Comprehensive Glaucoma Management – Novel Insights

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Abstract
The satellite symposium ‘Comprehensive Glaucoma management – Novel Insights’ was convened at the 2014 European Glaucoma Society Congress and included presentations from four experts who identified several factors in current practice for the assessment and treatment of glaucoma and provided valuable solutions to potentially improve outcomes. In glaucoma, there are multiple risk factors associated with disease progression: some cannot be controlled (e.g. age and the extent of existing glaucoma damage); others such as ocular perfusion pressure can be determined and sometimes influenced. The use of 24-hour intraocular pressure (IOP) monitoring provides a much more complete assessment of the effects of glaucoma treatments than is possible with single IOP measurements and adds to the clinical evaluation. Various eye medications for use in glaucoma contain benzalkonium chloride (BAK), which is known to cause superficial inflammation. The extent of BAK penetration into deep ocular tissue and associated damage is only now being realised with the use of novel chemical and imaging techniques. These findings highlight the importance of preservative-free medications. Treatment of glaucoma is also being improved with the use of fixed-dose combinations of molecules that facilitate treatment and, in terms of IOP lowering, are non-inferior to medications used separately. These improvements in glaucoma management are therefore likely to improve understanding of disease status, improve efficacy and ultimately decrease the risk of vision loss.

Keywords
Glaucoma management, risk factors, combination treatment, preservatives, 24-hour intraocular pressure monitoring

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How to Bring Risk Factors into Clinical Management of Glaucoma

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Multiple risk factors are associated with poor outcomes in glaucoma, including intraocular pressure (IOP), vascular factors, neurodegeneration, central corneal thickness, optic disc haemorrhages, immunological diseases, age and genetic influences (e.g. family history, ethnicity, gender).1 Among these, however, only the first three can be treated. Numerous studies have explored these factors, including the Advanced Glaucoma Intervention Study (AGIS).2 This involved a predictive analysis of 738 eyes and showed that individuals who initially had an IOP over ≥17.5 mmHg had a mean 1.89 unit increase of visual field worsening after 7 years compared with those who initially had IOP <14 mmHg (p<0.001). An associative analysis comparing individuals with IOP <18 mmHg at 100 % of clinic visits during the first 6 months versus those having IOP <18 mmHg on <50 % of the visits also showed that those with higher IOP were 1.93 visual units worse than those with lower IOP (p<0.001) after 7 years. These findings were supported by the Ocular Hypertension Treatment Study (OHTS).3 This was a randomised controlled trial (RCT) in which a population of 1,636 patients aged 40–80 years with IOP 24–32 mmHg were randomised to either topical ocular hypotensive medications or observation only. After 60 months, the cumulative probability of developing primary open-angle glaucoma (POAG) was 4.4 % in the medication group and 9.5 % in the observation group (p<0.0001). A subgroup in this study (n=1,301) showed that increased corneal thickness (above 555 or 588 µm) is associated with decreased glaucoma.4 It was concluded that individuals with ocular hypertension (OH) who are at moderate or high risk of developing POAG should receive ocular hypotensive treatment.
The importance of reducing IOP to minimise glaucoma progression was further emphasised by the Early Manifest Glaucoma trial (EMGT). This was the first RCT with sufficient power to investigate the effects of IOP reduction in patients with OAG. A total of 255 patients aged 50–80 years with early glaucoma, visual field defects and a median IOP of 20 mmHg were randomised to laser trabeculoplasty plus topical betaxolol hydrochloride or no initial treatment. Treatment reduced IOP by 25 % and this was maintained during 6 years follow-up. Treatment also significantly reduced progression (45 % versus 62 %; p=0.007) and significantly delayed it. Stratifying the results by IOP (< or >21 mmHg), pseudoexfoliation, mean deviation and age (>68 years) all showed advantages for treatment.

Therefore in treating glaucoma, it is important to establish the target IOP for each patient. This target is based on several factors: the extent of glaucoma damage (early or advanced), life expectancy (long or short), the IOP when untreated (high or low) and the rate of progression (slow or fast). IOP, however, is affected by several major factors as shown by a case example of a middle-aged man with advanced POAG. Treating such patients is not always straightforward.

Case example:
Male aged 50
Glaucoma diagnosis 12 years ago, IOP 28 mmHg in both eyes
Advanced POAG in both eyes
Reason for referral: believed to have progression in right eye
Visual acuity: 1.0 without correction in both eyes
Central corneal thickness: 562/571 µm (normal)
Therapy in both eyes: Tafluprost 1x, Brimonidine 2x
IOP during office hours: 10–15 mmHg

This patient had a low diurnal IOP but had shown continual decline in visual acuity and Heidelberg retinal tomography showed clear deterioration. Blood pressure (BP) monitoring, however, revealed a 30 % drop in systolic pressure at night that could result in increased IOP. This phenomenon often occurs in patients with arterial hypertension who are over-treated with anti-hypertensive drugs at night. In this case, the nocturnal systolic pressure decrease was reduced to half its previous size following the administration of salt tablets.

The Low-pressure Glaucoma Treatment Study (LOGTS) compared the treatment of low pressure glaucoma with brimonidine with timolol in 178 patients and explored the importance of BP and perfusion pressure in glaucoma development. Brimonidine produced significantly greater reduction in visual field deterioration than timolol. The study also showed that greater age (hazard ratio [HR]: 1.41/decade older), receiving systemic betablocker (HR: 5.56), migraine (HR: 4.37), low mean perfusion pressure (HR: 1.21 mmHg) lower) were significant risk factors for glaucoma progression.1

The LOGTS also investigated the occurrence of optic disc haemorrhages and noted them in 4 % of patients in patients with high pressure glaucoma but in 39 % of patients with normal pressure glaucoma. The pathogenesis of these haemorrhages is unknown but they were markedly more frequent with timolol than brimonidine treatment. Risk factors for optic disc haemorrhages was shown to be receiving a systemic beta blocker (HR: 5.56), migraine (HR: 4.37), low mean perfusion pressure (HR: 1.13) and low systolic BP (HR: 1.04).8

Further work conducted in Korea has shown that progression of glaucoma is more rapid if there are greater fluctuations in ophthalmic perfusion pressure (OPP). Patients with low OPP fluctuations progress less rapidly (see Figure 1). OPP is often calculated using the equation:

\[ \text{OPP} = \frac{2}{3} \text{BP} - \text{IOP} \]

The value derived, however, may be incorrect for some glaucoma cases in which a more accurate value would be determined using the equation:

\[ \text{OPP} = \frac{2}{3} \text{BP} - \text{central retinal venous pulsation pressure (CRVPP)} \]

Recent work has shown that individuals with or without mild glaucoma (mean deviation in visual field [MD] > –6), the IOP and CRVPP values are similar (both 14 mmHg). However, in individuals with moderate to severe glaucoma (MD ≤ –6), IOP and CRVPP values are substantially different (11.0 mg versus 39.8 mmHg). In such cases, therefore, actual OPP may be much greater than calculated values indicate and the risk it poses may consequently not be recognised.7 The relationship between these factors therefore is that a decrease in ophthalmic BP decreases results in a decrease in OPP decreases but an increase in IOP increases in OPP result in a corresponding decreases in OPP.8

- There are many known or assumed risk factors for the development or progression of glaucoma
- Only few risk factors for glaucoma progression are treatable
- An underestimated risk factor for glaucoma progression is reduced ocular perfusion pressure
- OPP is frequently miscalculated and consequently underestimated
Medications given to treat glaucoma often cause annoying symptoms such as irritation, stinging and burning and these affect quality of life, but are usually considered to be a compromise of controlling IOP and progression of the disease. The effects of these medications, however, are not always limited to the ocular surface. Various studies have shown the effects of topical glaucoma medications on the conjunctival cells and the trabecular meshwork. Less-visible effects of these medications include subclinical inflammation, goblet cell loss and fibroblast stimulation. Topical glaucoma medications and their duration of use have also been associated with poor outcomes or failure of filtering surgery resulting from increased infiltration by inflammatory cells. These medications have also been shown to raise levels of various including cytokines such as monocyte chemo-attractant protein 1, which is associated with post-operative scarring. The inflammation caused by glaucoma medications may also increase the likelihood of bleb failure following filtration surgery. Reduction in goblet cells in microcysts in the blebs is believed to stop the flow of aqueous humour leading to bleb failure.

Benzalkonium chloride (BAK) is a commonly used preservative in glaucoma medication and this has been shown in clinical and animal model studies to stimulate cytokine secretion (e.g. fractalkine and extracellular matrix metalloproteinase inducer (EMMPRIN) expression). BAK has also been reported to destroy goblet cells in ex vivo and in vitro studies. This was supported by the Preservative Exposure and Surgical Outcomes (PESO) study, a chart review investigation conducted in Canada, which showed that in 128 patients with glaucoma, time to surgical failure in those receiving higher pre-surgical daily doses of BAK-containing medication was shorter than those with less BAK exposure (p=0.008). In addition, the proportion failing was markedly greater among those who received ≥6 drops medication/day than those receiving 1–2 drops/day (see Figure 2).

In some cases glaucoma medications appear to become less effective over time and IOP increases with less controlled inflammation. Some attribute this worsening inflammation to the use of eye drops with preservatives rather than a consequence of the disease. Refractory glaucoma has been improved using preservative-free eye drops. It has been hypothesized that progression of the disease. The effects of these medications, however, include subclinical inflammation, goblet cell loss and fibroblast stimulation, as well as increased cytokine secretion (e.g. fractalkine and extracellular matrix metalloproteinase inducer (EMMPRIN) expression). BAK has also been shown to destroy goblet cells in ex vivo and in vitro studies. This was supported by the Preservative Exposure and Surgical Outcomes (PESO) study, a chart review investigation conducted in Canada, which showed that in 128 patients with glaucoma, time to surgical failure in those receiving higher pre-surgical daily doses of BAK-containing medication was shorter than those with less BAK exposure (p=0.008). In addition, the proportion failing was markedly greater among those who received ≥6 drops medication/day than those receiving 1–2 drops/day (see Figure 2).

Exposure to BAK stimulates inflammatory cells and factors (e.g. cytokines); inflammation increases with time of exposure to BAK. Studies using mass spectrometry show accumulation of BAK in deep ocular tissues (e.g. trabecular meshwork) in animal and human samples.
Why Should We Evaluate 24-hour Efficacy?

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In managing glaucoma, it is vital to understand that it is a 24-hour disease in which IOP can vary markedly throughout the day. Taking one or two IOP values during office visits provides insufficient data to determine peak values during the day and night and can miss a great deal of IOP-related disease, possibly leading to suboptimal management. Progression in glaucoma is affected by IOP and variations in OPP as discussed earlier.

The value of 24-hour IOP monitoring was shown in a small case review study in the UK in which the peak IOP among patients with glaucoma during 24-hour monitoring was on average 4.9 mmHg higher than the peak clinic IOP value (p=0.0001). Peak IOP values occurred outside office hours in 51.7% of patients and 24-hour IOP monitoring resulted in a change of clinical management in up to 79.3% of patients. In another study conducted in the US among 32 patients with glaucoma, the mean peak 24-hour IOP was 16.8 ± 3.2 mmHg, which was significantly higher than peak office IOP of 14.7 ± 3.2 mmHg (p<0.001). In addition, the mean IOP fluctuation during 24-hour monitoring was 6.9 ± 2.9 mmHg, which was significantly greater than 3.8 ± 2.3 mmHg during office hours (p<0.001). In this study, 24-hour monitoring was influential and resulted in 36% of patients receiving an immediate treatment change.

Several studies have identified an association between lower systemic BP at night and raised IOP leading to optic nerve damage. Performing 24-hour or possibly daytime IOP curves is therefore beneficial to better understand the pathology. IOP curves taken before and after treatment are also highly valuable to gain a true efficacy profile of glaucoma treatments. An example of this approach was a study conducted in Greece that included 77 patients with POAG involving a crossover comparison of fixed combinations of dorzolamide/timolol (DTFC) or brimonidine/timolol (BTFC) after a 2-month run-in period or treatment with timolol. Both the fixed combinations significantly improved 24-hour IOP compared with timolol (p<0.001). However, the mean 24-hour IOP level was lower for DTFC compared with BTFC (difference: –0.7 mmHg; p=0.001).

In another prospective crossover study conducted in Greece, the preservative-free (PF) prostaglandin tafluprost 0.0015% (Taflotan or Salfutan) was compared with branded preservative-containing prostaglandin latanoprost 0.005% (KalaTan) as monotherapy, dosed in the evening, in patients with either POAG or OH. Patients were randomised to receive one of the treatments for 3 months before switching to the other therapy for a further 3 months. Patients were required to have an untreated baseline IOP of 24–33 mmHg and were monitored in habitual positions, with Goldmann tonometry at 10:00, 14:00, 18:00 and 22:00 daily, and Perkins supine tonometry at 02:00 and 06:00 daily.

Of 40 enrolled patients, 38 completed the study. 52.6% were female and the mean age was 66.7 years (standard deviation: 9.1 years). The mean 24-hour IOP (24.9 mmHg) was significantly reduced with both prostaglandins compared with baseline (p=0.001) (see Figure 3). Tafluprost treatment produced similar mean 24-hour efficacy compared with latanoprost (17.8 versus 17.7 mmHg; p=0.041). Latanoprost treatment resulted in significantly better 24-hour trough IOP values (15.9 versus 16.3 mmHg; p=0.041) but tafluprost produced significantly lower 24-hour IOP fluctuation (3.2 versus 3.8 mmHg; p=0.008). Differences in IOP values for both prostaglandins during the 24-hour period were all non-significant (see Table 1). Adverse events were seen in 22% of patients treated with latanoprost and 14% of patients treated with preservative-free tafluprost.

This study was important in that it was the first evaluation of 24-hour efficacy of PF tafluprost compared with latanoprost in newly diagnosed patients with either POAG or OH and revealed identical mean lowering over 24 hours with these treatments (mean difference was only 0.1 mmHg). It is interesting to note that the efficacy profile of PF tafluprost would not have been detected without a complete 24-hour study. This trial therefore highlights the value of a complete 24-hour efficacy assessment in determining the true efficacy of a novel anti-glaucoma medication.

The prostaglandins in this crossover study provided meaningful 24-hour IOP reduction of approximately 29%. This finding was consistent with an earlier meta-analysis of three prostaglandins in for POAG/OH treatment.
(bitamoprost, travoprost and latanoprost) in which IOP reduction was in the range 24–29 %). The findings were also in line with a more recent comparison of five RCT’s showing that in glaucoma, tafluprost decreased trough IOP values by 25.6 % to 29.2 %, decreased diurnal IOP by 27.7 % to 35.1 % and decreased peak IOP values by 28.4 % to 35.9 %. The described crossover study results were supported by results of a small study comparing tafluprost and latanoprost in healthy subjects that was conducted in Japan. The study recorded a mean 24-hour IOP difference of 0.1 mmHg between the two prostaglandins and showed that latanoprost preferentially lowered IOP during the day and tafluprost preferentially lowered it at night. Tafluprost was associated with a greater reduction in IOP at 24 hours after administration. This was in agreement with various studies showing greater 24-hour trough IOP reduction with latanoprost, but significantly lower 24-hour IOP fluctuation is seen with PF medications have become popular in glaucoma due to the reduced potential for ocular toxicity but little is known about their 24-hour efficacy. As initial therapy, PF-tafluprost provides superior tolerability, and uniform 24-hour IOP control. The true level of IOP is often underestimated with single IOP measurements. Studies show that a diurnal or 24-hour curve can provide greater insight into the success of control measures and their ability to achieve a target IOP.

The current Terminology and Guidelines for Glaucoma state that “the goal of treatment is to maintain patients’ visual function and related quality of life at a sustainable cost by lowering IOP.” The target IOP selected depends on several main factors: the extent of glaucoma damage (glaucoma status), life expectancy, level of IOP when untreated and the rate of disease progression. It is vital that these parameters are known in order to decide the most appropriate treatment. Various landmark studies including the Collaborative Normal Tension Glaucoma study (CNTGS), the Early Manifest Glaucoma Trial (EMGT) and AGIS have shown that the higher the mean IOP over 8 years of follow-up, the greater the visual deterioration. A mean 12.3 mmHg showed no visual deterioration whereas a mean of 20.2 mmHg resulted in a 3-point worsening in visual defect score over 8 years. It is therefore critical that IOP is adequately controlled long term.

Using a single medication, it is unlikely that IOP could be reduced from a baseline level of 25–26 mmHg to 12 mmHg. A comparison of bitamoprost, latanoprost and travoprost in 410 patients with glaucoma or OHT and treated for 12 weeks showed IOP reductions from 25–26 mmHg to 16–17 mmHg, which is above the ideal target level. It is often necessary therefore to use two or more medications to increase the effect. This was shown in the OHTS in which, after 5 years, 40 % of the 1,636 patients with POAG were receiving ≥2 medications and 9 % were receiving ≥3 medications.

When choosing adjunctive therapy, the EGS guidelines state that one agent should be added to initial therapy, which should be from a different class. The number of drops and dosing frequency should be minimised to facilitate adherence to treatment and, if possible, a fixed-dose combination (FDC) should be used. This factor in glaucoma treatment was highlighted by a study of 100 patients in the US in which, among those receiving one medication, 49 % were compliant. However, among those receiving ≥2 medications, only 32 % were compliant. An additional problem with multiple eye drops is that each one can wash out the previous one if it is given too soon. A classic study from the 1970s showed that for eye drops given after an interval of 30 seconds, only 55 % of the previous eye drop dose was retained, for a 2-minute interval retention rose to 67 % and for a 5-minute interval, retention was 100 %. The benefits of FDCs have been shown in various randomised clinical trials. Among these, a 6-month, randomised, active-controlled, parallel group, multicentre phase III study compared a PF-FDC with a non-FDC (NFDC) of tafluprost 0.0015 % and timolol 0.5 % given concomitantly in patients with OAG or OH. This combination is due to be introduced soon. Patients treated for 6 months with either FDC and NFDC of tafluprost 0.0015 % and timolol 0.5 % showed significant reductions in IOP from baseline, but there was little difference between treatments. Diurnal IOP profiles were almost identical for the two treatments and conjunctival hyperaemia mean change of severity score versus baseline were also similar. The FDC treatment was non-inferior to NFDC and there was little difference in adverse event incidence.
Further evidence supporting the use of a FDC of PF-tafluprost and timolol was provided by a 6-month randomised multicenter study that compared the efficacy and safety of PF tafluprost 0.0015 %/timolol 0.5 % FDC with its individual components.1•4 Patients with glaucoma (n=711) were divided into those with previous timolol use (n=233) and those with previous prostaglandin use (n=488). The previous timolol group was then randomised to receive either FDC PF tafluprost 0.0015 %/timolol 0.5 % once daily (OD) (n=95) or PF timolol 0.5 % OD (n=94) and the previous prostaglandin group was randomised to either FDC PF tafluprost 0.0015 %/timolol 0.5 % OD (n=188) or tafluprost alone (n=187). The results shown in Figure 4 show a greater reduction in IOP from baseline at four daily timepoints for the FDC compared with timolol alone in both those who had previously received timolol and those who previously received prostaglandin treatment.

Among patients who had previously received timolol, there were slightly greater hyperaemia severity scores in the FDC-treated patients compared with timolol-alone. In those who previously received prostaglandins, however, lower hyperaemia severity scores were reported among those receiving FDC compared with timolol-alone. A combined analysis of the non-inferiority and superiority data from this and the previous study (FDC versus concomitant NFDC and FDC versus separate timolol or tafluprost alone)1•4,15 shows a powerful IOP-lowering efficacy of the tafluprost/timolol FDC (see Figure 5). The analysis shows that decreases in diurnal IOP are correlated with greater baseline IOP values; a baseline IOP of <22 mmHg resulted in a diurnal IOP decrease of 31% compared with a baseline IOP of >31 mmHg that resulted in a decrease of 40%.

Conclusion
The above presentations have provided novel insights in the current management of glaucoma and identified shortcomings in disease status recognition and treatment, but also proposed valuable solutions. It is increasingly agreed that each patient with glaucoma or OH should have their risk factors for disease progression fully identified. In particular, it is important that OPP is correctly determined and measures such as anti-hypertensive medications are used to control it and limit further damage. In many regions, glaucoma medications containing BAK as a preservative continue to be used. While these are known to cause surface inflammation, the extent of penetration into deeper ocular tissues during long-term exposure is only now becoming apparent. BAK reaches the lens capsule and trabecular meshwork and even nervous tissues. It is important that this aspect of BAK is recognised and PF medications are used to avoid further inflammation and potential vision damage.

For many years IOP was measured only at single timepoints, mostly during office visits. This approach misses large potential variations during the day or night and can substantially misguide the management of the disease. It is appropriate to obtain 24-hour IOP profiles in patients showing worsening of the disease. To achieve adequate IOP lowering it is often necessary to use more than one medication, this increases the burden of treatment and decreases compliance. The use of FDCs, can help to reduce this problem. FDCs have been shown to be non-inferior to medications used separately in terms of efficacy and have good safety and tolerability. Such combinations are simple to use and may become treatments of choice in glaucoma.

Improved recognition and assessment of glaucoma risk factors, the use of 24-hour IOP monitoring, the use of PF medications and the selection of FDCs is likely to substantially improve the understanding of this disease and enable better treatment. Taken together, each of these four factors has the potential to substantially improve patient management and clinical outcomes. Glaucoma remains a serious threat to vision worldwide and it is critical that these improved practices, as set out in current guidelines,1•4 are adhered to as widely as possible.

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