blue light, the examiner looks through a biprism tonometer tip and turns its dial to adjust the force exerted by the tonometer's arm on the cornea. When the inner edges of the two hemi-circles formed by the tear meniscus around the prisms touch, the reading on the dial should represent the IOP. Like every applanation tonometry technique, however, the GAT is widely regarded as imperfect and a number of parameters can induce false readings.[68,69] These include corneal biomechanical properties such as corneal thickness, curvature or hysteresis, previous refractive surgery, excessive tear film, or patient-dependent factors, such as breath-holding or squeezing of the lids. Several studies have also reported that GAT was subject to wide inter-examiner variability.[70] Finally, GAT only measures the IOP over a couple of seconds, and needs to be repeated, in the form of a tension curve, to provide a representation of IOP variations over a longer period of time.[71]

While the latest EGS Guidelines do not advocate for the evaluation of IOP variations, they acknowledge that "evaluating the IOP at different times of the day can be useful in selected patients".[72] In practice, some ophthalmologists rely on diurnal tension curves or phasing to assess diurnal IOP variations in selected patients. This typically involves 4-5 GAT measurements spread over office hours or, more rarely, two-hourly measurements over 24 hours.

1.4.3.2. Unmet needs in intraocular pressure evaluation

The high dependency of glaucoma specialists on IOP measurements and the limitations of GAT highlight the need for more precise and reliable tonometers that would not be observer-dependent or influenced by the biological variability of the eye. Besides, despite growing evidence over the last century of the highly dynamic nature of IOP, static tonometry representing only infrequent snapshots of the IOP remains the standard of care in glaucoma management. Debates over the role of IOP variations in glaucoma pathophysiology as well as the challenges of measuring and quantifying rapid out-of-office IOP variations has hindered research. Despite growing concern that IOP variations may play a role in glaucoma progression, these remain vastly understudied and misunderstood. Yet, if glaucoma management must rely on the achievement of target pressures, research is warranted to ascertain the impact of unmonitored out-of-office IOP variations on glaucoma progression, to better quantify these variations, and to gain an understanding of their causative factors. Recently, the technical advances in the field of IOP telemetry have made the study of continuous and long-term IOP evaluation possible.

1.4.3.3. Intraocular pressure control

The ultimate goal of glaucoma management is to prevent the progression of the disease and maintain the visual function and quality of life of patients for their lifetime.[66] At present, IOP remains the only modifiable risk factor for glaucoma progression, and IOP control is therefore the cornerstone of all glaucoma treatments.

When target IOP is not achieved or when glaucoma progression is confirmed, the EGS Guidelines recommend initiating or escalating treatment.[66] First line treatments for glaucoma typically include pharmaceutical options delivered via eye drops or selective laser trabeculoplasty. Four classes of medications are currently approved for topical use in the treatment of glaucoma in Europe: prostaglandin agonists, beta-blockers, alpha agonists, and carbonic anhydrase inhibitors. EGS Guidelines advise to exhaust all non-invasive options, with a combination of up to three different classes of medications, before considering surgical options.[66] Yet, due to the progressive nature of glaucoma, approximately 23% of patients require surgery within 20 years of diagnosis.[73]

For decades, surgical options for the control of IOP in glaucoma were limited to one type of procedure: filtering surgery.[74] Over the last two decades, however, unprecedented innovation in the field of minimally invasive glaucoma surgery (MIGS) has led to an explosion in the number of techniques and devices available to glaucoma specialists. MIGS techniques can be classified in five categories based on their anatomical target of action: the trabecular meshwork, Schlemm's canal, the subconjunctival space, the suprachoroidal space and the ciliary body.[75] With new techniques or devices reaching the market every year, there are currently over a dozen of surgical options to control IOP. Yet, there is, to date, no clear consensus guiding treatment choice, and surgical techniques are often guided, in clinical practice, by the magnitude of IOP reduction sought and by individual ophthalmologists' preferences.

1.4.3.4. Unmet needs in intraocular pressure control

In the early 2010's, the "10-10-10 Goal" was defined as a set of criteria to guide innovation in glaucoma surgery.[76] The ambition was to develop the ideal surgical technique that would take less than 10 minutes to perform and achieve single-digit IOPs that would last for more than 10 years. To date, there is no evidence that any of these goals were reached. Yet, technological advances continue to deliver new surgical techniques year on year, and the glaucoma specialist armamentarium has become so vast that treatment choices are often guided by personal preferences and experience.[75] Nevertheless, glaucoma is a multifactorial disease and recent literature abounds with suggestions that specific clinical or demographic characteristics may influence the outcomes of different treatments.[77,78,79,80,81,82] Although this implies that tailoring treatment options to individual patients' characteristics may be beneficial, specific clinical recommendations guiding personalized therapeutic choices remain scarce. Targeted research efforts are therefore warranted to elucidate the specific factors influencing glaucoma treatment outcomes.

1.5. Thesis statement

The present thesis is based on the two cornerstones of glaucoma management: (1) IOP monitoring and (2) IOP control.

(1) Although IOP has long been known to be highly dynamic, most therapeutic decisions in glaucoma management are based on a single static in-office measurement. Little is known about IOP variations outside clinic, and as such new protocols are needed to observe and quantify these variations, and explore their relevance to glaucoma management.

(2) Despite the knowledge that IOP control and surgical outcomes may be influenced by a number of clinical or demographic factors, there is no unified recommendation guiding the choice of surgical treatment in glaucoma. Research is therefore needed to better understand individual factors influencing treatment outcomes in glaucoma.

2. Chapter 2 - Redefining intraocular pressure

2.1 Introduction

The measurement of IOP is central to the monitoring and treatment of glaucomatous eyes. Although the significant variability of IOP was described over a year ago, static IOP measurement remains the standard of care in glaucoma clinics, and little is known about out-of-office IOP fluctuations. This may be explained by the ongoing debate over the clinical relevance of IOP variations and the technical difficulties inherent to measuring IOP continuously over extended periods of time. Yet, the advent of IOP telemetry has recently made semi-continuous IOP monitoring possible in human patients, opening new avenues of research on out-of-office IOP variations.

Clinically, several secondary analyses of IOP measurements at successive visits from large clinical trials suggested that long-term IOP variations may directly contribute to glaucoma progression.[62,63] Yet, none of these trials were specifically designed to examine this correlation, and these post hoc observations should be confirmed by dedicated studies.

The study of circadian IOP variations has been permitted through scheduled intermittent tonometry in sleep laboratories. The observation that most eyes exhibit a peak 24-hour IOP overnight led to the speculations that IOP may be influenced by AH dynamics, body position, and fluctuation in hormonal levels, such as melatonin and glucocorticoids.[83] Yet, the precise impact of these factors has long been a challenge to explore outside of a laboratory setting.

Knowledge of short-term IOP variations is mostly limited to anecdotal observations due to the practical and technical challenges posed by continuous tonometry. Indeed, until recently, most tonometric devices could only measure static or short-term rhythmic fluctuations of IOP. Yet, animal models and laboratory studies have suggested that a wide range of external factors including eye rubbing, blinking or saccades may have a significant effect on IOP.[84]

All these observations demonstrate the limitations of the current standards of care for glaucoma monitoring involving only a few static IOP measurements a year. Over the last few years, technological advances in semi-continuous IOP measurement have allowed to better describe and explore the role of out-of-office IOP variations.[85] This body of research relies on these novel pressure telemetry devices to study 24-hour IOP variations and assess their impact on glaucoma progression and management.

2.2 Article 1 – Studying the impact of intraocular pressure variations on glaucoma progression

2.2.1 Context and rationale

GAT is currently considered the gold standard technique for IOP measurement. Yet, the technique is largely considered imperfect, not only because of its relative imprecision, but also because its static nature fails to reflect the dynamic nature of IOP. This is despite the suggestion that IOP variations may be an individual risk factor for glaucoma progression. This hypothesis, however, was only verified by secondary post hoc analyses of IOP measured over successive visits in large clinical trials databases.

Recently, the development of new devices has allowed to examine IOP variations more accurately and objectively. One of these devices is the Triggerfish® contact lens sensor (CLS; Sensimed AG, Lausanne, Switzerland). This silicone soft contact lens relies on strain gauge to measure semi-continuous changes in biomechanical forces at the limbus, including subtle intraocular volume changes. While the resulting measurement is only a surrogate for IOP and cannot be directly converted into mmHg, several studies showed the Triggerfish® CLS provided a fair representation of IOP variations, through 30-second bursts of 300 measurements every 5 minutes over a 24-hour period.[85] Based on the Triggerfish® CLS output, De Moraes et al. identifies a number of individual parameters to describe and quantify IOP variations. Evaluating these parameters in 445 open-angle glaucoma patients, they identified the common characteristics of IOP variations exhibited by patients who exhibited the fastest disease progression in their cohort.[86] From these observations, Sensimed® AG developed an algorithm in an attempt to predict glaucoma progression based on IOP variation analysis.

The aim of this study was therefore to evaluate the accuracy of a progression report (PR) algorithm based solely on clinical history and 24-hour IOP variation profiles to predict the risk of glaucoma progression. Not only would the validation of such an algorithm provide another measure to identify patients at risk of rapid glaucoma progression and improve their care, but it would also confirm the importance of IOP variations as an independent risk factor in glaucoma progression, and as such, as an essential biomarker to consider in the management of glaucoma.

2.2.2 Methods

This study was retrospective and was carried out across two investigation centres, in Lausanne, Switzerland, and in Denver, USA. It was approved by the respective, local institutional review boards (IRB) and conducted in full compliance with the Declaration of Helsinki.

All open-angle glaucoma patients who had undergone a complete 24-hour Triggerfish® CLS recording between December 2012 and November 2017 at either of the investigation sites were retrospectively enrolled if they had taken at least 2 reliable visual field tests prior to the recording, and 3 reliable visual field tests within the 2 years after their recording. Fast progression was defined as a worsening in mean deviation (MD) at a rate of more than 1 dB a year.

Two glaucoma fellows were asked to review the enrolled patients' notes up to the date of their CLS recording, and to assess their risk of rapid progression. They were allowed to use all available data up to the date of the CLS recording but were blinded to the patient's identity and to any information beyond the date of the recording.

CLS output data and basic medical information were fed into the PR to produce a risk report for each patient.

2.2.3 Key results

The study demonstrated that, in the assessment of the risks of glaucoma progression in 30 eyes with reliable visual fields and CLS recording, the agreement was good between both glaucoma fellows' assessments, and between one of them and the PR. The agreement between the other assessor and the PR was only fair.

The PR was as accurate as either of the glaucoma fellows at predicting fast glaucoma progression (Figure 1). Indeed, the correlation between each of the assessment and actual rates of progression were r = 0.31, r = 0.43 and r = 0.57 for the first fellow, the second fellow, and the PR, respectively.

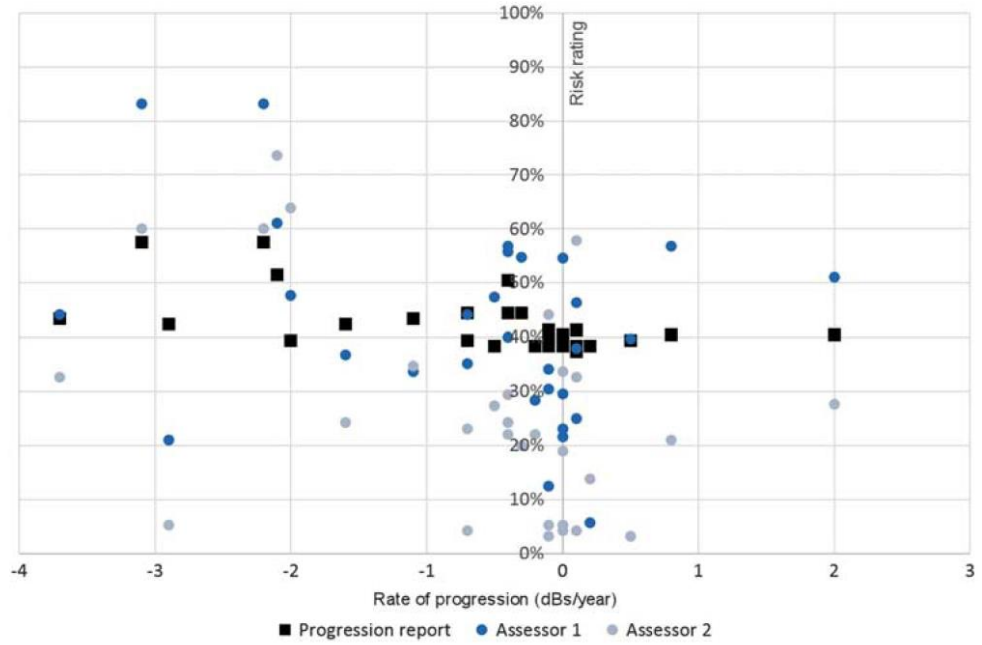


***Figure 1** - Risk of progression as estimated by the progression report (square), Assessor 1 (dark circle) and Assessor 2 (light circle) shown against the actual MD progression in dBs/y (x-axis) – Source: Author's own work (Article 1).*

2.2.4 Impact and Reflection

In their post hoc analysis of the AGIS database, Nouri-Mahdavi and colleagues had suggested that long-term IOP variations may be an independent risk factor for glaucoma progression.[87] Yet, technical challenges had limited primary research in this field and long prevented the study of the impact of short-term IOP variations.

The present study was the first to confirm that an algorithm could be as accurate as experienced specialist doctors at predicting rapid glaucoma progression. More interestingly, the algorithm used in the PR does not involve any IOP measurement, which is currently at the core of most clinical decisions in glaucoma. This was also the first study to evaluate the diagnostic potential of 24-hour physiological IOP variations measured during sleep and wakefulness using a semi-continuous sensor and a predictive algorithm. It confirmed the role

of short-term and circadian IOP variations in glaucoma progression, irrespectively of absolute intraocular pressure values. These results were supported by a subsequent study by Tojo et al.[88] looking at the role of short-term IOP variations in glaucoma progression, and highlighted the need for a change of paradigm in glaucoma practice by challenging the importance of static IOP measurements. From a research point of view, this study reaffirmed the importance of gaining a better understanding of IOP variations, their nature, mechanisms and causative factors.

In clinical practice, the present study reinforced the notion that 24-hour IOP profiles have a role to play in glaucoma diagnosis and management. It suggests that IOP modulation may be as important as IOP reduction in controlling glaucoma progression and has led to an increased awareness of the issue of IOP fluctuations. However, while assessing the interconnections between IOP variations and visual function changes is highly relevant from a clinical perspective, it also exposes the study to the same limitations as that of all forms of functional testing. Indeed, perimetry is a subjective test with high inter-test variability, and while a number of steps were used to minimize the risk of bias, such as the use of a minimum of five examinations per patient and the exclusion of suboptimal measurements, estimating the rate of functional progression remains difficult. Furthermore, the widespread use of the Triggerfish® CLS and predictive algorithms in clinical practice is being held back by a number of factors, both practical and economical. First, while its predictions of the PR are impressive from a statistical point of view, the risk-scores generated by the PR tend to be clustered around the mean, with little discrimination between slow (41% mean risk-score) and fast progressors (44% mean risk-score), meaning the algorithm will have to be refined in order to offer clinically relevant guidance. In hindsight, this issue may be partially explained by the distribution of the scores across the Likert scale, and could have been analysed under the scope of central tendency statistics. However, I only developed a sense of these statistical issues through my work on subsequent projects. Second, as a predictive tool, the algorithm would need to be formally validated and approved in order to become commercially available in most countries. Finally, CLS remain expensive and resource-demanding, and are therefore not readily available in most healthcare systems. This status-quo was illustrated by American policy makers Healthy Blue's recommendation that continuous IOP monitoring may currently remain "investigational and not medically necessary" in the USA quoting technical limitations, although they acknowledged the potential clinical benefits illustrated in Articles 1 and 5.[89] In the era of artificial intelligence, there is however no doubt that this study will serve as a proof-of-concept for future algorithms that will emerge in the coming years in an attempt to make the risk stratification in glaucoma more automated and standardized. This keen interest in new technologies to help automatized glaucoma assessment was evidenced by the news articles reporting on our findings from Article 1 in 'Review of Ophthalmology'[90] and Healio's 'Primary Care Optometry News'.[91]

From a personal point of view, this project was the first I contributed to in this corpus of studies, and the first time I worked on a multi-centre project. Coordinating research efforts across different centres and continents, in a pre-COVID era when the use of videoconferences was less conventional, was both challenging and stimulating to me. It has undoubtedly contributed to the foundations of my subsequent development as a lead investigator, and paved the way for future research that would address some of the main limitations of this

study, notably by assessing the capability of the PR to predict more reliable structural progression.

2.3 Article 2 – The effect of daily activities on intraocular pressure

2.3.1 Context and rationale

While the study reported in Article 1 confirmed the influence of short-term and circadian IOP variations on glaucoma pathogenesis and rapid disease progression, little is known about the nature and causes of out-of-office IOP variations.

Most of the data available result from the study of non-human primates. These animal studies confirmed two essential hypotheses. First, they suggested that the magnitude of daytime IOP fluctuations may be even greater than anticipated. Indeed, in non-human primates, daytime IOP was shown to spike by more than 5 mmHg as many as 5000 times per hour.[92] Second, they confirmed the influence of exogenous factors and external forces on these fluctuations, with intense albeit transient fluctuations associated with blinking, rubbing or eye movement.[93] In humans, some population surveys, laboratory experiments and anecdotal evidence have suggested that lifestyle choices and day-to-day activities may have a similar direct effect on IOP. Notably, simulated sleep in face-down position was estimated to cause a sustained IOP elevation of 2.5 mmHg,[94] and the IOP spike observed during resistance training reached a mean of 40.7 mmHg.[95] Yet, the design of these studies, relying mainly on a limited number of rebound tonometry measurements at set intervals, precluded the analysis of instantaneous IOP variations, mean peak ratio, and sustained changes that were shown to potentially contribute to glaucoma progression.

The aim of this study was to determine the effect of lifestyle and external factors on short-term and circadian IOP variations in human subjects, over a 24-hour period. The conclusions of this study would allow to evaluate the impact of out-of-office activities on IOP and guide the design of further studies in order to explore the impact of pressure variations associated with specific activities on glaucoma pathogenesis and progression. Ultimately, this would allow clinicians to better counsel their patients and tailor their treatments to better control lifestyle-induced IOP variations.

2.3.2 Methods

This prospective single-centre study was conducted at the University of California San Diego. It was approved by the local IRB and conducted in full compliance with the Declaration of Helsinki.

Glaucoma patients enrolled from a specialist clinic were fitted with a Triggerfish® CLS in one eye chosen at random. They were then instructed to resume their daily routine and to keep a diary of any notable activity or event. After 24 hours of CLS recording, subjects returned to the investigation centre to have the CLS removed. Subject diary entries were analysed, and the most commonly reported activities were selected and grouped under major headings. Namely, ‘Walking and cycling’, ‘Resistance training’, ‘Emotional stress’, ‘Yoga and meditation’, and ‘Alcohol consumption’.

CLS measurement obtained before, during and after each studied event were extracted and averaged by 30-minute periods. The average of all measurements recorded 60 to 30 minutes prior to an event was used as the reference baseline for each individual event. Recorded variations during and after each event were compared to the reference value using a paired t-test.

2.3.3 Key results

Significant short-term variations in IOP profiles were recorded in all participants. Forty events matching one of the selected headings were reported in the subject diaries, across 22 of the Triggerfish CLS recording sessions.

- Walking and cycling (n = 10) caused a small but significant rise in IOP profile during the event ($p = 0.018$), followed by a gradual reduction in IOP profile that was not statistically significant.
- Resistance training (n = 11) caused a significant rise in IOP profile from the onset of the event, that persisted through 120 minutes after then end of the training session ($p < 0.007$).
- Yoga and meditation (n = 4) were associated with an acute reduction in IOP profile from the onset of the event, that persisted through 120 minutes after the end of the activity, although none of these variations reached statistical significance level ($p > 0.380$).
- Emotional stress (n = 13) correlated with a significant gradual rise in IOP profile from the onset of the stressful stimulus through 120 minutes ($p < 0.038$).
- Alcohol consumption (n = 2) correlated with a significant reduction in IOP profile at the time of consumption ($p = 0.049$). (Figure 2)

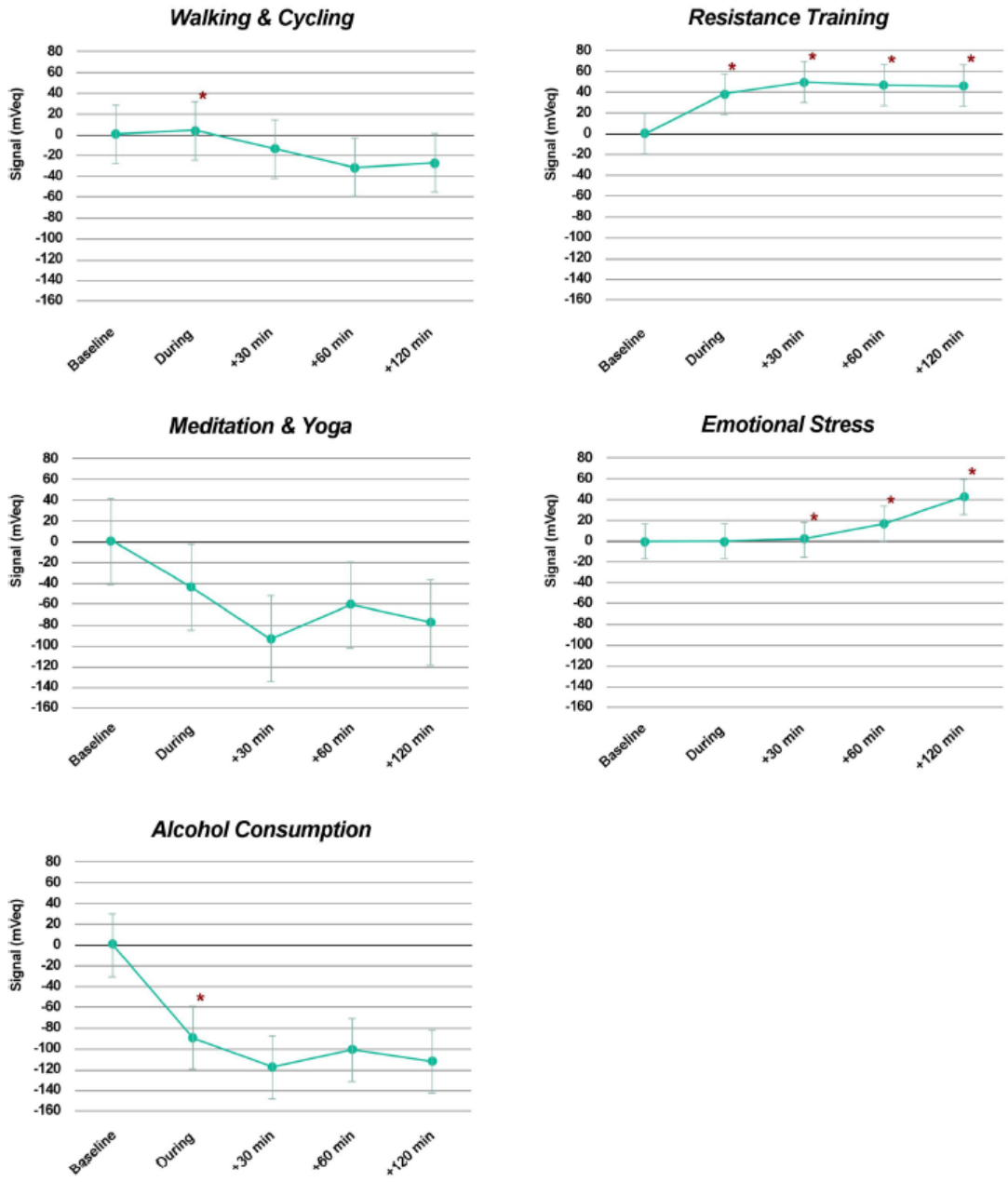


Figure 2 - Mean effect of each group of activities on intraocular pressure-related signal recorded in mVeq, during the event, within 30 min of the end of the event, between 30 and 60 min of the end of the event, and between 90 and 120 min of the end of the event, compared to baseline measurements set at 0 mVeq (30 ‑60 min before the start of the event). Vertical bars represent the 95% confidence interval, and asterisks represent statistically significant differences from baseline ($p < 0.05$). Source: Author's own work (Article 2).

2.3.4 Impact and reflection

This study confirmed that significant IOP variations occur constantly through the day and may be driven by many day-to-day activities, lifestyle choices and emotional situations. The design of the present study differs significantly from all previous research in the field through two key aspects. First, instead of using set-interval tonometry measurements, it relied on CLS to achieve semi-continuous assessment of IOP variation over 24-hour periods. This approach had

the advantage of achieving considerably more frequent measurements over longer periods of time, without interfering with the subjects' activities or requiring them to adopt any specific position. Second, instead of using protocoled lab-controlled activities, this study explored the effects of unimpeded real-life events and activities, as they were perceived by the participants.

This is particularly relevant to the study of psychological events that are inherently subjective, such as psychological stress, and can be difficult to standardize in a traditional research setting. By chance, a number of recordings were carried out at the time of the Great Blackout, when widespread power outage affected San Diego, causing significant amount of stress to some study subjects, and thus accounting for the high number of 'Emotional stress' events reported. Nevertheless, the absence of standardization of the reported activities is also the main limitation of this study, as it did not allow to control for cofounding factors, and relied solely on the sole description and times provided by the subjects. On this note, in the present study, a significant number of subjects' diaries were either incomplete or blank. In hindsight, this is a clear illustration of the importance of preparation and briefing in any project involving subject cooperation. Indeed, emphasizing and reinforcing the role of a comprehensive and precise diary to participants at each visit would have provided more detailed data and would have increased the statistical power of the analysis. I am confident that this learning point has influenced the way I subsequently briefed study participants, stressing the importance of their role and adherence the protocol on every occasion. This has undoubtedly contributed to the high retention rates achieved in most of my other clinical trials, included those described in Articles 7, 8 and 9.

While the exploratory nature of this study only evidenced the significant influence of common day-to-day events and activities on IOP variations, it did not assess the impact of lifestyle-associated IOP fluctuations on glaucoma progression. However, considering the potential correlation between short-term IOP variations and rapid glaucoma progression suggested by the study reported in Article 1, these new findings raise an important question for clinical practice and further research. These clear clinical implications along with fact this study was the first exploratory analysis of short-term out-of-office IOP variations explain why this report received significant scientific and media attention. Its results were presented at a number of international conferences including the World Glaucoma Congress, the Eye & Tech[2] and the Macula & Genoma Foundation conference. They were also reported in the American Academy of Ophthalmology's EyeNet Magazine,[96] in the International Glaucoma Review 22-1[97] and in OSI's 'What's in the news?'.[98]

2.4 Article 3 – Weekly and seasonal intraocular pressure variations

2.4.1 Context and rationale

Article 2 showed that external factors have a direct influence on instantaneous and short-term IOP variations, and Article 1 suggested that these short-term variations may constitute a risk factor for glaucoma progression. Long-term fluctuations, however, have long been speculated to play a role in the disease pathogenesis, and there is growing evidence that these variations may be an independent risk factor for glaucoma progression, especially in eyes with lower

mean IOP.[61] However, these observations are often based on ad hoc analyses of inter-visit measurements at irregular and infrequent intervals, and although these have previously identified an impact of seasons and climate, primary data on these fluctuations remain scarce.[99,100]

The main reasons for this scarcity of data are the technical and practical difficulties in obtaining frequent IOP measurements over prolonged periods of time. Indeed, in order to elicit seasonal variations, cohorts would have to be followed over at least a couple of years, and recordings would have to be frequent and numerous enough to minimize the influence of confounding factors and short-term fluctuations. In recent years, the advent of novel telemetry devices has permitted this through the use of implantable sensors such as the Eyemate® (Implandata Ophthalmic Products GmbH, Hannover, Germany). This intraocular transducer that may be implanted during cataract (Eyemate-IO) or glaucoma surgery (Eyemate-SC) is made of 8 pressure sensor that remain in the patient's eye indefinitely, either within the sulcus or into the suprachoroidal space.[85] The sensors can then automatically measure IOP at a frequency of up 10 Hz or allow for non-automated monitoring through the use of a contactless patient-operated handheld device.

The aim of this study was to observe the effect of weekdays and seasons on long-term IOP variations in human subjects over several years. The observations from this study would allow to better understand long-term IOP variations that were previously shown to affect glaucoma progression.

2.4.2 Methods

This prospective observational multi-centre study was conducted at Lausanne (Switzerland), Bochum (Germany), Mainz (Germany), München (Germany) and Sulzbach (Germany). It was approved by the local IRB and conducted in full compliance with the Declaration of Helsinki.

Patients with primary open-angle glaucoma and clinically-significant cataract were enrolled from specialist clinics and underwent cataract surgery combined with Eyemate-IO implantation. They were then instructed to measure their IOP as often as desired, but at least four times daily.

All obtained measurements were used for analysis. The highest daily IOP ("peak IOP") was identified for each individual eye and day. The mean daily and monthly IOP, as well as the mean daily and monthly peak IOPs were averaged. Analysis of variance (ANOVA) was used to examine the significance of such variations.

2.4.3 Key results

A total of 106,754 IOP readings over 15,811 measurement days were recorded and analysed. These confirmed the presence of significant weekly and seasonal variations in IOP. Seasonal IOP variations followed a biphasic pattern, with significantly lower IOP in summer and higher IOP in winter (Figure 3). Weekly IOP variations were significantly lower at the weekend and higher on Wednesdays (Figure 4).

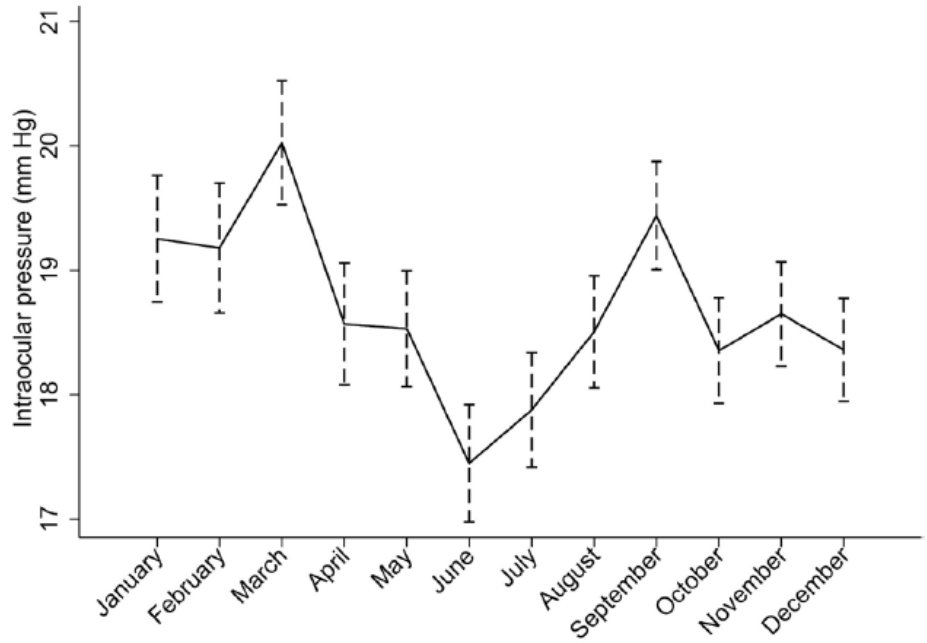


Figure 3 - The variations in average intraocular pressure between weekdays. Source: Author's own work (Article 3).

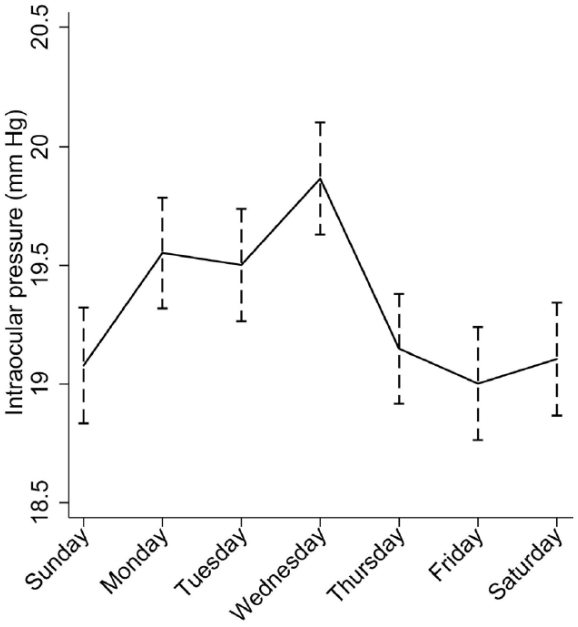


Figure 4 - The variations in average intraocular pressure between calendar months. Source: Author's own work (Article 3).

2.4.4 Impact and reflection

The present study confirms that IOP exhibits clear seasonal and weekly patterns through the analysis of the largest IOP database measured using an intraocular sensor. This specificity minimizes the impact of confounding factors and significantly increases the power of the analysis. It confirms the findings from several earlier analyses suggesting that IOP is higher in winter than in summer, with variable variation amplitudes. While the mechanisms responsible for such fluctuations remain elusive, temperature, light exposure and hormonal fluctuations

are suspected factors. Interestingly, the present study was also the first study to identify a significant difference in IOP between weekdays and weekends. While the reasons for these variations remain unclear, psychological stress or fluctuation in treatment adherence may account for these variations. The identification of this new physiological phenomenon was fascinating from a scientific point of view, as it required an in-depth exploration of the regulatory mechanisms in order to produce valid hypotheses for these observations. Another particularity of this project was the extremely high volume of data that required a refinement of my data collection, handling and analysis techniques. The automatization and programming skills I acquired through this project proved invaluable during subsequent studies - notably Article 7.

The seasonal pattern of IOP variations demonstrated in the present study was subsequently confirmed by Liao et al. in a cohort of healthy volunteers.[101] Clinically, they confirmed that this season-to-season variability did not only affect mean IOP, but also the profile and repeatability of 24-hour IOP curves. Another clinical application of the present study was illustrated by Terauchi and colleagues' subsequent project in which they showed that greater magnitudes of seasonal IOP variations were protective against glaucoma progression.[102] This was further supported by Jang and colleagues' recent report that the risk of developing optic disc haemorrhages, that were associated with glaucoma progression, showed similar seasonal fluctuations with a lower risk in summer.

The novel nature and the clinical relevance of the observed patterns in the present study have led to a dissemination of our results through mainstream and specialist media. Published in the British Journal of Ophthalmology, our findings were reported in the International Glaucoma Review,[103] as well as in 'Review of Optometry',[104] 'Practice Update',[105] and 'Ophthalmology 360'.[106]

2.5 Article 4 – Assessing new technology in contact lens sensors

2.5.1 Context and rationale

Articles 1, 2, 3 analysed IOP variations and their effect on glaucoma progression. While the former confirmed that fluctuations in IOP had an impact on the pathophysiology of glaucoma and suggested that their monitoring may have a role to play in glaucoma management, the latter studies evidenced the fact that both intrinsic and extrinsic factors influence IOP variations in the short- and the long-term. All these studies relied on CLS and implantable sensors to record IOP variations at shorter intervals, over longer periods of time, and in more realistic conditions than what can practically be achieved with traditional tonometry. Yet, despite the clear advances that these novel techniques permitted in the understanding of IOP variations, these techniques are not without limitations. I had previously highlighted these in a comprehensive review of IOP telemetry techniques published in 'Expert Review of Ophthalmology', and drawing a roadmap for the development of the field (5.3 - Additional publication 1).[83]

Namely, the Triggerfish® CLS is a relatively simple and non-invasive tool allowing for convenient analysis of immediate and short-term IOP-related variations over 24 hours.

However, the only commercially-available CLS suffers the major drawback of only recording subtle variations in corneal diameters through strain gauges as a substitute for actual IOP. While these variations were shown to accurately represent IOP variations, they are only recorded in an arbitrary unit (mVeq) which cannot be converted into IOP.[83] This specificity reduces the interpretability of results and may induce some biases from confounding factors. The Eyemate® implantable sensors have solved this limitation by using pressure sensor cells to measure actual IOP directly inside the eye, thus minimizing the risk for biomechanically induced biases. While these implants were shown to be safe and accurate, they however come with the significant inconvenience of requiring surgical implantation, and their use is thus reserved for patients with more advanced glaucoma. In order to solve these limitations, Sensimed® AG developed a novel CLS fitted with central pressure sensors capable of continuous 24-hour measurement of intraocular pressure in millimeters of mercury (mmHg).

The aim of this Phase 2 clinical study was to assess the safety and efficacy of this novel CLS over 24-hour recording periods. The validation of this novel technology would provide a proof of concept for true non-invasive real-time IOP monitoring, paving the way for more accurate studies to explore the physiology and impact of immediate and short-term IOP variations in healthy and glaucomatous eyes.

2.5.2 Methods

This prospective single-centre study was conducted at the [W] eye clinic, in Poznan. It was approved by the local IRB and conducted in full compliance with the Declaration of Helsinki.

Open-angle glaucoma patients enrolled from a specialist clinic were fitted with a novel Pressure Measuring Contact Lens (PMCL) in one eye. Pneumatonometry was performed in both eyes immediately before PMCL fitting and after PMCL removal. Pneumatonometry was also performed in the non-study eye before, during, and after a series of provocative tests, while the PMCL recorded IOP continuously in the study eye. Paired t-tests were used to compare each pneumatonometry measurement with its nearest PMCL measurement in the fellow eye.

2.5.3 Key results

The PMCL was well tolerated and only one notable adverse event was recorded. Over the 24-hour recording period, 88.0% of all paired fellow eyes measurements were within 5 mmHg of each other. During water drinking test, a significant increase in IOP was detected both by the PMCL in the study eye (2.4 ± 2.5mmHg; p = 0.03) and by the pneumatonometer in the fellow eye (1.9 ± 1.9 mmHg; p = 0.02). The average difference in successive same-eye IOP measurements made by pneumatonometry and with the PMCL was 2.0 ± 4.3mmHg at fitting and 6.5 ± 15.2mmHg at removal.

2.5.4 Impact and reflection

The present trial is a proof-of-concept for this novel type of CLS, and confirms that non-invasive contact lenses may achieve high-frequency IOP measurements over 24-hour. However, the agreement between consecutive same-eye measurements was greater at the time of fitting than at removal, and detailed analysis of individual IOP charts reveals an

overnight drift in the PMCL measurements. The reasons for this drift remain unclear but it can be speculated that changes in corneal surface may affect measurements, and should become a focus for further development of the device. Nevertheless, the agreement between PMCL measurements and pneumatonometry is comparable to that of widely used tonometers and GAT. Further to the validation of this technology, the Japanese public company SEED CO Ltd. announced the acquisition of majority interest in SENSIMED SA, the company that had developed the PMCL technology. More recently, the results published in Article 4 were cited in an updated review of tonometry devices in the Journal of Clinical Medicine.[107]

From a personal point of view, this project was the first phase 2 clinical trial evaluating novel biomedical technology I took part in. The sound knowledge and expertise in the field of IOP telemetry I had developed through previous studies and reviews was a key asset in the design and the execution of this trial. Undeniably, having a clear idea of the current technological limitations, physiological variations and common technical issues was very valuable in selecting the most appropriate tests and designs in order to provide a meaningful assessment of this novel technology. Indeed, some CLS device specificities such as the inability to measure IOP in the study eye during the recording period, the difficulties in using GAT in different body positions, or the interferences caused by metal frame spectacles, precluded the use of traditional designs of other trials assessing tonometry devices. Through these considerations and my contribution to this study, I developed new sets of skills in the design, execution and supervision of clinical trials. These skills proved invaluable in subsequent studies, leading to my participation in more advanced projects with international research groups such as Stanford University.

3. Chapter 3 – Understanding individual factors influencing the outcomes of glaucoma surgery

3.1 Introduction

The overarching goal of all glaucoma management strategies is to preserve patients' visual function and quality of life, often by halting or slowing the progression of the disease.[64] While glaucoma is ultimately a disease of the retinal ganglion cells, to date, the only known modifiable risk factor remains IOP. Lowering IOP therefore remains the sole focus of glaucoma management.

Primary treatment of open-angle glaucoma is typically with topical antiglaucoma medications or selective laser trabeculoplasty (SLT). Over the years, a number of evidence-based clinical guidelines have been developed to guide the choice in medical therapy and evaluate the role of laser treatments in glaucoma management. Traditionally, there used to be only one surgical option for patients whose glaucoma continued to progress despite maximum tolerated medical treatment. Over the last two decades, however, a vast number of novel surgical devices and techniques were developed, giving glaucoma specialists an unprecedented armamentarium to control IOP.[74,108] Yet, despite anecdotal evidence that surgical outcomes can vary extremely widely from patient to patient, there is yet no clinical recommendation to guide the choice of surgical technique.

This lack of consensus was recognised as one of the main unmet needs in glaucoma by the European Vision Institute.[109] This body of research focused on the study of MIGS devices in order to identify factors influencing individual outcomes, and eventually guide treatment choice in a more personalized and evidence-based manner.

3.2 Article 5 – The current state of minimally invasive glaucoma surgery – a meta-analysis

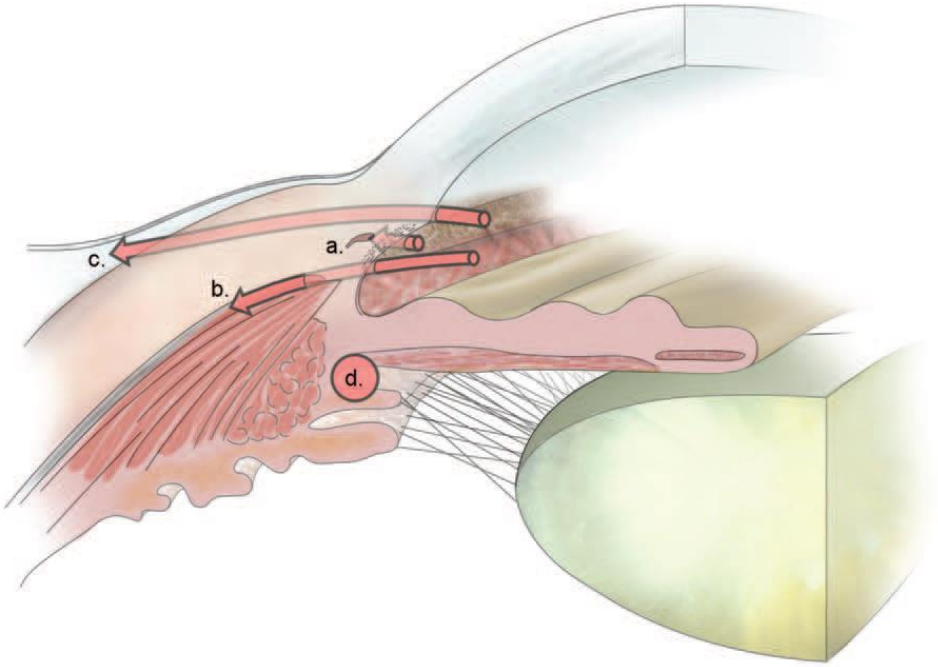
3.2.1 Context and rationale

Although the superiority of filtering surgery and glaucoma draining devices in advanced glaucoma or eyes requiring significant IOP reduction is undisputed, these techniques owe their efficacy to the use of antimetabolites that modulate natural wound healing and fibrosis.[110] However, this breakthrough in the glaucoma surgery has also led to a rise in the rates of late complications that exceed 30% in some reports.[111] For this reason, and despite sound evidence that early glaucoma surgery improves long-term visual outcome,[112] most glaucoma guidelines recommend to exhaust all medical and laser options before resorting to filtering surgery.[64] This conundrum has stimulated the search for novel, less invasive surgical techniques to bridge the gap between medical therapies and filtering surgery. Since the start of the years 2000, rapid innovation in the field of MIGS has seen dozens of novel surgical techniques emerge. By definition, MIGS have a more favourable safety profile than traditional filtering surgery, involving less scleral dissection, which in turn permits shorter surgical and

recovery times. While MIGS tend to achieve significantly less IOP reduction than traditional filtering techniques, they should offer meaningful IOP or treatment reduction.

MIGS are typically classified based on their mechanism of action. They may target the trabecular meshwork and Schlemm's canal, the subconjunctival space, the suprachoroidal space or the ciliary body (Figure 5). Each of these groups encompasses several individual techniques, all of which present their own risk profiles, advantages and limitations. Yet, to date, the indications for these techniques remain unclear and there is no recommendation to guide the choice of technique. Therefore, in practice, surgical choices tend to be guided by personal experience and preferences.

The aim of this meta-analysis was to provide a comprehensive review of the literature on MIGS and an overview of the techniques available as well as their respective safety and efficacy. This would allow glaucoma specialists to make more informed choices for their surgical techniques, and provide a roadmap to address the unmet needs in the field.



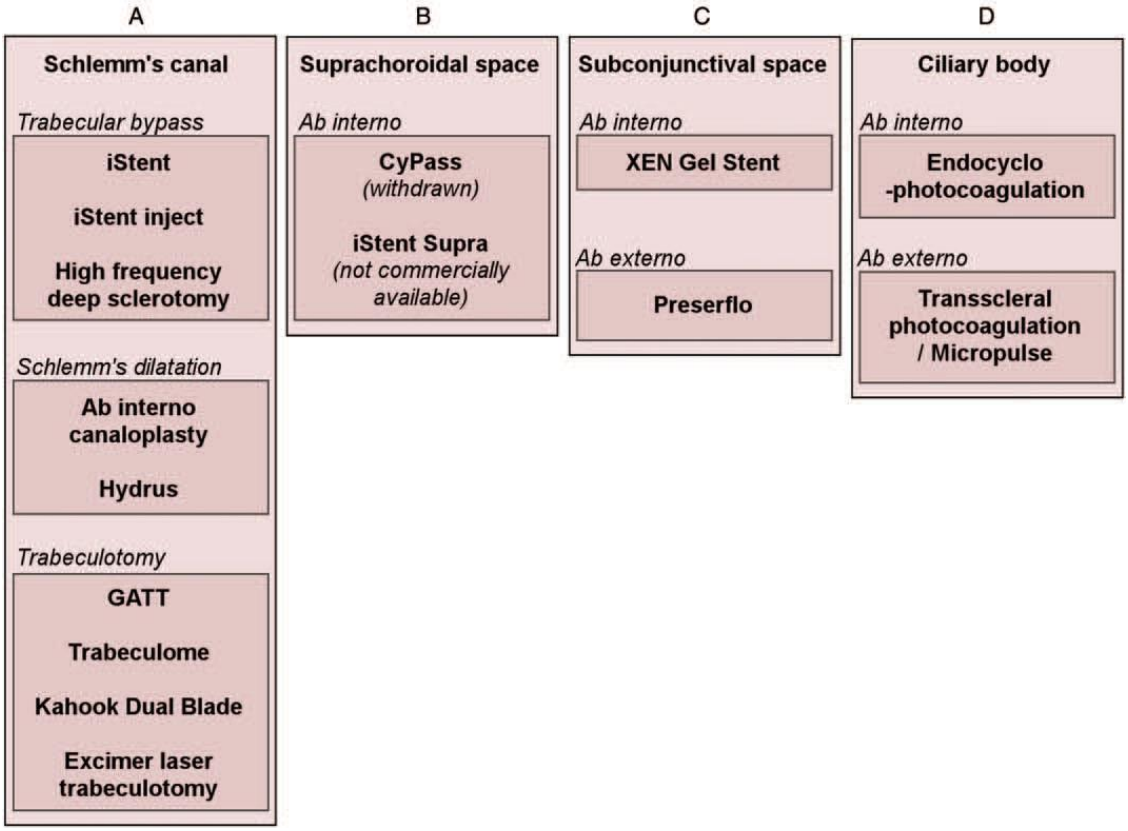


Figure 5 - Illustration of different anatomical and technical approaches of minimally invasive glaucoma surgeries. GATT indicates gonioscopy-assisted transluminal trabeculotomy. Source: Author's own work (Article 5).

3.2.2 Methods

The present meta-analysis adheres to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

A systematic search through the electronic databases of medical literature was carried out using keywords referring to the following MIGS:

- Trabectome, excimer laser trabeculotomy,
- Kahook Dual Blade,
- Gonioscopy-assisted transiluminal trabeculotomy,
- Ab interno canaloplasty,
- Hydrus microstent,
- High frequency deep sclerotomy,
- iStent trabecular micro-bypass,
- iStent inject,
- CyPass supraciliary micro-stent,
- Transscleral cyclophotocoagulation,
- Endo-cyclophotocoagulation,
- Preserflo microstent,
- XEN 45 gel stent.

The database search returned 2567 peer-reviewed publications. Non-English articles, non-clinical studies, case reports, paediatric studies, as well as trials with a mean follow-up period shorter than 6 months were excluded. In total, 77 articles encompassing a total of 7570 eyes were analyzed. For all comparative studies, the weighted mean difference and 95% confidence interval were calculated.

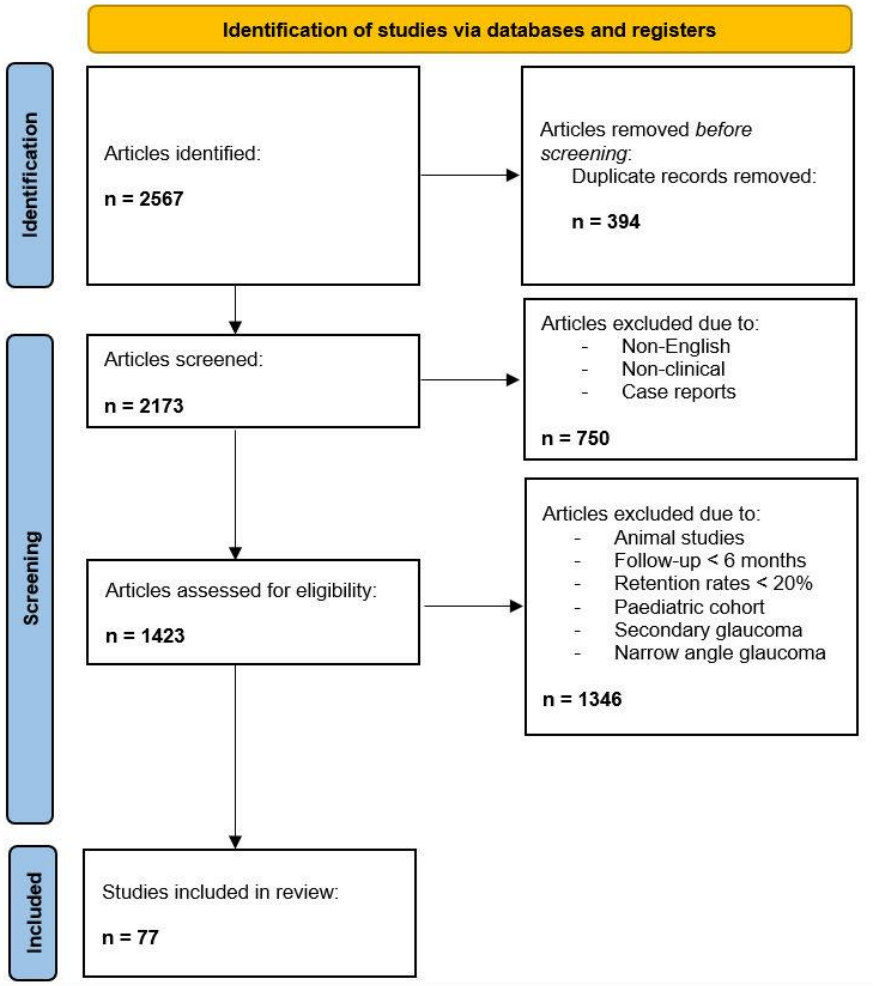


Figure 6 – PRISMA flow diagram describing the number of articles identified, excluded and reviewed at different phases of this meta-analysis. Source: Author's own work (Article 5).

3.2.3 Key results

All studied techniques had a favourable safety profile compared to that of filtering surgery. Most techniques also proved to be more efficient at lowering IOP than standalone cataract surgery, with IOP reductions between 20% and 50%, and wide variations observed between individual studies and techniques (Figure 6). It suggests, however, that subconjunctival drainage techniques may be more likely to achieve low-teen IOP than other MIGS approaches.

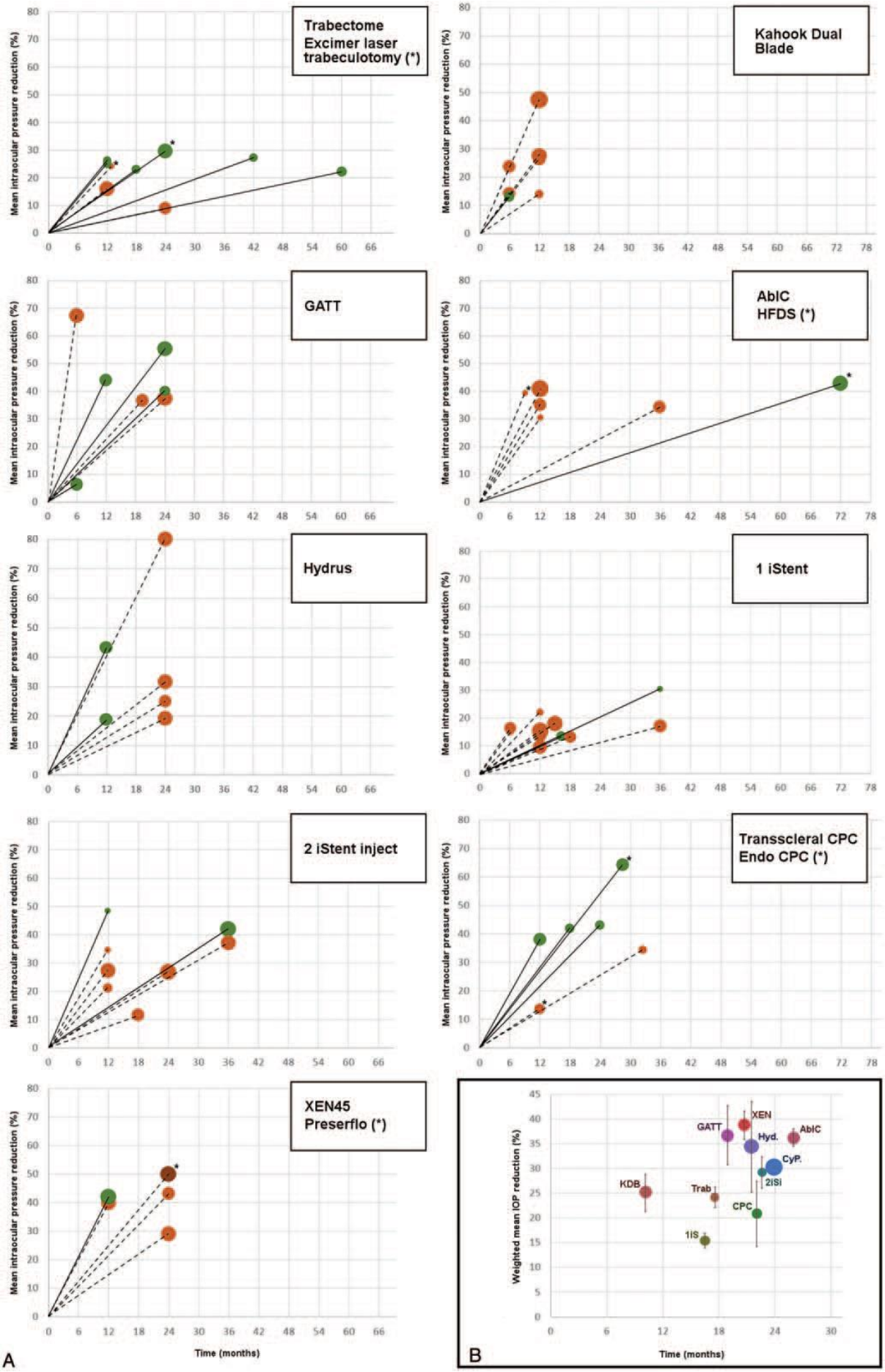


Figure 7 – (A) The top 9 graphs summarize the surgical outcomes at the final timepoint in each analyzed study. The horizontal axis represents the duration of the study and the vertical

axis represents the percentage of intraocular pressure reduction. The size of the dots is proportional to the reduction in antiglaucoma medications, larger dots representing greater magnitudes of reduction. Studies on standalone procedures are represented with solid lines, while studies on procedures combined with cataract surgery are represented with dotted lines. When two procedures are shown on the same graph, the asterisks marks the alternative procedures. (B) The bottom right graph summarizes the results of the meta-analysis. Each dot represents a surgical technique. The weighted mean intraocular pressure reduction of all reported studies for each surgical technique are plotted on the vertical axis while the weighted mean durations of the studies are plotted on the horizontal axis. The vertical bars show the 95% confidence interval. The surgical techniques are referred to in the graph with the following abbreviations: 1iS indicates 1 iStent; 2iSi, 2 iStent inject; AbIC, ab interno canaloplasty; CPC, cyclophotocoagulation; CyP., CyPass; GATT, gonioscopy-assisted transluminal trabeculotomy; Hyd., hydrus; IOP, intraocular pressure; KDB, Kahook Dual Blade; Trab, trabeculotomy; XEN, XEN45 gel stent. Source: Author's own work (Article 5).

3.2.4 Impact and reflection

The present meta-analysis confirmed the viability of a number of MIGS techniques in a large number of eyes across a number of clinical studies. It confirms the intuitive assumption that different approaches to aqueous drainage may have different outcomes, with a greater IOP-lowering potential in sub-conjunctival drainage techniques. However, no MIGS technique yet consistently achieves the single-digit IOP that are the ideal post-operative outcomes. Besides, this review highlights the lack of comparative studies or large cohort studies that would allow to identify individual biomarkers that influence surgical outcomes, and achieve individualized treatment.

While the lack of published evidence in the literature did not permit the drawing of firm guidance over the use of MIGS in glaucoma, this meta-analysis provided an overview of the current knowledge on MIGS and identified specific needs that will guide research towards clearer clinical recommendations. These include recommendations for future trials to standardize their report of key outcome measures and cohort characteristics, to include a standard therapy control group, and to extend follow-up periods beyond 2-5 years in order to provide an evaluation of the techniques' sustainability and late complications. Ideally, future MIGS study should also be randomized, report washed-out IOP and include a progression marker as a long-term outcome measure. This would improve the generalisation and comparability of results on MIGS trials, allowing surgeons and patients to make more informed decisions on surgical techniques, and further improving our understanding of individual factors influencing the outcomes of glaucoma surgery.

These conclusions were extensively relayed in the literature including comprehensive reviews,[113,114,115] and professional recommendations in Canada,[116] Brazil,[117,118] India[119] and France,[120] as well as at conferences, including the plenary sessions of the World Glaucoma Conference 2021 or Sir Professor Peng Khaw's specialist lecture to Moorfields Eye Hospital's glaucoma fellows. The conclusions and illustrations of this article are also featured in a Report to the Medical Services Advisory Committee of the Australian Government's Department of Health.[121] Beyond the scientific impact of this work, however, I feel that the skills developed through the execution of this first meta-analysis, such as the adherence to PRISMA methodologies or weighted mean calculations, but also the awareness I gained of common

limitations to existing studies, have helped me grow as a more confident and independent researcher. The amount of time and work required to process and analyse such a vast number of manuscripts single-handedly, however, is immense, and if I should undertake another meta-analysis, I would ensure I am supported by a team of research fellows or assistants.

3.3 Article 6 – Ab interno canaloplasty

3.3.1 Context and rationale

Beyond the main conclusions outlined above, Article 5 identified ab interno canaloplasty (AbIC) as a safe and promising surgical technique for the management of open-angle glaucoma. This MIGS technique derives from Robert Stegmann's ab externo visco-canalostomy, in which the sclera was dissected until Schlemm's canal is identified, unroofed, and dilated with high viscosity hyaluronic acid.[122] The aim of this guarded filtration surgery was to provide similar IOP reduction to trabeculectomy while minimising the risk of complications associated with anterior chamber entry. Despite some undeniable assets, the procedure still involved extensive conjunctival and scleral dissection, and remained invasive. AbIC was designed on the same working principle of Schlemm's canal viscodilation, but relied on an ab interno approach to reduce conjunctival manipulation and invasiveness. Several studies identified in Article 5 confirmed the IOP-lowering potential and safety profile of AbIC. Strikingly, the scatter plot of all the results analysed in Article 5 showed considerably less variability in the results of AbIC studies than in other MIGS techniques. While the increased interstudy agreement may suggest that AbIC is less dependent on individual factors than other surgical technique, long-term results were also considerably scarcer, thus precluding any generalisation or clinical recommendation.

The aim of this study was therefore to confirm the published outcomes of AbIC in open-angle glaucoma, and lay the foundation of a long-term cohort study of this technique. This would improve the comparability of this technique with other MIGS and traditional glaucoma surgeries, and assess its viability for the long-term management of glaucoma.

3.3.2 Methods

This retrospective single-centre study was conducted at the Ophthalmologic Network Organisation (OnO), in Geneva. It was approved by the local IRB and conducted in full compliance with the Declaration of Helsinki.

The surgical technique for AbIC is described in detail in Article 6. In a nutshell, at the end of phacoemulsification, after intraocular lens implantation, the trabecular meshwork was punctures nasally with the tip of a needle. Under gonioscopic view, an iTrack microcatheter (Ellex Inc., Adelaide, Australia) was fed through Schlemm's canal through 360°. Compressed viscoelastics (Healon GV; Abbott Laboratories, Chicago, IL, USA) was then injected as the catheter was progressively retracted, in order to produce viscodilation.

Every consecutive AbIC procedure carried out over a 4-year period at the investigation centre was included in the analysis. For all enrolled patients, demographic, pre-operative and post-operative data were retrospectively collected from their medical records. Eyes for which 12-month post-operative data were not available were excluded from efficiency analysis. All

available data was included in the safety analysis. Intraocular pressure was chosen as the primary outcome measure, and complete success was defined as an unmedicated IOP reduction of 20% or more 12-month post-operatively.

3.3.3 Key results

A total of 71 eyes were included in the analysis, with 12-month data available for 54 of them. Twelve months after surgery, 46% of eyes fulfilled the complete success criteria, with a mean IOP reduction from the procedure of 39.8% (-9.4 mmHg ; $p < 0.001$) and a concomitant 79.3% reduction in the number of medications used (-2.3 medications ; $p < 0.001$). Peroperative hyphema was observed in all patients, and as many as 22.2% of all operated eyes experienced post-operative IOP spikes over 30 mmHg. Over one in ten patients required further surgery due to uncontrolled IOP despite maximal medical therapy.

3.3.4 Impact and reflection

The present study confirmed the results reported by other author groups with a comparable magnitude of IOP reduction at 12 months.[123,124] In terms of safety, however, we observed higher rates of peri-operative complications, particularly in the form of early post-operative IOP spikes. While the precise reasons for these discrepancies could not be ascertained, retrospectively, a number of contributing factors could be suggested. First, the fact that all the reported cases were performed by a single surgeon may overemphasise the role of inter-operator technical variability related, for example, to the amount of viscoelastic device injected during the procedure or, in combined surgery, the extent of retrolenticular visco-aspiration. Then, one of the specificities of the Swiss healthcare system is that surgeons tend to follow-up their post-operative patients more frequently than in some other countries, and it is not uncommon to schedule three or four post-operative appointments within the first post-operative week. This would naturally lead to an increased detection of early post-operative IOP spikes. Thirdly, at the time of publication, the present study was the second largest cohort of AbIC procedures after that of Gallardo and colleagues.[125] Studies with smaller sample sizes may not have been adequately powered to detect these complications. Finally, several other studies of AbIC were sponsored by pharmaceutical companies that produce the catheters used to performed the procedure, potentially leading to funding bias. Besides, the fact that the rates identified in the present study are similar to that reported following similar procedures such as goniotomy or ab externo canaloplasty, tends to support the validity of these observations.

These observations made me consider the importance of outcome selection and sample sizes in clinical trials, as well as the role of health economy and funding in research. These considerations had a significant impact on my subsequent projects, and notably in the studies that have led to the production of Articles 7 and 8. I will therefore discuss these aspects in more details in the relevant sections. Nevertheless, the methodology of the present study was relatively simple as it was designed to verify a single hypothesis, validate primary outcome measures against the literature, and lay the foundations for longer-term analyses. Nevertheless, its results were used in the NICE's advisory committee[126] and Cigna's Medical Coverage Policy[127] to evaluate the outcomes of AbIC. Although no longer-term report was yet reported, the results of a 36-month analysis were presented at the 15th Congress of the

European Glaucoma Society.[128] This analysis will soon be published in a peer-reviewed journal, and a further analysis will be performed at 60 months if data allows.

3.4 Article 7 – XEN 45 gel stent

3.4.1 Context and rationale

One of the main conclusions of Article 5 was the apparent superiority of subconjunctival drainage techniques compared to other MIGS approaches in terms of IOP-lowering potential. Indeed, subconjunctival drainage has been the preferred approach for glaucoma surgery since the development of modern trabeculectomy by Cairns in 1968.[129] This approach involves the creation of an artificial drainage pathway allowing the aqueous humour to bypass the trabecular outflow pathway and drain into a virtual space under the conjunctiva: the filtration bleb. Subconjunctival drainage techniques present certain advantages, such as the fact that their drainage facility is independent from trabecular health or episcleral venous pressure, and can therefore achieve sub-physiological IOP. However, these advantages are intrinsically associated with some limitations, and the creation of a filtration bleb has been associated with some potentially sight-threatening complications. The main challenge faced by glaucoma surgeons when performing subconjunctival filtration surgery is to generate the right about of outflow resistance in order to achieve the desired long-term IOP in spite of various unmeasurable and dynamic patient-dependent factors such as subconjunctival resistance and fibrosis. While the advent of antimetabolites in the early 1990's has dramatically improved surgeons' control over the latter, leading to a greater efficiency and longevity of filtration procedures, the widespread use of mitomycin C (MMC) has also led to a rise in complication rates including bleb leaks, bleb-related endophthalmitis and severe hypotony.

Building upon the IOP-lowering potential of trabeculectomy, a number of engineers and clinicians have sought to optimise the concept of traditional filtration surgery by simplifying the surgical procedure and standardising the drainage facility. The XEN 45 gel stent stems from these researches. Based on the Hagen-Poiseuille equation, the dimensions of this 45 µm by 6 mm gelatine tube were chosen to produce an outflow resistance of 6-8 mmHg under physiological conditions, thus minimising the risk of hypotony. Besides, the ab interno implantation technique via a 27-gauge injector rids the need for conjunctival manipulation or dissection, making the procedure less invasive or traumatic.

The aim of this study was to assess the safety and efficacy of the XEN 45 gel stent in open-angle glaucoma, to evaluate the role of this procedure in the landscape of glaucoma surgery.

3.4.2 Methods

This prospective single-centre study was conducted at the Glaucoma Research Centre, in Lausanne. It was approved by the local IRB and conducted in full compliance with the Declaration of Helsinki.

Consecutive patient presenting with either progressive open-angle glaucoma despite maximal medical therapy or intolerance to medical therapy at the investigation centre over an 18-month period were prospectively enrolled. All participating patients underwent MMC-augmented XEN 45 gel stent implantation, either as a standalone procedure or combined with

cataract surgery if clinically significant cataract was present. Regular post-operative visits were scheduled through to 36 months. The primary outcome measure was the surgical success rate, which was defined as a clinically relevant combination of criteria including absolute IOP threshold (≤ 15 mmHg), relative IOP reduction (≥ 20%), and the absence of serious complications, visual loss or further surgery. The proportion of eyes exhibiting visual field progression ≥ 1dB of mean deviation was also reported as a secondary outcome.

Multivariate logistic regression analysis was used to identify significant risk factors for surgical failure. As some enrolled patients underwent bilateral surgery, in order to minimise bias, the analysis was performed twice: first including all available data, and then using only data from one randomly selected eye per patient.

3.4.3 Key results

A total of 149 eyes were enrolled, with 36-month data available for 92 of them. Three years after surgery, 31.5% fulfilled all the criteria of complete success. Over half of eyes (55.4%) required at least one needling revision and a quarter (26.1%) required further surgery to achieve IOP control. Over the 3-year follow-up, 16.3% of eyes exhibited ≥ 1dB visual field progression, and 1.1% experienced adverse events leading to a loss of visual acuity ≥ 2 lines. Regression analysis showed that male gender, requiring needling revisions or undergoing a combined procedure were all risk factors for surgical failure in primary open-angle glaucoma. Interestingly, combined procedures were not associated with worse outcomes in pseudoexfoliative glaucoma.

3.4.4 Impact and reflection

The present trial confirmed the safety of the XEN 45 gel stent over 36 months, and in hindsight, it has obviously fuelled the debate over its minimally-invasive nature and its efficiency. XEN 45 gel stents have been marketed as MIGS devices based on their ab interno approach that results in minimal tissue disruption, short surgical time, and rapid patient recovery. Yet, the fact that more than half of the implanted eyes required further invasive transconjunctival procedures in order to maintain filtration has led to questions over the minimally-invasive nature of the procedure as well as patient information. Indeed, if informed consent must include a list of the most frequent or serious complications, it should also most certainly mention the observed rates of post-operative procedures and surgical success. Yet, the definition of success can be very subjective and patient-dependant. While the design of the present trial was mostly standard and in line with World Glaucoma Association guidelines, the primary outcome measures were adjusted to provide glaucoma surgeons with a clinically relevant measure. They resulted from the fine-tuning of international guidelines to integrate some elements of real-life relevance in line with patients and doctors' expectations, such as lower IOP thresholds and the absence of serious complications, after extensive consultation with international colleagues. This produced a relatively low 3-year success rate of 31.5%. However, as the overarching goal of glaucoma treatment is to preserve patients' visual function rather than achieving a specific IOP, a functional outcome measure was included. Interestingly, this showed that only 16.3% of operated eyes progressed by more than 1 dB over the 3-year period, or 0.33 dB per year. In comparison, in a cohort of 583 treated glaucoma patients, Heijl et al. reported a median progression rate of 0.62 dB per year.[130] This suggests

that, despite not necessarily reaching the IOP threshold for surgical success, 83.7% of patients who received the XEN 45 gel stent progressed at least 50% less than the observed median progression over 3 years. This observation contradicts the IOP-based success rates and further supports our theory by which glaucoma surgery may not only slow glaucoma progression by reducing IOP levels, but also through a normalisation of its fluctuations.[82] Eventually, this may lead us to rethink the commonly accepted outcome measures in glaucoma trials, and adapt our outcome measures to answer the most relevant questions.

This trial represents the largest cohort of XEN 45 gel stent implantations with the longest follow-up period. The execution of this study represented several hundreds of hours of work to produce, not only the present report, but also an on-going series of reports and ad hoc analyses, the latest of which describes the surgical outcomes of XEN 45 gel stents at 60 months and is currently under review by Ophthalmology Glaucoma. While the present articles was amongst Acta Ophthalmologica's top cited papers in 2021, the corpus of articles I published based on this trial were collectively cited a total of 238 times, including in some textbooks[131] and international clinical guidelines such as the World Glaucoma Association Consensus on glaucoma surgery (5.3 - Additional publication 2-4).[132] Our results were presented at a number of international conferences including the 8th World Glaucoma Congress, and led me to write several textbook chapters on subconjunctival drainage devices.[133,134] Illustrations from these publications even featured on the cover of Journal of Glaucoma (vol. 27, August 2018). In all these respects, this project was an invaluable source of knowledge and experience to me as a researcher, challenging my preconceived ideas on glaucoma trial design and allowing me to explore beyond the publication of the report, the dissemination of the results. In many ways, it has provided me with the tools I needed to design the study presented in Article 8.

3.5 Article 8 – iStent inject

3.5.1 Context and rationale

As opposed to the subconjunctival approach illustrated in Article 7, the trabecular approach relies on the potentiation of a physiological pathway to increase aqueous outflow facility and lower IOP. These techniques have the advantage of mostly preserving the integrity of the conjunctiva and the iridocorneal angle structures. They are theoretically less traumatic than subconjunctival filtration procedures, and may not impair the outcome of any subsequent traditional filtering surgery that may become required. For these reasons, this approach is often recommended in mild open-angle glaucoma. Nevertheless, despite its sound theoretical assets, there is still considerable debate over the efficiency of trabecular MIGS. One of the most researched devices in this category, the iStent inject, is a 360-µm-long titanium stent designed to facilitate aqueous outflow from the anterior chamber into Schlemm's canal by bypassing the trabecular meshwork. While the technique has become popular amongst surgeons with over a million devices sold worldwide, there is no clear consensus over the use and indications of the iStent inject, which was reported to produce IOP reductions ranging from 11.6% to 48.4% in different trials (Article 5). This variability in surgical outcomes has led to questioning over the efficiency and the working principle of trabecular micro-bypass devices.

The aim of this study was to assess the safety and efficiency of the iStent inject device, and to explore the reasons for the variable outcomes reported in the literature. This would allow the

international community to draw clearer recommendations on the indications for this device, and advance research in the design of novel, more effective MIGS.

3.5.2 Methods

This prospective single-centre study was conducted at the Glaucoma Research Centre, in Lausanne. It was approved by the local IRB and conducted in full compliance with the Declaration of Helsinki.

All patients with symptomatic cataract and concomitant mild-to-moderate open-angle glaucoma over a 9-month period at the investigation centre were offered to participate in this study. Every enrolled patient underwent cataract surgery combined with the implantation of two iStent inject devices. Post-operative clinical data were collected through 12 months, and included two imaging visits, at 3- and 12-month. At these visits, the implanted devices were located under optical coherence tomography (OCT), and several anterior segment images were obtained according to a set protocol. Images were reviewed by a blinded assessor who assessed the position of each iStent inject according to anatomical landmarks and measured Schlemm's canal's diameters in each OCT image. Associations between device positions, Schlemm's canal dimensions and surgical outcomes were explored. An interim analysis was performed at 3-month (Article 8) and a final report was published at 12-month.[135]

3.5.3 Key results

A total of 25 eyes were included and underwent cataract surgery combined with dual iStent inject implantation. Three months after surgery, a 3.3% reduction in IOP and a 76.5% reduction in the number of anti-glaucoma medications were observed, with 64% of eyes achieving an unmedicated IOP of 18 mmHg or less. OCT scans of the anterior segment showed that 45.7% of visible devices were buried within the trabecular meshwork instead of protruding into the anterior chamber. In operated eyes, the mean major diameter of Schlemm's canal was 275.7 ± 171.8 µm temporally, while it was 126.9 ± 60.3 µm in fellow unoperated eyes ($p = 0.03$). There was a positive association between the proximity of the device to Schlemm's canal and the post-operative dimensions of the canal, as well as an inverse correlation between Schlemm's canal dimensions and post-operative IOP.

3.5.4 Impact and reflection

The present study confirmed that dual iStent inject implantation has a measurable anatomical effect on Schlemm's canal, which is directly correlated to post-operative IOP. More generally, it suggested that even a focal bypass of the trabecular meshwork may facilitate aqueous outflow and achieve circumferential dilation of Schlemm's canal (Figure 7). Besides, this report identified three main hypotheses that may account for the high variability in the reported outcomes of iStent inject. First, it was observed that almost half of the devices (45.7%) were too deeply implanted, and thus, did not connect the anterior chamber to Schlemm's canal. Statistical analyses also confirmed the logical assumption that buried iStent injects were associated with worse surgical outcomes. Implantation technique may therefore play a significant role in the reported outcomes. Second, the reported effect of trabecular bypass on Schlemm's canal was only observed in mild-to-moderate glaucoma, and may not be

generalizable to more advanced stages of the disease. Indeed, Yang et al. described how high IOP and chronic glaucoma cause Schlemm's canal to collapse, leading to structural adhesions and herniations that may become irreversible as the disease progresses.[136] Patient selection may therefore have a significant impact on the reported results. In hindsight, exploring the impact of glaucoma severity, expressed as visual field MD, on the magnitude of Schlemm's canal dilation in the present analysis may have contributed to answer this question. Finally, all participants in the present study had well controlled, stable glaucoma. The aim of the dual iStent inject implantation was therefore not to lower IOP, but rather to reduce the medical burden. This explains why the mean post-operative IOP reduction observed in this report was minimal, while the reduction in anti-glaucoma medications was significant. The design of the study as well as the healthcare system in which the study is executed can therefore dramatically influence the observed outcomes. The identification of these factors has contributed to the understanding and the interpretation of MIGS studies, and has allowed the refinement of trabecular micro-bypass surgery. When interpreting the results of this study, it is also worthwhile noting that 4 patients underwent bilateral surgery, which may produce statistical biases in the evaluation of surgical outcomes. This was not taken into account at the time of the study as its primary aim was to assess the anatomical position of the surgical devices and to explore their effects on iridocorneal structure angles. However, in hindsight, the use of different statistical methods such as linear mixed models or multivariable Cox proportional hazard models would have been more appropriate to minimize the risk of bias.

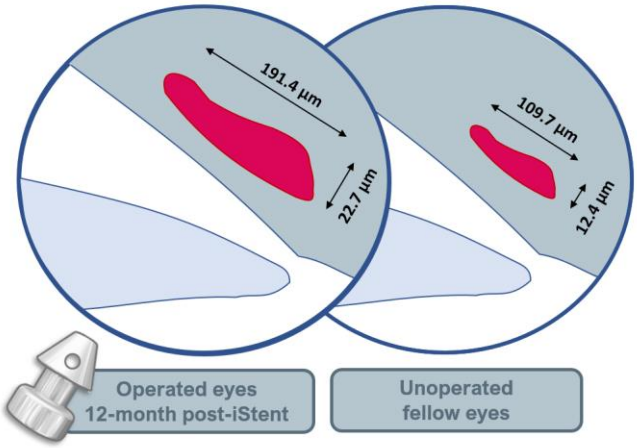


Figure 8 – Mean dimensions of Schlemm's canal measured 500 micrometers away from the sites of iStent inject implantation (left) and at the temporal limbus in unoperated fellow eyes (right), 12 months after surgery. Source: Author's own work.[137]

The present study was the first to examine the anatomical effect of trabecular bypass devices and the correlation between anatomical changes and surgical outcomes, and as such, it received considerable attention from specialist media. It featured in the American Academy of Ophthalmology (AAO) editors' choice,[138] in Australian magazine Insight News,[139] and in British magazine EyeNews.[140] It was also reviewed and commented by Professor Tanuj Dada in the editors' selection of International Glaucoma Review,[141] and cited on AAO's EyeWiki.[142] Besides, the conclusions of the present study served as the rationale to develop novel trabecular micro-bypass devices. Indeed, following the publication of Article 8, Glaukos Corp, the manufacturer of the iStent inject device, refined its design and announced, in 2020, the iStent inject W. This novel trabecular micro-bypass device was similar to the original iStent inject, only with a larger flange designed to optimise device positioning and prevent over-

implantation. To defend the rational behind this novel device, the company offered me honorarium in exchange for sponsored lectures, webinars and articles. As a result, the conclusions of Article 8, as well as the subsequent analyses resulting from the same study (5.3 - Additional publication 5), featured in a sponsored article in EuroTimes,[135] and a sponsored educative video summarizing my research is being produced by Glaukos Corp.

Nevertheless, despite the significant impact this study had within the industry, it was not without limitations. First and foremost, the study does not abide by the principles and recommendations I had personally set in Article 5. Indeed, the size of the cohort and the study period were restricted by limited funding, which also precluded the use of a control group or medication washout. Furthermore, at the time I wrote the original protocol, the study device was only approved for dual implantation combined with cataract surgery. This generated a number of confounding factors that impacted the generalisation of the study results, and clearly illustrated the impact of sponsors and regulators on research design. However, experience has shown me that a track record of impactful publications as a primary investigator tends to facilitate the attraction of sponsors as well as the communications with regulators, thus enhancing the potential of further research projects.

4 Conclusion

As of 2022, glaucoma is still the leading cause of irreversible blindness worldwide.[143] Yet, over the last decades, research has dramatically improved the diagnosis, quality of life, and prognosis of patients with glaucoma. Indeed, less than half-a-century ago, glaucoma was diagnosed based on direct ophthalmoscopy and Goldmann perimetry, and there were little more options to control IOP than pilocarpine and trabeculectomies.[144] In these days, the primary aim of glaucoma therapy was to maintain IOP below 21 mmHg, and limited investigation or treatment options left little room for individual considerations.

Through the years, developments in every domain of science, from imaging and physiology to engineering and sociology, have benefitted medical research and contributed to improving our understanding of glaucoma as a whole. While the pathogenesis of glaucoma remains elusive, the multifactorial nature of the disease is now indisputable, and it is now clear that the traditional conception by which elevated IOP is the primary cause of glaucoma was a little simplistic. Research has been gradually revealing the dynamic nature of IOP, and how static in-office IOP represents only a small part of the picture. Indeed, there is ample evidence that IOP varies widely in the short-, intermediate- and long-term, under the influence of many endogenous and exogenous factors, and a vast number of sources has confirmed that these variations contribute directly to the pathophysiology of glaucoma. My research has contributed to confirming the influence of lifestyle (Article 2), weekdays, and seasons (Article 3) on IOP variations, as well as the independent role of these fluctuations on glaucoma progression (Article 1). This realisation has highlighted a need for a change in paradigm, while opening a new avenue for research.

As new treatment options emerged, so did the need for evidence-based recommendations to guide treatment choices. Indeed, while filtering surgery was traditionally used in last resort when all medical therapies failed to control glaucoma, the advent of MIGS profoundly transformed the landscape of glaucoma treatment. Although MIGS have rapidly grown in popularity by bridging the gap between medical treatment and filtering surgery, there is yet no consensus on these procedures' indications. In recent years, however, there has been growing interest over patient-specific considerations, and evaluating the surgical outcomes of MIGS has become a strong focus of research. My research contributed through the assessment of some of the most promising techniques such as AbIC (Article 6), XEN 45 gel stent (Article 7) and iStent inject (Article 8), identifying factors that may influence the outcome, and suggesting recommendations for patient selection, technical refinement, or research design (Article 5). Overall, it has been a fascinating experience to be part of these fundamental transformations of the specialty, and it will be exciting to witness how further research will build on these initial findings to draw new clinical guidelines and improve glaucoma care.

Although the corpus of articles I have produced through my study of glaucoma has attracted over 450 citations and a number of accolades, these studies had some common limitations. First, as all clinical trials were single-centre studies, involved no more than two surgeons, and focused on a relatively homogenous cohort, results may not be generalisable to other populations or to technical variations. Besides, while some studies involved masking procedures, none of the studies were randomised controlled trials, which would have improved the comparability of the studied procedure with reference treatments, and reduced

the risk of bias, as highlighted in Article 5. From a statistical point of view, the inclusion of both eyes of identical patients as well as the pairwise handling of missing data may have introduced statistical biases. Finally, each study had its specific limitations that were detailed in their respective discussion sections.

Despite of these limitations, these publications had a lasting impact in their field by identifying new factors of influence in glaucoma progression and treatment, thus highlighting areas for future research. Indeed, despite significant developments in the last few years, the study of IOP variations is still at its beginnings. While the corpus of publications presented through this thesis have confirmed that IOP fluctuations played a role in the pathogenesis of glaucoma, and have illustrated both the extent of IOP variations and how they were influenced by all sorts of factors and events, a number of hypotheses still need to be confirmed in order to draw clinical recommendations from these primary reports. First, the role of exogenous IOP fluctuations in the pathogenesis of glaucoma will need to be ascertained in order to guide clinical management and patient counselling. As the role of lifestyle in glaucoma progression has been questioned for decades and large observational cohort studies are unlikely to be applicable to the study of punctual activities, the development of novel assessment modalities such as the detection of apoptosing retinal cells (DARC) may contribute to the advancement of the field.[145] Second, the effect of medical and surgical treatments in the modulation of IOP fluctuations will need to be studied more systematically. Then, like research has established the risk of glaucoma progression at different IOP levels,[21] the risk posed by IOP fluctuations patterns, amplitudes and characteristics will need to be quantified in order to enable an informed risk-benefit evaluation for their treatment. Technological advances are making IOP telemetry more accessible to clinicians and patients, and the volume of data generated combined with progress in artificial intelligence will vastly contribute to the evaluation of the risks associated with the dynamic nature of IOP.[85] Finally, clinical trials confirming the protective effect of IOP-normalising procedures in the presence endogenous or exogenous fluctuations will also be needed to validate the clinical relevance of such treatments. Confirming this hypothesis would enable glaucoma specialists to select the most appropriate treatment strategy, based on the risk profile established not only through static tonometry, but also through the evaluation of IOP variations.

Concerning glaucoma treatments, MIGS has given patients and doctors the opportunity to tailor glaucoma management to their needs. Nevertheless, there is no consensus on the indications for most MIGS procedures, and their use tends to be guided by surgeons' experience and patients' requests. In the meta-analysis presented in Article 5, I reviewed the available literature on MIGS and identified gaps in knowledge. While the trials described in this thesis evaluated the efficiency of three promising MIGS techniques, and identified specific factors influencing their outcomes, they also highlighted a number of areas of improvement for current trials. Further research will therefore need to assess new surgical techniques against commonly accepted reference treatments, using unified randomised controlled designs in order to provide a basis for comparison. Besides, biobanks and large cohort studies involving detailed reporting of clinical, demographic, and genetic data, will be needed to analyse individual factors influencing treatment outcomes. The advent of artificial intelligence and deep learning will considerably assist the analysis of these high volumes of data, and the development of truly personalised medicine.[76,146] Yet, beyond the evaluation of currently existing techniques, research should ultimately turn towards the development of novel treatments strategies in order to improve glaucoma care. This process, however, will be gradual and incremental, as interconnected laboratory and translational research identify new

areas of interest for glaucoma treatment. Indeed, while IOP control and the “10-10-10 Goal” were the ambition of glaucoma specialists through the 2010’s, a decade later it may be time to redefine our goals and rather aim for the preservation of retinal ganglion cells, visual function, and quality of life.

The journey through each of these projects and publications has contributed to my growth as an independent researcher and as a person. When I was introduced to glaucoma research, I had already carried out several service improvement audits, published an ophthalmology case report, and worked on two master thesis in architecture, but I had no first-hand experience of clinical trials. My first publications in the field involved a lot of reading, not only to gain a better understanding of the specialty, but also initially to develop a sense of the structure, the form, and the etiquette of scientific writing. Then, more reading followed, to gradually understand the main limitations associated with key trial designs, and how good planning and sound protocol design could dramatically strengthen a study. What certainly took me the longest to acquire, however, was a sense of the state of knowledge in the specialty, and an idea of how to further advance it. It has been a steep learning curve, but a fulfilling one, and beyond the scientific knowledge, clinical trial design experience, and grant application acumen, these years of research have also taught me or helped me refine essential life skills and aptitudes, such as teamwork, management, supervision, education, public speaking, or networking, to name a few. These developments have allowed me to grow into a confident academic, and to move closer to my objectives of being part of the international scientific community and advancing patient-centred care in glaucoma. Indeed, after several years coordinating the Swiss Glaucoma Research Foundation’s research projects, I have recently joined Stanford University as a visiting scholar. Thus, my next challenge will be the design and execution of some ambitious multi-centre pivotal studies to evaluate novel IOP-independent treatment strategies, driven by the hope that one day, glaucoma articles may no longer start with the traditional opening line: “Glaucoma is the leading cause of irreversible blindness”.

5 Annexes

5.1 Peer testimonials on the impact of the author's research

- ***Professor Jay Katz***

A statement from Prof. Jay Katz, Chief Medical Officer of Glaukos Corporation, Director Emeritus of the Glaucoma Service at Wills Eye Hospital, and Professor of Ophthalmology at the Thomas Jefferson University, confirmed the role and impact of my research on the recent and future development of MIGS in the treatment of glaucoma.

- ***Professor André Mermoud***

A statement from Prof. André Mermoud, Clinical Director of the Swiss Visio Network, and former Associate Professor of Ophthalmology at the Jules Gonin Eye Hospital, in Lausanne, Switzerland, confirmed the practice-changing impact my publications have had in the field of clinical glaucoma.

5.2 Statements from co-authors confirming contribution

- ***Professor Kaweh Mansouri***

A statement from Prof. Kaweh Mansouri, Lead Clinician at the Glaucoma Research Centre, in Lausanne, Switzerland, and President of the Swiss Glaucoma Research Foundation confirmed my contribution to the research institution and to the publications he has co-authored.

- ***Doctor Jean-Marc Baumgartner***

A statement from Dr Jean-Marc Baumgartner, Consultant Ophthalmologist at the Ophthalmologic Network Organization, in Geneva, Switzerland, confirmed my contribution to the publication he has co-authored.

5.3 Additional publications by the author

- ***Additional publication 1:*** *Gillmann K, Bravetti GE, Niegowski LJ, Mansouri K. Using sensors to estimate intraocular pressure: a review of intraocular pressure telemetry in clinical practice, Expert Review of Ophthalmology, 2019. 14:6, 263-276. doi: 10.1080/17469899.2019.1681264*

- ***Additional publication 2:*** *Gillmann K, Bravetti GE, Mermoud A, Rao HL, Mansouri K. XEN Gel Stent in Pseudoexfoliative Glaucoma: 2-Year Results of a Prospective Evaluation. J Glaucoma. 2019 Aug;28(8):676-684. doi: 10.1097/IJG.0000000000001295. PMID: 31162174.*

- ***Additional publication 3:*** *Gillmann K, Bravetti GE, Rao HL, Mermoud A, Mansouri K. Impact of Phacoemulsification Combined with XEN Gel Stent Implantation on Corneal Endothelial Cell Density: 2-Year Results. J Glaucoma. 2020 Mar;29(3):155-160. doi: 10.1097/IJG.0000000000001430. PMID: 32108690.*

- ***Additional publication 4:*** *Gillmann K, Bravetti GE, Rao HL, Mermoud A, Mansouri K. Bilateral XEN Stent Implantation: A Long-term Prospective Study of the Difference in Outcomes Between First-operated and Fellow Eyes. J Glaucoma. 2020 Jul;29(7):536-541. doi: 10.1097/IJG.0000000000001520. PMID: 32341321.*

- ***Additional publication 5:*** *Gillmann K, Mansouri K, Ambresin A, Bravetti GE, Mermoud A. A Prospective Analysis of iStent Inject Microstent Implantation: Surgical Outcomes, Endothelial Cell Density, and Device Position at 12 Months. J Glaucoma. 2020 Aug;29(8):639-647. doi: 10.1097/IJG.0000000000001546. PMID: 32433094.*

6 Abbreviations

AAO	American Academy of Ophthalmology
AbIC	ab interno canaloplasty
AGIS	Advanced Glaucoma Intervention Study
AH	aqueous humour
ANOVA	analysis of variance
BP	blood pressure
CIGTS	Collaborative Initial Glaucoma Treatment Study
CLS	contact lens sensor
CNTGS	Collaborative Normal Tension Glaucoma Study
DARC	detection of apoptosing retinal cells
EGS	European Glaucoma Society
EMGT	Early Manifest Glaucoma Trial
FEBO	Fellow of the European Board of Ophthalmology
GAT	Goldmann applanation tonometer
IOP	intraocular pressure
IRB	institutional review board
LC	lamina cribrosa
LiGHT	Laser in Glaucoma and Ocular Hypertension
MArch	Master in Architecture
MBA	Master in Business Administration
MBBS	Bachelor of Medicine, Bachelor of Surgery
MD	mean deviation
MIGS	Minimally invasive glaucoma surgery
MMC	mitomycin C
mmHg	millimeters of mercury
mVeq	millivolt equivalent
NICE	National Institute for Health and Care Excellence
OCT	optical coherence tomography
OHTS	ocular hypertension treatment study
OnO	Ophthalmologic Network Organisation
PMCL	pressure measuring contact lens
PR	progression report
PRISMA	Preferred Items for Systematic Reviews and Meta-Analyses
RGC	retinal ganglion cell
RNFL	retinal nerve fibre layer thickness
SLT	selective laser trabeculoplasty
UKGTS	United Kingdom Glaucoma Treatment Study

7 Table of figures

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