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Chapter

Risk Assessment of Ocular Hypertension and the Use of Medication

Claire Chow and Poemen Pui-man Chan

Abstract

Ocular hypertension (OHT) is the only known modifiable risk factor of glaucoma development. Intraocular pressure (IOP)-lowering therapy reduces the risk of glaucoma development. The 5-year risk of glaucoma conversion is <10% for untreated OHT patients. Cost-effectiveness analyses suggested that it is not cost-effective to treat all patients with OHT. Treatment should be targeted towards the higher-risk group—namely, patients with older age, a higher level of IOP, a thinner central corneal thickness (CCT), a larger vertical cup-to-disc ratio (VCDR) and a smaller pattern standard deviation (PSD) value on visual field (VF) test. These risk factors were established by the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS). However, there is significant variability in the measurement of the currently known risk factors, especially if the assessment is taken from a longitudinal perspective. This can lead to overtreatment or under-treatment: the former exposing the patient to unnecessary side effects of IOP-lowering eye drops and the latter putting the patient at risk of developing glaucoma. The advancement of new VF algorithm and ocular imaging can lead to the identification of new approaches to risk stratification and, thus, more specific treatment for OHT patients.

Keywords: ocular hypertension (OHT), glaucoma 5-year risk calculator, vertical cup-to-disc ratio (VCDR), intraocular pressure (IOP)

1. Introduction

Glaucoma is a leading cause of irreversible blindness worldwide [1]. Subjects with ocular hypertension (OHT) are known to have a higher risk of glaucoma development. OHT is defined as a mean intraocular pressure (IOP) ≥24 mmHg from two separate consecutive measurements without structural and functional evidence of glaucoma [2]. Patients with OHT are usually treated with IOP-lowering therapy based on the effectiveness of reducing the risk of glaucoma development according to the result of the Ocular Hypertension Treatment Study (OHTS) [3], which demonstrated a cumulative probability of 9.5% of developing primary open-angle glaucoma (POAG) in 5 years in the untreated OHT patients, compared with 4.4% in the treated group (patients who received IOP-lowering therapy). Hence, the incidence of POAG could be reduced by about 50% with adequate IOP reduction. In clinical practice, it is not uncommon that we adopt a treatment approach of liberally prescribing IOP-lowering medication based on the study results.

On the other hand, the result of the OHTS also reflects that only <10% of the untreated OHT patients developed glaucoma in 5 years, compared to the 4.4% of the treated group. Hence, the number needed to treat to prevent one glaucoma development is 20. Indeed, it has been shown that treating all patients with OHT is not cost-effective [4, 5]. The estimated incremental cost of treating all OHT patients to prevent one subject from developing glaucoma was US$89,072 [4]. This is considered not cost-effective according to the standard of The National Institute for Health and Care Excellence (NICE), which classified a treatment as cost-effective at the level of risk when the incremental cost-effectiveness ratio (ICER) is equal to or less than US$50,000 [6]. Furthermore, long-term treatment with IOP-lowering medications can impose significant inconvenience and undesirable side effects to patients, such as ocular surface disease. For instance, a study that involved 537 OHT and POAG patients showed that side effects from medication can independently contribute to health-related quality of life scores, which could be as worse as 0.11 [7]. This is equivalent to the utility loss of patients with early to moderate stage of glaucoma [8, 9]. Therefore, selective and targeted use of medication is not merely a health economic issue; unnecessarily treating low-risk OHT patients would expose them to undesirable medication side effects without beneficial gain.

2. Risk stratification and cost-effectiveness of treating ocular hypertension

A more cost-effective approach is to treat OHT subjects who have higher risk of developing POAG—namely, an older age, a higher level of IOP, a thinner central corneal thickness (CCT), a larger vertical cup-to-disc ratio (VCDR) and a smaller pattern standard deviation (PSD) value on visual field (VF) test. These are risk factors of POAG development according to the joint data of the OHTS [2] and the European Glaucoma Prevention Study (EGPS) [10]. These are the two major multicentre, randomised control trials (RCTs) that involved patients with OHT. Stewart et al. suggested that it is cost-effective to treat patients with older age (≥76 years old), higher intraocular pressure (≥29 mmHg), thinner central corneal thickness (≤533 μm) and wider vertical cup-to-disc ratio (≥0.6) [4]. Kymes et al. suggested that treating OHT patients with IOP ≥24 mmHg and a ≥ 2% annual risk of glaucoma development is likely to be cost-effective [5]. Weinreb et al. suggested a risk stratification strategy: observation for patients with lower than average risk of POAG conversion (5-year risk of <5%), collaborative treatment decision between doctor and well-informed patient for those with moderate risk (5-year risk of 5–15%) and treatment for all subjects with higher than average risk (5-year risk of >15%) [11]. Based on this risk stratification strategy, it was demonstrated that nearly half (43.9%) of low-risk OHT eyes could safely have their medications reduced over 1 year, realising substantial savings [12]. In this study, only 1 out of 107 eyes (0.93%) developed a repeatable VF defect in the first year [12].

The 5-year risk of POAG development can be calculated using the available risk calculator, which was developed based on a predictive model that utilised the joint data of OHTS and EGPS [13]. The calculation is based on the risk factors as mentioned—age, IOP, CCT, VCDR and PSD value of VF. It has the advantage of integrating multiple risk factors into one quantitative, estimated percentage risk of glaucoma development in OHT subjects. This can facilitate treatment decision because high-risk subjects can be identified based on simultaneous and quantitative consideration of all these available risk factors; thus, allows a more straightforward

and cost-effective approach of treatment; and reduces unnecessary patient exposure to medication side effects.

3. Variability of risk factor measurement and the effects on risk assessment

It is important to note that, similar to most multivariate prediction models derived from prospective studies [14], we are making several assumptions when we apply the 5-year risk calculator to guide treatment decision: [1] we assume that the baseline variables that were measured are the most predictive of the risk of glaucoma development, [2] the model also assumes that the risk of glaucoma progression is linear, and [3] patients who are being assessed have similar clinical characteristics as the participants in the OHTS and EGPS.

However, the variability of baseline risk factor measurements is a known phenomenon. IOP is well known to vary from visit to visit [15], which can be due to regression to the mean phenomenon, diurnal variation as well as order of IOP measurement [15]. This variability is also observed in the performance of VF, hence the PSD value [16]. Results of VF examination can be affected by patients' subjectivity and the substantial test-retest variability. The PSD value is a weighted standard deviation of the differences between the measured and normal reference visual field at each test location. A higher PSD value merely suggests a more irregular 'hill of vision', which can contribute to variability in patients' responses and/or areas of focal loss. Given that, by definition, OHT subjects do not have glaucomatous VF defect, the PSD value tends to be low. Therefore, a slight variability in patients' responses can contribute to a significant change in its value. Care must be taken when interpreting PSD value as a stand-alone figure.

Therefore, the apparently more comprehensive risk stratification strategy that is based on the 5-year risk calculator can face several fundamental challenges. As discussed, the variability of IOP measurement and PSD value, even during baseline assessment, may add a considerable source of error to the risk calculation. Furthermore, due to the within-subject changes in risk factors' values during follow-up, the correlation between baseline and updated values may diminish with time [17]. One study has demonstrated that risk calculation is variable over time and that longitudinal changes in baseline variables correspond with changes in the risk estimation of glaucoma development [18]. In the study, the 5-year risk of POAG development was calculated by incorporating different measurements that assume the best-case scenario (baseline age, lowest PSD, highest CCT and lowest IOP) and the worst-case scenario (final age, highest PSD, lowest CCT and highest IOP). For the VCDR, a value of ±0.2 was applied to model interobserver and intraobserver variability (i.e. -0.2 in addition to the best-case scenario and + 0.2 in addition to the worst-case scenario). It was found that, within the same individual, the mean risk of POAG conversion could increase by almost 10-fold when comparing the worst- and best-case scenarios (5.0% vs. 45.7%, $P < 0.01$). Hence, risk stratification is dynamic, and risk estimations should be recalculated during follow-up visits as variables can fluctuate significantly within the same individual over time.

It is important to note that the VCDR data that derived the risk calculator was based on VCDR measurements on the optic disc stereophotography of the OHTS and EGPS cohorts. In the RCTs, the measurement and evaluation of the optic nerve head (ONH) were performed by highly trained, independent graders at designated optic disc centres that followed a strict protocol in a non-clinical setting [19]. In clinical practice, the assessment of ONH and the measurement of VCDR by individual ophthalmologists

are susceptible to intraobserver and interobserver variability [20]. The precision and quality of the ONH evaluation is unlikely to match those in the RCTs.

Nowadays, imaging technologies such as confocal scanning laser ophthalmoscopy by Heidelberg retinal tomography (HRT) and optical coherence tomography (OCT) provide an objective and reproducible measurement of optic disc parameters. However, different techniques of evaluating ONH (hence the VCDR measurement) may not agree with each other. For instance, there is a poor agreement in the optic disc measurements obtained from HRT and OCT [21]. A study that compared VCDR measurement obtained with OCT, HRT and stereophotography in untreated OHT patients showed that there were poor agreement and lack of interchangeability between different techniques [22]. This is due to the differences between

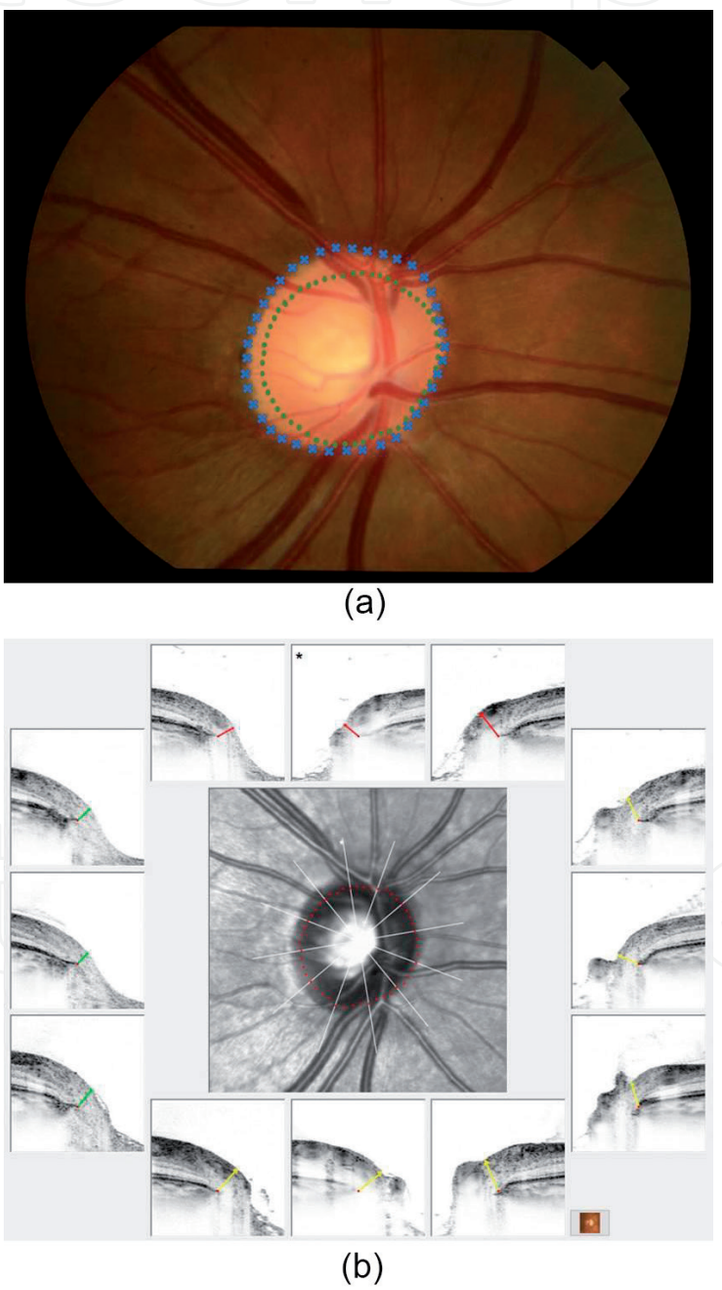

Figure 1.
Optic disc of a normal right eye (a) and corresponding spectral-domain optical coherence tomography (OCT, (b)) delineating the anatomical measurements of disc margin. The green dots on the fundus photo represent the Bruch's membrane opening (BMO) identified by spectral-domain optical coherence tomography (OCT). The blue crosses represent the disc margin that was identified by an examiner with stereophotography. Hence, the green dots and blue crosses represent the potential disc margins that could be identified by different examiners (adapted from Chauhan BC and Burgoyne CF 2013 [25]).

the techniques in defining optic disc margin and optic disc cup. The assessment of ONH in HRT and stereophotography relies on the examiners to define the disc margin, which can be variable. Spectral-domain OCT demonstrated that the 'perceived disc margin' of HRT and stereophotography rarely correlate with the Bruch's membrane opening (BMO) (**Figure 1**) [23, 24], which is considered to be the true outer border of the neural tissue because axons cannot pass through an intact Bruch's membrane to exit the eye [25]. The BMO is also unaltered under larger change of IOP [26]. Hence, it is a more reliable landmark, especially for eyes with OHT. Spectral-domain OCT is arguably more accurate in defining the ONH because it defines the BMO at every clock hour. It can also reliably identify the cup margin by measuring the minimum distance between the BMO and the internal limiting membrane in all meridians; the built-in software can then define the maximal vertical diameter to be the vertical cup diameter. In comparison, the definition of vertical cup diameter by stereoscopic photography and HRT are likely to be less accurate. Both are based on subjective judgement of examiners in defining the cup and disc margin. In some cases of small cups that do not pass through the midline of the optic disc, HRT has difficulties in calculating the VCDR because it obtains the vertical cup diameter along the vertical axis at the midline of the disc. Hence, the value of VCDR becomes '0' if the cup does not pass through the vertical midline.

The study that compared VCDR measured by OCT, HRT and stereophotography of the ONH in patients with untreated OHT also investigated how the degree of disagreement extended to their corresponding 5-year risk estimation when other risk factors were kept contant [22]. In the study, ONH images of 140 untreated OHT eyes (of 75 patients) were taken by fundus camera (stereoscopic images), OCT and HRT. ONH stereophotographs were evaluated with a stereo-viewer by two glaucoma specialists, and the VCDR was measured with the ImageJ software. VCDR measurements obtained with stereophotography, OCT and HRT were used to calculate the estimated 5-year risk. The study showed that there was disagreement in VCDR measurements between the three methods. This disagreement also extended to their corresponding 5-year risk estimation of POAG development [22]. When the comparison was made on the Bland–Altman plots, the range of discrepancies tended to widen with increasing mean risk, especially beyond the estimated

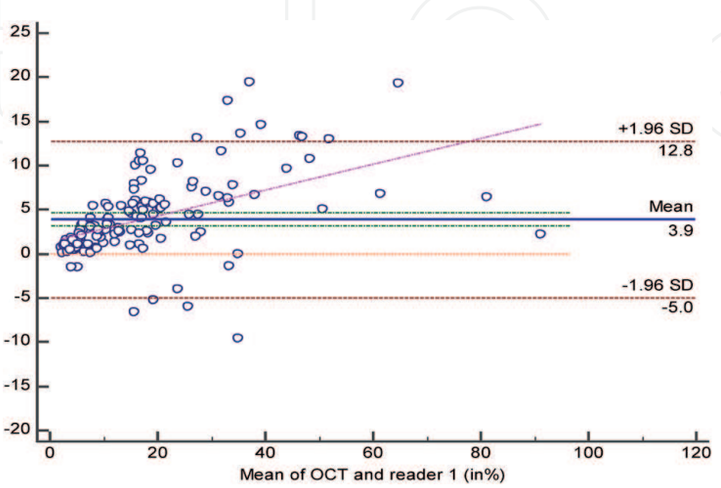

Figure 2.
Bland-Altman plot: comparison of 5-year risk estimations of POAG conversion that were calculated by vertical cup-to-disc ratio measured by different vertical cup-to-disc ratio measured by spectral-domain optical coherence tomography (OCT) and stereophotography performed by a glaucoma specialist. Notice that the range of discrepancies widen with increasing mean risk, especially beyond the estimated risk of >15%. OCT, optical coherence tomography; reader 1, stereophotography evaluation (adopted from Chan PP et al., 2019 [22]).

risk of >15% (**Figure 2**). We should be careful when using the 5-year risk of >15% as our treatment threshold when using VCDR values that are obtained from different measurement techniques. This can dramatically alter the management approach for any OHT subjects, especially if they have a relatively high baseline estimated risk and/or larger VCDR. In the cohort of untreated OHT eyes from this study, up to 72 eyes (51.2%) would require treatment if OCT was used for assessing the VCDR, according to the ≥15% 5-year risk cut-off. On the other hand, only 54 eyes (38.6%) would require treatment if the VCDR measurements were obtained from stereophotography by one of the glaucoma specialists. Therefore, one must be cautious when applying the risk estimation obtained from the other means of measuring VCDR.

4. Detection of retinal nerve fibre layer defect and early diagnosis of glaucoma

The diagnosis of glaucoma requires a confirmed glaucomatous VF defect that correlates with structural change. A glaucomatous visual field loss is defined as a cluster of ≥3 non-edged points in the PSD plot in a single hemifield with p value <5%, one of which must have a p value <1%; glaucoma hemifield test outside normal limits; and PSD with p value <5%. Any one of these criteria, if repeatable, was considered as sufficient evidence of a glaucomatous VF defect [27]. This has been considered as the gold standard of diagnosing glaucoma. OCT has gained popularity in the past decades and is now the standard for assessing structural damage of retinal nerve fibre layer (RNFL) and ONH for the detection of structural glaucomatous change. Indeed, RNFL and ONH measured by OCT were shown to be useful in differentiating normal eyes from even mild glaucoma [28]. Evidence suggests that RNFL thinning measured by OCT can detect glaucomatous damage several years before detectable functional deficits by VF testing [28–30]. The 10th World Glaucoma Association consensus meeting stated that 'detecting progressive glaucomatous RNFL thinning and neuroretinal rim narrowing is the best currently available gold standard for glaucoma diagnosis [31]'. This emphasised the importance of detecting RNFL abnormalities in terms of the diagnosis of glaucoma. Since OCT is becoming an invaluable tool for detecting early changes of ONH and RNFL thinning, especially because of its repeatability and objectiveness, it is logical to suggest that a risk scoring system for OHT patients should include OCT measurements.

On the contrary, the measurement of VCDR by stereoscopic photography or during clinical examination remains the only parameter in the risk calculator that reflects the structural status of the complex architecture of the ONH. During the slow and progressive process of glaucoma development, enlargement of VCDR could happen much later than the occurrence of RNFL thinning and other subtle structural glaucomatous damage. It is important to note that the powerful and carefully designed OHTS and EGPS were performed in the era when OCT was not widely used as an investigative tool. The two studies ruled out glaucoma patients from OHT mainly based on VF criteria and the absence of detectable structural damage on stereoscopic photography. Therefore, it might not be cavalier to suggest that a portion of these subjects might already have 'asymptomatic disease' (or preperimetric glaucoma) (**Figure 3**), and this damage was undetectable on stereoscopic photography, which was also suggested by Weinreb et al. [11]. The ever-evolving OCT technology and the concepts of ONH assessment can provide valuable data and new parameters for further refinement of the existing risk calculator, for instance, integrating other factors of OHN and RNFL based on OCT measurement [22]. The glaucoma risk model needs refinement that involves the advancing OCT technologies and concepts in measuring VCDR. Reliable risk estimation is

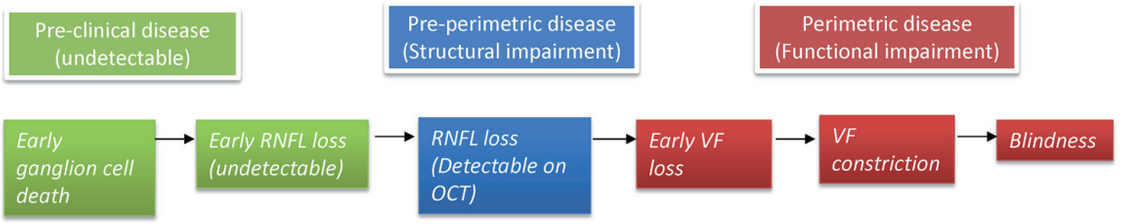

Figure 3.
Spectrum of disease in glaucoma. RNFL, retinal nerve fibre layer. OCT, optical coherence tomography. VF, visual field (adapted from Weinreb et al., 2004 [11]).

important as it may guide treatment decision, which in turn has consequences on both health economics and patients' quality of life.

5. The new trends of early detection of glaucoma and disease progression

5.1 Detecting of RNFL thinning and disease progression

Evidence shows that RNFL abnormalities can often be evident without detectable VF damage [32–35]. Therefore, measuring the change of RNFL is likely to be useful in detecting early disease progression. Spectral-domain OCT is now the invaluable investigation tool for glaucoma patients because it can measure RNFL thickness reliably [36] with high sensitivity and specificity to detect glaucoma [37, 38] and its progression [39]. Commercially available software event-based algorithm, such as the Guided Progression Analysis (GPA, Carl Zeiss Meditec), can detect progressive RNFL thinning using RNFL thickness maps. A study has demonstrated that GPA can detect and visualise different patterns of progressive RNFL thinning [39]. Trend-Based Progression Analysis (TPA) is another algorithm for detecting progressive RNFL thinning by measuring the rate of change in RNFL thickness for each superpixel of the RNFL thickness map (50 x 50 superpixels). A study that involved 139 POAG patients (240 eyes) followed up for ≥5 years showed that progressive RNFL thinning determined by GPA and TPA was predictive of detectable functional decline in glaucoma. The study showed that TPA outperformed GPA in detecting more eyes with progressive RNFL thinning at a similar level of specificity (84.2% vs. 81.7% for TPA and GPA, respectively) [40]. Furthermore, TPA also provides visualisation of the distribution of the rate of RNFL thinning. It was suggested that the detection of progressive RNFL loss can serve as a biomarker to reflect disease deterioration behaviour and hence guide glaucoma management [40]. However, TPA is not without its limitations. A minimum of four follow-up visits is required for the construction of the TPA, and performance can be undermined with fewer visits. In situations where there are abrupt RNFL changes or in eyes with large test-retest variability, the event-based analysis may be more useful [41]. The authors concluded that TPA enhances but may not replace GPA for topographic analysis of RNFL thinning.

5.2 The dynamic target IOP, disease progression and quality of life: The LiGHT trial

Clinical trials usually define a treatment IOP-lowering target. For instance, the OHT study aimed for an IOP lowering by 20% from baseline for patients in the treatment arm [3], whereas the Collaborative Normal Tension Glaucoma (CNTG) study targeted an IOP lowering by 30% from baseline [42]. The Laser in Glaucoma

and Ocular Hypertension (LiGHT) trial is a multicentre RCT that compared eye drops versus selective laser trabeculoplasty as first-line treatment for POAG or OHT [43]. The study is unique with its well-constructed algorithm for detecting disease progression and guiding treatment escalation [44]. It has a novel approach to defining target IOP. Firstly, the target IOP is specific for each patient at baseline, based on disease severity and lifetime risk of loss of vision at recruitment (e.g. different target pressure and percentage IOP reduction according to the disease stratification suggested by Mills et al. [45]). Secondly, the IOP was adjustable based on IOP control and disease progression [44]. The disease progression (either glaucoma deterioration or conversion of OHT to POAG) was determined by a decision support software based on objective visual field and optic disc imaging criteria. Disease progression was defined as 'strong evidence', with the Humphrey GPA software showing 'likely progression' and/or HRT rim area > 1% per year (at $P < 0.001$), and 'less strong evidence' with GPA showing 'possible progression' and/or HRT rim area > 1% per year (at $P < 0.01$). 'Likely visual field progression' is the presence of three or more points on the GPA at <0.05 probability for change on three consecutive occasions, while 'possible visual field progression' is the same criterion but on only two consecutive occasions [44]. Optic disc progression was defined as the rate of neuroretinal rim loss exceeding 1% of baseline rim area/year on a minimum of five repeat HRT images, where this is equivalent to approximately twice the value of normal age-related rim area loss [22]. Following treatment escalation, there is a resetting of both the target IOP and visual field and optic disc baselines against which future assessments will be compared with.

Although the LiGHT trial is probably more complex in its target IOP setting algorithm compared with other glaucoma trials which defined treatment success based on the proportion of patients achieving a particular target percentage reduction of IOP, it resembled closer to our clinical practice. For instance, further IOP lowering beyond the 'target IOP' is probably required for patients with progressive disease. In some cases, patients might request to reduce medication use even when the target IOP is not achieved (e.g. OHT patients with IOP at 24 mmHg who do not want treatment and show no signs of POAG conversion). Furthermore, the LiGHT trial is also unique in that it included the evaluation of quality of life as an outcome measure. These are all novel features that might become important components for future glaucoma study design.

6. Conclusion

It is more cost-effective to selectively treat OHT subjects who have a higher risk of POAG conversion. However, risk assessment can be difficult due to the variabilities in the measurement of the baseline variables of the glaucoma risk calculator. In the era of advancing OCT technology and knowledge of glaucoma, there may be a need to refine our existing risk assessment methodology.

Conflict of interest

All authors have no financial/proprietary interest in the subject matters of the manuscript.

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