Effect of prostaglandin analogues on central corneal thickness in patients with glaucoma: A systematic review and meta-analysis with trial sequential analysis

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The objective of this meta-analysis was to evaluate the effect of prostaglandin analogues (PGA) on central corneal thickness (CCT) in patients with glaucoma. Key electronic databases were searched for randomized controlled trials (RCTs) involving the CCT effects of prostaglandin use for glaucoma. Primary outcome measures were the mean difference in the CCT measurement from baseline to the last available assessment. Intraocular pressure and other corneal changes were recorded as secondary. Efficacy estimates were measured by their weighted mean difference (WMD) with 95% confidence intervals (CIs) by using the random-effects model for primary and secondary outcomes. Trial sequential analysis was used to determine if the current evidence was sufficient and conclusive. Eight RCTs met our inclusion criteria. A total of 879 patients were included. The overall effect showed that PGA's had a significant CCT lowering effect (WMD = −7.04, 95% CI: −10.07 to −4.00, P < 0.00001). We pooled results of 5 RCT's on Traboprost (WMD = −10.44, 95% CI: −16.80 to −4.08, P = 0.001), seven trials on Latanoprost (WMD = −4.73, 95% CI: −9.70 to 0.25, P = 0.06), and three trials on Bimatoprost (WMD = −11.88, 95% CI: −21.03 to −2.73, P = 0.01). The WMD across groups in > 6 months of PGA use was −11.37 (95% CI: −17.17 to −5.58, P = 0.0001), and in < 6 months of PGAs group was −8.35 (95% CI: −12.01 to −4.69, P < 0.00001), suggesting a longitudinal effect of PGAs on CCT.

In conclusion, Bimatoprost and Traboprost caused a statistically significant reduction in the thickness of the central cornea. Though only a few studies were included, the narrow confidence intervals and adequate sample size suggest that these findings are valid.

Key words: Central corneal thickness, glaucoma, open angle, Prostaglandins, Synthetic

Glucoma, a form of slowly progressive optic neuropathy, has emerged as one of the leading causes of irreversible blindness worldwide.[1,2] In the management of glaucoma, intraocular pressure (IOP) remains the only modifiable risk factor, and lowering IOP has been the current goal of any therapy.[3-5]

Prostaglandin analogues (PGA) and prostamides have emerged as the first line in the management of glaucoma in the past decade.[6,7] Latanoprost (0.005%), travoprost (0.004%) and tafufropost (0.0015%) are the PGAs used. Bimatoprost (0.03 and 0.01%), is the prostamide and unoprostone (0.15%) is the eicosanoid that have been used as ocular hypotensives. PGAs activate matrix metalloproteinase (MMP) in the ciliary bodies, cause the breakdown of extracellular matrix, and reduce resistance to uveoscleral outflow.[8-10] Induction of MMP occurs in trabecular meshwork and cornea. This has been hypothesized to be the causal factor for reduction in central corneal thickness (CCT) following the use of topical prostaglandins.[11-13]

Multiple authors have reported a reduction in CCT in patients under treatment with topical PGAs.[1,3,14,15] However, the results of their studies have not been consistent. Some authors[8,12,16] reported that a decrease in CCT in patients using either PGAs was not significantly different. No significant difference in CCT was found in patients treated with PGA in an Italian multicenter study.[17] Arcieri et al.[13] reported that only bimatoprost induced a statistically significant reduction in CCT, while according to Sawada et al.[18] and Schloter et al.[19] travoprost caused maximal reduction in CCT. Bafa et al.[20] in their study concluded that latanoprost and bimatoprost increased CCT. This fact has been supported by many studies that suggested that PGAs, especially latanoprost, induce collagen gel contraction in the corneal stroma and rounding of corneal cells, which increases the CCT. However, Muruyama et al.[19] and Liu et al.[20] concluded that latanoprost reduced CCT. Panos et al.[21] noticed a reduction in CCT with tafufropost after a year-long therapy. Wiswanathan et al.[22] and Helmy H et al.[23] concluded after 3 years of study that PGAs in monotherapy or in combination caused a significant corneal thinning suggesting a long-term effect of these medications. The effects of PGAs on CCT are still uncertain.

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To the best of our knowledge, no meta-analysis has been conducted to assess the effects of PGA on CCT. We aimed to undertake this systematic review and meta-analysis to summarize the existing evidence on the effects of PGAs on CCT and to investigate whether long-term topical treatment with prostaglandin analogues can significantly affect the CCT in patients with a diagnosis of glaucoma or ocular hypertension (OHT) taking these medications as the first-line therapy.

Methods

Study registration and reporting
The presented study has been registered at PROSPERO before data analysis (CRD42021241216). This meta-analysis followed the current Cochrane collaboration guidelines for performing a meta-analysis. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Ethics approval is not applicable. A comprehensive literature search was performed to identify the RCTs investigating the effects of prostaglandins on CCT.

Search strategy
We established a search strategy with title, abstract, medical subject headings [MeSH], and clinical outcomes. Text words and medical subject headings were combined freely. We searched independently the following databases—PubMed, Ovid Medline, Google Scholar, and Cochrane Central Register of Controlled Trials—to identify potentially eligible studies. We used the following MeSH (medical subject headings) terms and keywords: Glaucoma, open angle, ocular hypertension, latanoprost, bimatoprost, travoprost, tafluprost, prostaglandin analogs, central corneal thickness, and randomized controlled trials (RCTs). The commercial names Travatan, Lumigan, and Xalatan were also searched. We also contacted the authors of trials for study clarifications, where required. Searches were not limited by date, language, sex, or age. The bibliography of retrieved manuscripts and systematic reviews were searched to identify additional trials pertaining to data encompassing our primary outcome of interest. The detailed search strategy is shown in Supplementary Digital Content 1, which depicts the keyword-based search for inclusion terms.

Eligibility criteria
Our search strategy followed the population, intervention, comparison, outcome, study (PICO) design principle.

Articles were selected based on the following criteria: Population: Patients with primary open-angle glaucoma, normal-tension glaucoma (NTG), or OHT; age ≥18; without sex, region, or race restriction. Intervention and Comparison: Any prostaglandins, latanoprost (0.005%), bimatoprost (0.03%), travoprost (0.004%), tafluprost (0.0015%), and unoprostone initiated at the same time. Studies evaluating a fixed combination of prostaglandins with any other antiglaucoma medications that met the inclusion criteria were included. Outcome: Weighted mean difference (WMD) in the CCT measurements from baseline to the last available assessment, expressed in μm, were recorded as the primary outcome. Intraocular pressure and other corneal changes (endothelial cell density, coefficient of variation, and percentage of hexagonality) were recorded as secondary. Study design: Fully reported randomized trials. Crossover randomized trials were also included.

Exclusion criteria: Reviews, retrospective studies, prospective non-randomized studies, duplicate publications and animal studies, case reports, abstracts, and reports with incomplete data were excluded.

Study selection: Three investigators (RK, AS, DP), working independently, scanned all abstracts and obtained the full-text reports of records, which indicated or suggested that the study was a randomized trial evaluating prostaglandin therapy. After obtaining full reports of the trials, the same reviewers independently assessed eligibility from full-text papers.

Data extraction: The same reviewers (RK, AS) conducted data extraction independently using a standardized pre-piloted form. The following information was recorded from each study: authors of the trial, publication year, location of the study, study design (double-blind or single-blind), parallel or cross-over interventions, sample size, participants characteristics (number, mean age, and sex), location of the trial, length of follow-up, type of glaucoma, CCT value from baseline to endpoint, IOP, and other corneal changes. Disagreements were resolved by discussion or consensus involving a third investigator. Study evaluation included general methodological quality features assessing methods of randomization, allocation concealment, use of intention-to-treatment analysis, and methods of blinding.

Quality assessment
The methodological quality of the studies was generally good. We performed quality assessment of trials with the Cochrane bias risk assessment tool (The Cochrane Collaboration) for RCTs. The risk of bias tool covers six domains of bias and seven items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome date (attrition bias), selective reporting (reporting bias), and other bias. The tool involves assigning a judgment of high, low, or unclear risk of bias for each item. Discrepancies in ratings were solved by discussion between two authors. Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence was noted in one study, and selection bias due to inadequate concealment of allocations prior to the assignment was observed in a few studies.

Statistical analysis
Meta-analysis was conducted using the Review Manager (RevMan 5.4.1, Cochrane Collaboration, Copenhagen, Denmark, 2014). When data on a particular outcome were available from at least two studies, we combined and analyzed these data. Cochrane Chi-square test and I² (inconsistency) for heterogeneity were used to assess interstudy heterogeneity. The Chi-square test measures whether observed differences are compatible with chance alone, and I² assesses the % of the effect variability estimates caused by heterogeneity rather than sampling error. The random-effects model was used for all analyses. For continuous variables, mean differences (MDs) were compared using the inverse-variance (I-V) method. Subgroup analysis was performed based on the type of prostaglandin and duration of use. P < 0.05 was considered statistically significant. Publication bias was checked by exploring asymmetry in funnel plots and Egger’s regression test. Additionally, a sensitivity analysis was conducted excluding studies of poor quality (Jadad score < 3).
Trial sequential analysis

Trial Sequential Analysis Viewer [TSA software (version 0.9.5.10 Beta)] was used to calculate the required information size (RIS) for meta-analysis and evaluate treatment benefits based on the sample sizes. The risk of type I error was set at 5% with a power of 80%, the variance was calculated from the data obtained from the included trials, and the relative risk reduction was set at 20%. When cumulative Z-curves crossed sequential monitoring boundaries, a sufficient level of evidence was obtained for the intervention. When Z-curves did not cross the boundaries, the conclusions for the intervention were not justified.

Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

The certainty of the evidence was summarized using the GRADE evidence approach for individual outcomes. The strength of recommendations reduces the potential to facilitate critical appraisal and improve communication of judgments. GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, 2020 [developed by Evidence Prime, Inc] was used to facilitate the development of evidence summaries and recommendations.

Results

Characteristics of trials

The process for literature search and study selection is outlined in Fig. 1. The literature search identified 68 potentially relevant manuscripts based on the abstract. Ten randomized trials that evaluated the effect of prostaglandin on CCT and met our inclusion criteria were considered for analysis. Two RCTs were excluded as relevant data could not be retrieved. Finally, we included eight trials reporting 879 patients in the analysis.

Two crossover trials were included in our analysis. Arcieri et al. described a 4-week washout between each regimen of medications. However, in a study by Sawada et al., as there was no wash-out period between the drugs, only the first period data were considered for analysis to avoid the carryover effect. Seven studies on latanoprost, five on travoprost, three on bimatoprost, and one on any PGA were included. Two studies evaluated the effects of a fixed combination of latanoprost with other antiglaucoma (netarsudil and timolol) medications. Five studies had three intervention arms. Three studies had two intervention arms. The trial duration ranged from 1 month to 3.8 years. The range of the mean age was 38.69–77.7 years. According to the type of glaucoma, 33 subjects had POAG, 462 had OHT, and 15 had other types of glaucoma. In three studies, though data on the type of glaucoma were not presented, they included POAG or OHT patients. The characteristics of the eligible studies including Jadad scores are summarized in Table 1.

Efficacy analysis

The overall effect, expressed as μm, showed that prostaglandins had a significant CCT lowering effect (WMD = -7.04, 95% CI: -10.07 to -4.00, P < 0.00001), heterogeneity: Chih = 11.72, df = 15 (P = 0.70), and P = 0% [Fig. 2]. TSA suggested that accrued information size (n = 879) was more than RIS (n = 669). The cumulative Z-curve (blue line) with quadratic indications of each trial surpassed the traditional boundary (etched lines) for statistical significance during the inclusion of the trial. Further cumulative Z-curve crossed the trial sequential monitoring boundary, indicating that current evidence was sufficient to reach a firm conclusion [Fig. 3].

Primary outcome

To effectively compare the effects of prostaglandin on CCT, we adopted subgroup analysis according to the type and period
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Table 1: Characteristics of the included studies

| Study               | Region     | Center | Design     | POAG/OHT/ Others | Mean Age | Sex (M/F) | Drug used | No. of eyes included | Duration (months) | Jadad score |
|---------------------|------------|--------|------------|------------------|----------|-----------|-----------|----------------------|------------------|-------------|
| Sawada et al. 2012[26] | Japan      | Single | RCT/DB/C   | 42/0/0           | 53.2±11.8| 35/34     | LAT, TRAVO | 42                   | 11               | 5           |
| Zhong et al. 201[30] | China      | Single | RCT/DB     | 56/13/6          | 51±12.3  | NP        | LAT, TRAVO, Bimat | 69                   | 2.5-52         | 4           |
| Hatanaka et al. 2009[4] | Brazil     | Single | RCT/DB     | NP               | 68.5±9.2 | NP        | LAT, TRAVO, Bimat | 73                   | 2              | 3           |
| Lass et al. 2001[32] | USA        | Multicenter | RCT/DB/C  | 226/134/9       | 61±12   | 183/186   | LAT, TIM   | 369                  | 12              | 5           |
| Arcieri et al. 2008[13] | Brazil     | Single | RCT/DB     | 17/17/0          | 57.8±9.6| 14/20     | LAT, TRAVO, Bimat | 34                   | 1              | 5           |
| Wisely et al. 2020[25] | USA        | Multicenter | RCT/DB     | NP               | 63.6±11.2| 156/259   | LAT, NET   | 415                  | 3               | 5           |
| Stefan et al. 2007[17] | Romania    | Single | RCT/DB     | NP               | NP       | NP        | TRAVO, LAT | 52                   | 3               | 2           |
| Brandt et al. 2008[14] | USA        | Multicenter | RCT       | 0/298/0         | 59.8±8.8| NP        | Any PGA   | 298                  | 31              | 1           |

POAG, primary open-angle glaucoma; OHT, ocular hypertension; RCT, randomized controlled trials; DB, double-blind; C, cross over; LAT, latanoprost; TRAVO, travoprost; BIM, bimatoprost; TIM, timolol; NET, netarsudil; NP, not provided; PGA, prostaglandin analogue

Figure 2: Forest plot of central corneal thickness (µm) following treatment with prostaglandin analogue. The individual trials mean difference and confidence intervals are shown. The overall effects for each prostaglandin analogue and differences between subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. SD, standard deviation; CI, confidence interval; CCT, central corneal thickness; PGA- Prostaglandin analogues
the drug was used. The results showed that bimatoprost had a significant CCT lowering effect (WMD = -11.88, 95% CI: -21.03 to -2.73, \( P = 0.01 \)) followed by travoprost (WMD = -10.44, 95% CI: -16.80 to -4.08, \( P = 0.001 \)). Least affecton was by latanoprost (WMD = -4.73, 95% CI: -9.70 to 0.25, \( P = 0.06 \)). Two studies\(^{(3,24)}\) evaluated the effect of fixed combinations of latanoprost with netarsudil and timolol. Pooled data analysis of these two studies demonstrated an insignificant reduction in CCT (WMD = -3.38, 95% CI: -10.51 to 3.74, \( P = 0.35 \)) [Fig. 4]. We pooled seven, six, and three trials assessing latanoprost, travoprost, and bimatoprost, respectively, in the <6-month post-treatment [Fig. 5a] and a total of five trials in the >6-month post-treatment [Fig. 6a] analysis. The WMD across groups in the >6-month prostaglandin use was -11.37 (95% CI: -17.17 to -5.58), which was greater than that in the <6 months treatment with prostaglandins (WMD = -8.35, 95% CI: -12.01 to -4.69), suggesting a longitudinal effect of prostaglandins on CCT. TSA suggested that accrued information size (n = 418) in the <6-month PGA treatment group was more than that in RIS (n = 339), and the cumulative Z-curve crossed the trial sequential monitoring boundary, indicating that current evidence was sufficient to reach a firm conclusion [Fig. 5b] In the >6-month PGA treatment group, the Z-curve did not intersect any TSA boundaries, which indicates that the meta-analysis was underpowered to reach a conclusion [Fig. 6b].

### Secondary outcome

Of the seven studies included in the meta-analysis, two reported additional corneal effects and two reported intraocular pressure (IOP) changes. Wisely et al.\(^{(3)}\) presented the baseline to 3-month specular microscopy data in their study. Changes from baseline to month 3 in corneal endothelial cell density (ECD), coefficient of variation (CV), and % of hexagonal cells were clinically insignificant in all the groups studied. The results of two RCTs\(^{(3,30)}\) of this meta-analysis reporting ECD for latanoprost failed to demonstrate any effect on corneal endothelium (WMD = 4.57, 95% CI: -51.86 to 61, \( P = 0.87 \)) [Fig. 7]. The data on IOP change from baseline of two crossover studies demonstrated a significant reduction of IOP by PGA (WMD = -4.67, 95% CI: -6.65 to -2.69, \( P < 0.0001 \)) [Fig. 8]. Arcieri et al.\(^{(13)}\) studied the blood–aqueous barrier in patients on PGA by using a laser flare meter and found no significant differences in the mean flare measurements (\( P > 0.069 \)). Two trials\(^{(6,28)}\) reported conjunctival hyperemia and conjunctival irritation as the most common adverse event respectively.

### Sensitivity analysis

To investigate the influence of one study on the overall WMD, a sensitivity analysis (data not shown) was performed excluding studies of poor quality (Jadad score <3).\(^{(8,14,16)}\) Sensitivity analysis with these studies removed in the analysis, at a time showed that the corresponding global estimation was not changed.

### Publication Bias

This analysis had statistically significant coefficients (Omnibus \( P < 0.001 \), test for heterogeneity \( P = 0.700 \)). Egger’s test was not significant (\( P = 0.642 \)), indicating a low risk of publication bias (Supplementary Digital Content 2).

### Risk of bias summary and graph

Risk of bias summary and graph are presented in (Supplementary Digital Content 3). Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence was noted in one study,\(^{(14)}\) and selection bias due to inadequate concealment of allocations prior to the assignment was observed in a few studies.\(^{(3,8,9,14,16)}\)

### GRADE evidence

The relevant summary results are presented in Table 2 with “GRADE” evidence. The certainty of the evidence

![Figure 3: Trial sequential analysis (TSA) of the studies included in the meta-analysis demonstrated the required information size (RIS) to be 669](image)

![Figure 4: Forest plot of central corneal thickness (µm) following treatment with a fixed combination of latanoprost with other antiglaucoma medications. The individual trials mean differences and 95% CIs are shown. The overall effects for each prostaglandin analogue are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. SD, standard deviation; CI, confidence interval; CCT, central corneal thickness; PGA, Prostaglandin analogues](image)
was summarized as “moderate” for the outcome of CCT following treatment with a fixed combination of latanoprost with other antiglaucoma medications and corneal ECD following treatment with PGA due to “serious imprecision.”

For the rest of the studied outcomes, the certainty of the evidence was described as “high,” with a few methodological...
issues (inadequate randomization and inadequate allocation concealment) in a few studies.

Discussion

Our meta-analysis of eight RCTs involving 879 patients indicated a significant reduction in the CCT following topical therapy with prostaglandin analogues for glaucoma. According to our results, bimatoprost (0.03%) once daily caused a significant reduction in CCT, closely followed by travoprost. Latanoprost caused a reduction of corneal thickness that was statistically not significant. Further, our analysis showed travoprost to cause maximal, statistically significant

| Study or Subgroup | CCT > 6 months Treatment | Baseline | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------------------|----------|-------------------------------------|-------------------------------------|
|                   | Treatment Mean [µm] SD [µm] Total Mean [µm] SD [µm] Total Weight | | | |
| 5.2.1 Travoprost | Zhong 2011 A 552.08 6.14 12 568.25 7.68 12 28.2% -16.17 [-21.73, -10.61] | | |
|                   | Subtotal (95% CI) 12 12 28.2% -16.17 [-21.73, -10.61] | | |
|                   | Heterogeneity: Not applicable | | |
|                   | Test for overall effect: Z = 5.70 (P < 0.00001) | | |
| 5.2.2 Latanoprost | Lass 2001 B 562 38 118 569 39 118 18.2% -7.00 [-16.82, 2.82] | | |
|                   | Zhong 2011 B 530.33 19.52 15 545.8 20.22 15 11.6% -15.47 [-20.69, -1.25] | | |
|                   | Subtotal (95% CI) 133 133 29.7% -9.74 [-17.82, -1.65] | | |
|                   | Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0% | | |
|                   | Test for overall effect: Z = 2.36 (P = 0.02) | | |
| 5.2.3 Bimatoprost | Zhong 2011 C 538.78 16.92 18 555.17 19.72 18 14.5% -16.39 [-28.39, -4.39] | | |
|                   | Subtotal (95% CI) 18 18 14.5% -16.39 [-28.39, -4.39] | | |
|                   | Heterogeneity: Not applicable | | |
|                   | Test for overall effect: Z = 2.68 (P = 0.007) | | |
| 5.2.4 Any PGA | Brandt 2008 566 36.7 298 571 35.4 298 27.6% -5.00 [-10.79, 0.79] | | |
|                   | Subtotal (95% CI) 298 298 27.6% -5.00 [-10.79, 0.79] | | |
|                   | Heterogeneity: Not applicable | | |
|                   | Test for overall effect: Z = 1.69 (P = 0.09) | | |
|                   | Total (95% CI) 461 461 100.0% -11.37 [-17.17, -5.58] | | |
|                   | Heterogeneity: Tau² = 22.06; Chi² = 2.23, df = 4 (P = 0.06); I² = 57% | | |
|                   | Test for overall effect: Z = 3.85 (P = 0.0001) | | |
|                   | Test for subgroups: Chi² = 8.31, df = 3 (P = 0.04), I² = 63.9% | | |

Figure 6: (a) Forest plot of central corneal thickness (µm) following treatment with prostaglandin analogues for >6 months. The individual trials mean differences and 95% CIs are shown. The overall effects for each prostaglandin analog are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. SD, standard deviation; CI, confidence interval; CCT, central corneal thickness; PGA, Prostaglandin analogues. (b) Trial sequential analysis (TSA) of >6 months of prostaglandin analogue treatment subgroup demonstrated required information size (RIS) to be 490
reduction in the corneal thickness when used as monotherapy for glaucoma for <6 months. Both bimatoprost and travoprost equally reduced the corneal thickness beyond 6-month therapy.

In our meta-analysis, we observed an overall decrease of 7–10 µm in CCT following PGAs treatment. Arcieri et al.\(^{[13]}\) in their study confirmed that topical bimatoprost induced a statistically significant decrease in CCT, an effect they did not observe with latanoprost and travoprost. However, they observed that the change induced by bimatoprost was clinically small (1%), insufficient to promote significant changes in IOP measurements with Goldmann applanation tonometry. Doughty and Zaman et al.\(^{[31]}\) conducted a meta-analysis on human corneal thickness and its impact on IOP measures, and demonstrated that relationships between IOP and CCT measures could be different in different ethnic groups and acute and chronic (glaucoma) disease. They concluded that in eyes with glaucoma, a 10% difference in CCT would result in a 2.5 ± 1.1 mm Hg difference in IOP measures by applanation tonometry. However, as the corneal stromal matrix architecture is changed by PGA, the potential influence of CCT on IOP and use of IOP correction formula\(^{[31,32]}\) in these cases may not be accurate.\(^{[12,33,34]}\)

Schlote et al.\(^{[7]}\) performed a study over 12 months of travoprost treatment and showed a nonlinear CCT reduction that mainly occurred within the first 6 months of treatment but continued less intensively during the next 6 months. In a 4-year retrospective study by Maruyama et al.\(^{[19]}\) the mean CCT significantly decreased in the first 2 years of latanoprost treatment; however, no significant difference was found between the mean CCT at midpoint and that at final follow-up; only about 10 µm of CCT decrease was observed during the 4-year follow-up period, and IOP values were unaffected. Though our research on PGAs treatment for >6-month showed an increased thinning of cornea compared to short-duration treatment of these medications, suggesting a longitudinal effect of PGAs on CCT, the small sample size and high heterogeneity involving this outcome (>6 months) in our meta-analysis suggest that these results should be considered with caution.

All studies included in this analysis were randomized trials, which largely reduced confounders. There were three multicenter studies\(^{[3,14,30]}\) included in our analysis performed in multiple countries. Studies included did not differ in the concentration of the drug, frequency of dosing of medications, or measurement of CCT. In all the studies, included drug

| Study or Subgroup | Mean [cells/mm²] | SD [cells/mm²] | Total | Mean [cells/mm²] | SD [cells/mm²] | Total | Weight | Mean Difference | IV, Random, 95% CI | Mean Difference | IV, Random, 95% CI |
|------------------|-----------------|----------------|-------|-----------------|----------------|-------|--------|----------------|-------------------|----------------|-------------------|
| **8.2.2 Corneal Endothelial Cell Density** | | | | | | | | | | | |
| Less 2001 | 2,514 | 262 | 110 | 2,507 | 266 | 118 | 69% | 6.9% | 7.00 [60.62, 74.62] | | 7.00 [60.62, 74.62] |
| Wisely 2020 | 2,446.7 | 447.4 | 146 | 2,446.7 | 445.2 | 146 | 30.4% | 30.4% | -1.00 [-103.38, 101.38] | | -1.00 [-103.38, 101.38] |
| Subtotal (95% CI) | 264 | 100% | 100% | 264 | 100% | 100% | 4.57 [41.86, 61.60] | 4.57 [41.86, 61.60] | | |

**Figure 7:** Forest plot of corneal endothelial cell density (cells/mm²) following treatment with prostaglandin analogues. The individual trials mean differences and 95% CIs are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. SD-standard deviation; CI-confidence interval; CECD-corneal endothelial cell density; PGA-Prostaglandin analogues

| Study or Subgroup | Mean [mmHg] | SD [mmHg] | Total | Mean [mmHg] | SD [mmHg] | Total | Weight | Mean Difference | IV, Random, 95% CI | Mean Difference | IV, Random, 95% CI |
|------------------|-------------|-------------|-------|-------------|-------------|-------|--------|----------------|-------------------|----------------|-------------------|
| **8.2.1 Latanoprost** | | | | | | | | | | | |
| Arcieri 2008 B | 17.3 | 3.9 | 34 | 22 | 3.1 | 34 | 19.6% | 19.6% | -4.70 [-6.37, -3.03] | | -4.70 [-6.37, -3.03] |
| Sawada 2012 B | 11.4 | 2.2 | 21 | 13.9 | 2.5 | 21 | 20.4% | 20.4% | -2.90 [-3.62, -1.08] | | -2.90 [-3.62, -1.08] |
| Subtotal (95% CI) | 55 | 39.9% | 39.9% | 55 | 39.9% | 39.9% | -3.55 [-5.71, -1.40] | -3.55 [-5.71, -1.40] | | |

**Figure 8:** Forest plot of intraocular pressure change (mm Hg) following treatment with prostaglandin analogues. The individual trials mean differences and 95% CIs are shown. The overall effects for each prostaglandin analogues are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. SD, standard deviation; CI, confidence interval; IOP, Intraocular pressure; PGA, Prostaglandin analogues
was instilled once a day. An average of five consecutive CCT readings using ultrasonic pachymetry was taken for analysis in all the included studies. Intraoperator and interoperator of CCT were thus taken care of.[10] To avoid the effects of the diurnal variation of CCT,[11] all the measurements were carried out between 9 AM and 11 AM in two studies.[8,9] However, the time of measurement of CCT was not mentioned in the remaining studies. There was no significant heterogeneity in our analysis. Further, the confidence intervals of the pooled results were narrow, suggesting that our data are sufficient to reach a conclusion about this outcome. These factors make the results of our analysis more convincing.

Meda et al.[11] reported a positive correlation between CCT, corneal hysteresis (CH), and corneal resistance factor (CRF). An increase in these parameters following cessation of chronic use of PGA and a subsequent reduction following reinitiation of the medication was observed in their study. Though long-term treatment with PGA is associated with a small but significant thinning of the cornea, its clinical relevance on IOP measurements needs to be considered in glaucoma practice. Study of corneal biomechanics (CH) has provoked much interest in recent years for its implication in glaucoma, although the exact relationship between CH and glaucoma is yet to be understood. Corneal hysteresis has recently been claimed to be more strongly associated with diagnosis of glaucoma, risk of progression, and effectiveness of glaucoma treatment than CCT itself.[12] However, there is a paucity of data exploring the effects of prostaglandins on IOP, corneal hysteresis, and CCT simultaneously. Though knowledge of corneal hysteresis may allow us to treat each eye as a unique entity; its clinical adoption may be slower than pachymetry owing to the relative inexpensiveness, portability, and easy availability of pachymetry devices.

Limitations
Publication bias cannot be ruled out from the subgroup analysis because of the small number of studies in the subgroups. We included data only from full-paper publications; data from abstracts and international meetings were not included. Further, only published trials with available data were analyzed in our study; therefore, the inclusion of unpublished data could influence our conclusions. We excluded a trial by Bafa et al.[18] as relevant study data could not be retrieved. This trial, in contrast to the studies included, reported an increase in corneal thickness in patients on latanoprost; as such, inclusion of this study may have affected the overall outcome. Pooled data in the subgroup (>6 months) analyses were based on only a few trials. Further, TSA suggested that accrued information size (n = 461) in >6-month PGA treatment group was less than that in RIS (n = 490), indicating that current evidence was insufficient to reach a firm conclusion; thus, more research would be needed on the available evidence derived. Though most of the trials recruited newly diagnosed glaucoma patients or considered a 4-week washout for PGA and beta-blockers before the baseline reading was taken, in the study by Lass et al.,[20] during the 3-week run-in period, all the subjects were treated with timolol 0.5% one drop once daily. Though timolol was chosen because of its long track record of corneal safety, reversible increase in CCT following administration of timolol as reported by Grueb et al.[21] could have influenced their results. They also recruited three patients with pigmentary glaucoma in their study. This prompted us to perform a sensitivity analysis
by excluding this study. No significant change in the overall result (WMD = −7.04, 95% CI: −10.23 to −3.85) was observed.

Conclusion
In conclusion, bimatoprost (0.03%) and travoprost cause a small, statistically significant reduction in the thickness of the central cornea. As these drugs may significantly confound the routine IOP measurement despite modest changes in CCT, longitudinal CCT variation that may arise throughout the follow-up period of glaucoma patients treated with PGA, a proper IOP target attainment mandate performing pachymetry more than once by ophthalmologists in a glaucoma patient’s lifetime.

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Conflicts of interest
There are no conflicts of interest.

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Supplementary Digital Content 1

The Search Strategy. The search terms were used to search databases of PUBMED, OVID MEDLINE, CCRCT, and Google Scholar (modified to suit each specific database with abstract, keywords, and text with the removal of duplicates)

The Search Strategy

OVID- MEDLINE search

| Search No | Query                                      | Results   |
|-----------|--------------------------------------------|-----------|
| 1         | prostataglandin.mp. [mp=ti, ab, tx, ct]    | 85,516    |
| 2         | analog*.mp. [mp=ti, ab, tx, ct]            | 566,902   |
| 3         | travoprost.mp. [mp=ti, ab, tx, ct]         | 1,096     |
| 4         | latanoprost.mp. [mp=ti, ab, tx, ct]        | 3,233     |
| 5         | bimatoprost.mp. [mp=ti, ab, tx, ct]        | 1,318     |
| 6         | lumigan.mp. [mp=ti, ab, tx, ct]            | 323       |
| 7         | travatan.mp. [mp=ti, ab, tx, ct]           | 318       |
| 8         | xalatan.mp. [mp=ti, ab, tx, ct]            | 671       |
| 9         | central.mp. [mp=ti, ab, tx, ct]            | 1,526,176 |
| 10        | cornea*.mp. [mp=ti, ab, tx, ct]            | 119,471   |
| 11        | thickness.mp. [mp=ti, ab, tx, ct]          | 484,186   |
| 12        | 1 and 2                                    | 19,126    |
| 13        | 3 or 4 or 5 or 6 or 7 or 8                 | 4,143     |
| 14        | random*.mp. [mp=ti, ab, tx, ct]            | 2,082,342 |
| 15        | 9 or 10 or 11                              | 1,912,362 |
| 16        | 12 and 13 and 14 and 15                    | 554       |
| 17        | tafluprost.mp. [mp=ti, ab, tx, ct]         | 235       |
| 18        | unoprostone.mp. [mp=ti, ab, tx, ct]        | 235       |
| 19        | 13 or 17 or 18                             | 4,245     |
| 20        | 12 and 14 and 15 and 19                    | 563       |

Pubmed search

| Search number | Search Details                                      | Results   |
|---------------|-----------------------------------------------------|-----------|
| 23            | 20 AND 22                                           | 230       |
| 22            | Randomize *                                          | 12,88,985 |
| 20            | 18 AND 19                                           | 1,500     |
| 19            | 12 OR 13 OR 14                                       | 15,87,363 |
| 18            | 16 OR 17                                            | 26,024    |
| 17            | 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 10 OR 11              | 2,905     |
| 16            | 1 AND 2                                             | 24,506    |
| 14            | "thick"[All Fields] OR "thickness"[All Fields] OR "thicknesses"[All Fields] | 3,07,344  |
| 13            | "cornea"[All Fields]                                | 1,23,552  |
| 12            | "central"[All Fields] OR "centrally"[All Fields] OR "centrals"[All Fields] | 12,01,476 |
| 11            | "tafluprost"[Supplementary Concept] OR "tafluprost"[All Fields] | 245       |
| 10            | "unoprostone"[All Fields]                           | 194       |
| 8             | "travoprost"[MeSH Terms] OR "travoprost"[All Fields] OR "travatan"[All Fields] | 728       |
| 7             | "bimatoprost"[MeSH Terms] OR "bimatoprost"[All Fields] OR "lumigan"[All Fields] | 839       |
| 6             | "latanoprost"[MeSH Terms] OR "latanoprost"[All Fields] OR "xalatan"[All Fields] | 2,067     |
| 5             | "bimatoprost"[MeSH Terms] OR "bimatoprost"[All Fields] | 832       |
| 4             | "latanoprost"[MeSH Terms] OR "latanoprost"[All Fields] | 2,050     |
| 3             | "travoprost"[MeSH Terms] OR "travoprost"[All Fields] | 718       |
| 2             | "analog"[All Fields]                                | 10,32,092 |
| 1             | "prostaglandin * [All Fields]                      | 1,49,924  |
Supplementary Digital Content 2: Publication Bias. The Funnel Plots for CCT following PGA treatment. Regression test for Funnel plot asymmetry (Egger’s test). $P$ values were >0.05
Supplementary Digital Content 3: Risk of Bias Summary (a) and Graph (b)