Comparing Diurnal and Nocturnal Effects of Brinzolamide and Timolol on Intraocular Pressure in Patients Receiving Latanoprost Monotherapy

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Purpose: To compare the diurnal and nocturnal effects of brinzolamide and timolol on intraocular pressure (IOP) in patients already receiving monotherapy with latanoprost.

Design: Prospective, open-label, and crossover clinical trial.

Participants: Twenty-six patients with glaucoma or ocular hypertension (ages, 44–79 years) who were receiving treatment with 0.005% latanoprost once every evening.

Methods: Baseline data of 24-hour IOP were collected in a sleep laboratory while patients were receiving latanoprost monotherapy. Measurements were taken every 2 hours in the sitting and supine positions during the 16-hour diurnal/wake period and in a supine position during the 8-hour nocturnal/sleep period. Patients were randomly assigned to receive an add-on treatment with either 1% brinzolamide 3 times per day or 0.5% timolol gel forming solution once every morning for 8 weeks, and then crossed over to receive the other add-on treatment. At the end of each add-on treatment period, 24-hour IOP data were collected.

Main Outcome Measures: Diurnal and nocturnal IOP means were compared among the baseline, the brinzolamide add-on treatment, and the timolol add-on treatment.

Results: During the diurnal period, the mean IOP under brinzolamide or timolol add-on treatment was significantly lower than the baseline IOP in both the sitting and supine positions. There was no statistical difference between the 2 add-on treatments. During the nocturnal period, the supine IOP under brinzolamide add-on treatment was significantly lower than both the baseline and the timolol add-on treatment. There was no difference in nocturnal IOP between the timolol add-on treatment and the baseline.

Conclusions: In patients already receiving the latanoprost monotherapy, adding brinzolamide or timolol significantly reduced IOP during the diurnal period. However, only the brinzolamide add-on treatment had an IOP-lowering efficacy during the nocturnal period.

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Lowering intraocular pressure (IOP) reduces the risk of glaucoma onset and progression.[1,2] In clinical practice, initiating glaucoma treatment by lowering IOP usually begins with the use of a single topical drug, most often a prostaglandin analog. When the IOP lowering with a single topical drug is inadequate, an additional topical drug may be added as adjunctive therapy. Brinzolamide, a carbonic anhydrase inhibitor, and timolol, a β-adrenergic antagonist, are among the options used as adjunctive therapy. Efficacy of brinzolamide or timolol add-on treatment to lower IOP in patients already receiving monotherapy with latanoprost (Xalatan, Pharmacia & Upjohn, Kalamazoo, MI), a prostaglandin analog, has been verified during the diurnal/wake period.[3–8] Comparable efficacy during the nocturnal/sleep period is less clear for these add-on treatments.[6,7]

Nocturnal efficacy of an IOP-lowering drug can be different from its diurnal efficacy. Latanoprost given once in the evening lowers IOP throughout the 24-hour day[9–13] by increasing aqueous humor outflow.[14,15] Because both brinzolamide and timolol inhibit aqueous humor formation with no effect on aqueous humor outflow during the diurnal/wake period,[16–20] an additive IOP-lowering efficacy to latanoprost is expected for either add-on treatment. Compared with their diurnal effects on aqueous humor formation, timolol and brinzolamide have minimal and a smaller effect during the nocturnal period, respectively.[19,21] The absence of timolol's effect on aqueous humor formation during the nocturnal period may or may not control its nocturnal IOP-lowering efficacy when added to latanoprost.[7] The nocturnal IOP-lowering efficacy of brinzolamide adjunctive to latanoprost is also inconsistent.[6]

In the present study, we evaluated the diurnal and nocturnal IOP-lowering efficacies in a group of patients during the transition from latanoprost monotherapy to add-on treatment with brinzolamide or timolol.

Materials and Methods

The study was approved by the institutional review board, in accordance with the Health Insurance Portability and Accountability Act regulations, and registered as a clinical trial (http://www.

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clinicaltrials.gov, NCT00300079). Experimental subjects were recruited consecutively from patients with glaucoma or ocular hypertension seen at the Hamilton Glaucoma Center of the University of California, San Diego. Criteria for determining glaucoma and ocular hypertension were the same as used previously.[12] Eligible candidates, aged 40 to 80 years, had been receiving the 0.005% latanoprost monotherapy for more than 4 weeks. As judged by a glaucoma specialist (FAM, JRS, or RNW), the individual IOP target for a patient had not yet been reached and an additional topical drug was recommended. Patients were informed about this study and potential side effects of test drugs. Informed consents were obtained.

Each subject had a complete review of medical history and eye examination, including slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated funduscopy, and a visual field test.[12,22] Individuals who had prior eye surgery, history of ocular trauma or sleep disorder, ocular inflammation, narrow iridocorneal angle, bronchial asthma, severe cardiovascular condition, sulfa allergy, or routine use of systemic β-blocker for treating high blood pressure were excluded. Individuals who smoked or had an irregular sleep schedule, such as nightshift workers, were also excluded. The office IOP level was not used as an inclusion or exclusion criterion because previous studies indicated that the laboratory IOP profile may not correlate well with the office IOP.[12,22] Routine systemic medicines used by the subjects were documented, and subjects were asked to report any change in the use of systemic medication.

Subjects were receiving latanoprost monotherapy in both eyes at the time of enrollment. The baseline 24-hour IOP data were collected in the laboratory within a few weeks from the enrollment. Subjects were then randomly assigned in a crossover fashion to receive 1% brinzolamide (Azopt, Alcon, Ft. Worth, TX) or 0.5% timolol gel forming solution (Alcon) in both eyes. Brinzolamide was administered 3 times per day (on awakening, after lunch, and before bedtime), and timolol was administered once in the morning on awakening. All patients continued with the latanoprost eyedrops once in the evening before bedtime, separated by 5 minutes from the brinzolamide eyedrops, if applicable. The concomitant latanoprost treatment with add-on brinzolamide or timolol treatment continued for 8 weeks before the second 24-hour laboratory recording. The third laboratory recording was performed after switching to a different add-on treatment for 8 weeks.

Subjects were instructed to maintain a daily 8-hour bedtime with lights off for 1 week before each laboratory recording, and this 8-hour period was referred to as the nocturnal/sleep period. The actual length of sleep, however, may be less than 8 hours in some senior subjects. The bedtime schedules were verified using a wrist monitor for light exposure and arm movements (Actiwatch, Mini Mitter, Sunriver, OR) and a wake/sleep log. Subjects were asked to abstain from alcohol for 3 days and caffeine for 1 day before reporting to the laboratory at approximately 2 PM. Laboratory conditions and general experimental procedures have been described.[12] The 8-hour nocturnal/sleep period in the laboratory for each subject was adjusted to correspond to the recorded bedtime in the previous week. Times for IOP measurements were also individualized. Although the sleep and measurement schedules were individualized, laboratory data were aligned as if each subject had a sleep period from 11 PM to 7 AM. Subjects were encouraged to continue normal indoor activities in the laboratory. Food and water were available, and meal times were not regulated. Subjects self-administered the eyedrops under supervision in the laboratory.

Intraocular pressure, blood pressure, and heart rate were measured every 2 hours. Intraocular pressure was measured using a calibrated pneumatonometer (Reichert, Depew, NY). Topical 0.5% proparacaine was used as the local anesthetic. Every record of IOP measurement was evaluated according to commonly accepted standards.[23] Blood pressure and heart rate were measured immediately before the IOP measurements using an automated wrist blood pressure monitor (Omron, Model HEM-608, Vernon Hills, IL). Before bedtime, measurements were taken at 3:30 PM, 5:30 PM, 7:30 PM, and 9:30 PM. Subjects were instructed to lie in bed for 5 minutes before the supine measurements. They then sat for 5 minutes before the sitting measurements. Lights in individual sleep rooms were turned off at 11 PM. Supine measurements were taken at 11:30 PM, 1:30 AM, 3:30 AM, and 5:30 AM. A dim red room light ($<$10 lux) was used to assist the nocturnal measurements. Subjects were awakened, and the measurements were taken immediately and completed within a few minutes. Some sleep disturbance resulting from the nocturnal measurements was unavoidable. Influence of sleep disturbance on IOP was assumed to be equally applied to all 3 laboratory recordings. Regular room lighting was restored at 7 AM, and subjects were awakened. Measurements continued at 7:30 AM, 9:30 AM, 11:30 AM, and 1:30 PM. Timings of the measurements were documented using infrared camera-recording systems.

Data of IOP from both eyes were averaged. Mean arterial blood pressure was calculated as the diastolic blood pressure plus one third of the difference between the systolic and the diastolic blood pressures. Means of IOP, blood pressure, and heart rate were calculated for the diurnal period (7 AM to 11 PM) and the nocturnal period (11 PM to 7 AM) under the 3 treatment conditions. Diurnal and nocturnal ocular perfusion pressures were calculated in different body positions.[24] Statistical comparisons among the 3 treatment conditions were performed using the repeated-measures analysis of variance with post hoc Bonferroni test for all 3 possible comparisons. The reduction of IOP by each add-on treatment from the baseline IOP under the latanoprost monotherapy was calculated at each clock time point. The mean reduction in the nocturnal period was compared with the mean reduction in the diurnal period using the paired t test. The criterion for statistical significance was $P<0.05$.

Results

Thirty-two subjects were recruited, and 26 subjects completed the entire study. After enrollment, 1 subject was diagnosed with a congestive heart failure and 1 subject had a change of systemic medicine, which disqualified them to continue the study. An additional 4 subjects opted out of the study because of intolerance of the test drug (one or more of blurred vision, bitter taste, and allergic reaction) or difficulty in scheduling the laboratory sessions. The final group of 26 subjects completing the study included 10 men and 16 women who were 44 to 79 years old (63.6 ± 10.2 years, mean $\pm$ standard deviation). There were 17 Caucasians, 5 Asians, and 4 Hispanics. Twenty-four patients were diagnosed with glaucoma, and 2 patients were diagnosed with ocular hypertension. Their office IOP under latanoprost monotherapy was 20.4 ± 4.2 mmHg (range, 12–29 mmHg determined between 7 AM and 5 PM) measured by the Goldmann tonometer during the last clinic visit before the enrollment. Twenty of the 26 subjects were routinely using one or more systemic medicines that include anticholesterol, anti-inflammatory, antidepressant, estrogen replacement, and antihypertensive drugs (except β-adrenergic antagonists).

Figure 1 presents the 24-hour IOP profiles in the habitual body positions (sitting during the day and supine at night) under the 3 treatment conditions. During the 16-hour diurnal/wake period, IOP level under either the brinzolamide add-on treatment or the timolol add-on treatment was lower than under the latanoprost monotherapy. Diurnal IOP levels under the brinzolamide add-on treatment were similar to those under the timolol add-on treatment.

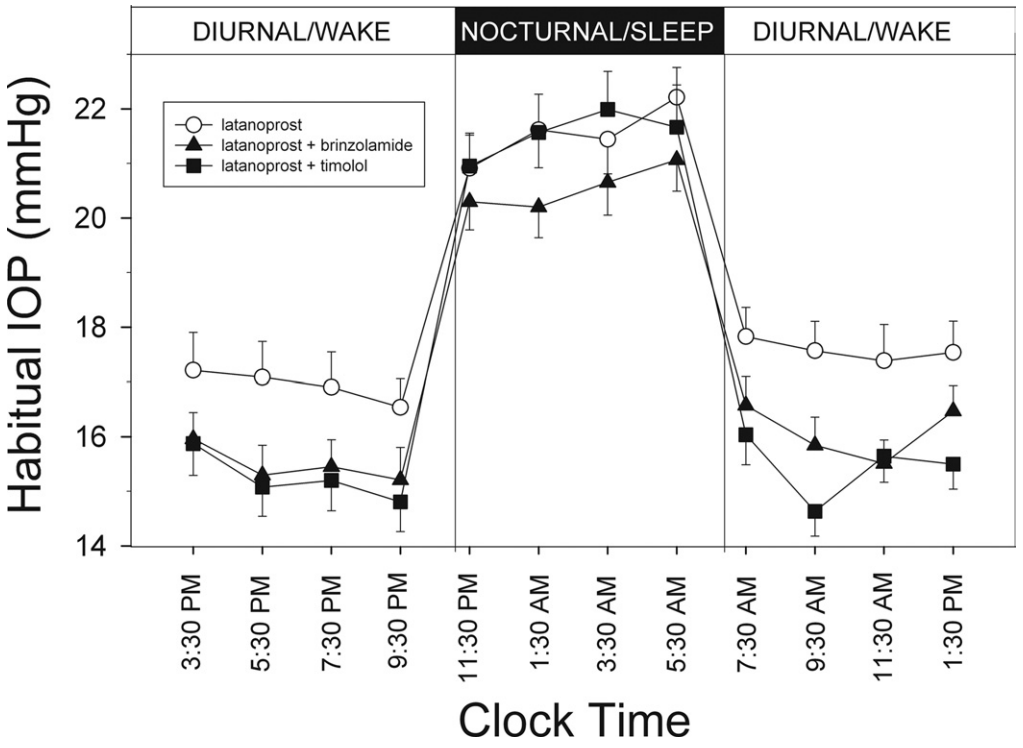

Figure 1. Profiles of 24-hour IOP in the habitual body positions. Measurements were taken sitting during the diurnal period and supine during the nocturnal period from the same 26 subjects. Latanoprost monotherapy (*open circles*), brinzolamide add-on treatment (*solid triangles*), and timolol add-on treatment (*solid squares*). Standard error of the mean (*error bars*).

Particularly, IOP readings were similar at 3:30 PM and 7:30 AM shortly after the application of brinzolamide eyedrops. Intraocular pressure increased during the transition from the diurnal period to the nocturnal period, when the body position changed from sitting to supine. During the 8-hour nocturnal/sleep period, IOP levels under the brinzolamide add-on treatment were lower than those under the latanoprost monotherapy and the timolol add-on treatment. Values of IOP under the timolol add-on treatment were similar to those under the latanoprost monotherapy. At the transition from the nocturnal to the diurnal period, while the body position changed from supine to sitting, IOP under either add-on treatment decreased more than under the latanoprost monotherapy.

Figure 2 presents the 24-hour supine IOP profiles, which were unaffected by posture. Under the latanoprost monotherapy, IOP gradually increased during the nocturnal period and peaked at the end of the nocturnal period. Intraocular pressure under the brinzolamide add-on treatment was lower than the baseline under the latanoprost monotherapy in both the diurnal and nocturnal periods. Under the timolol add-on treatment, IOP was different from the baseline in the diurnal period only.

Mean diurnal and nocturnal IOP levels under the 3 treatment conditions are presented in Table 1. In the diurnal period, sitting or supine IOP under either the brinzolamide or the timolol add-on treatment was significantly lower than the IOP under latanoprost monotherapy. There was no statistically significant difference in diurnal IOP between the brinzolamide and the timolol add-on treatments. In the nocturnal period, the IOP under the brinzolamide add-on treatment was significantly lower than that under the latanoprost treatment with or without adding timolol. No significant difference occurred in the nocturnal IOP between the timolol add-on treatment and the baseline. Comparing the time-dependent reduction of IOP by the brinzolamide add-on treatment with the baseline, the nocturnal reduction (1.0±1.9 mmHg; mean ± standard deviation) was smaller than the diurnal reduction in both the sitting and supine positions (1.5±1.5 mmHg and 1.3±1.8 mmHg, respectively). However, the difference between the diurnal and nocturnal reductions was not statistically significant ($P>0.05$). The difference in IOP reduction by the timolol add-on treatment was significant between the diurnal period (both sitting and supine) and the nocturnal period ($P<0.01$).

Under latanoprost monotherapy, the diurnal sitting mean blood pressure of 98.2±7.3 mmHg was significantly higher ($P<0.01$) than both the diurnal supine mean blood pressure of 88.9±9.0 mmHg and the nocturnal supine mean blood pressure of 86.4±11.5 mmHg (repeated-measures analysis of variance with post hoc Bonferroni test). The diurnal and nocturnal supine mean blood pressures were not statistically different. There was no significant reduction in the mean blood pressure by the brinzolamide add-on treatment or the timolol add-on treatment in either the diurnal period (sitting and supine positions) or nocturnal period (supine position). Calculated ocular perfusion pressures showed no difference among the baseline, brinzolamide add-on treatment, and timolol add-on treatment. A reduction of heart rate by the timolol add-on treatment occurred in the diurnal period ($P<0.05$; 4.0 beats/min in the sitting position and 3.3 beats/min in the supine position), but not in the nocturnal period.

Discussion

In patients being treated with latanoprost, there was no difference in the IOP-lowering efficacy between the brinzolamide and the timolol add-on treatments during the diurnal period. During the nocturnal period, the difference in IOP between the brinzolamide add-on treatment and the

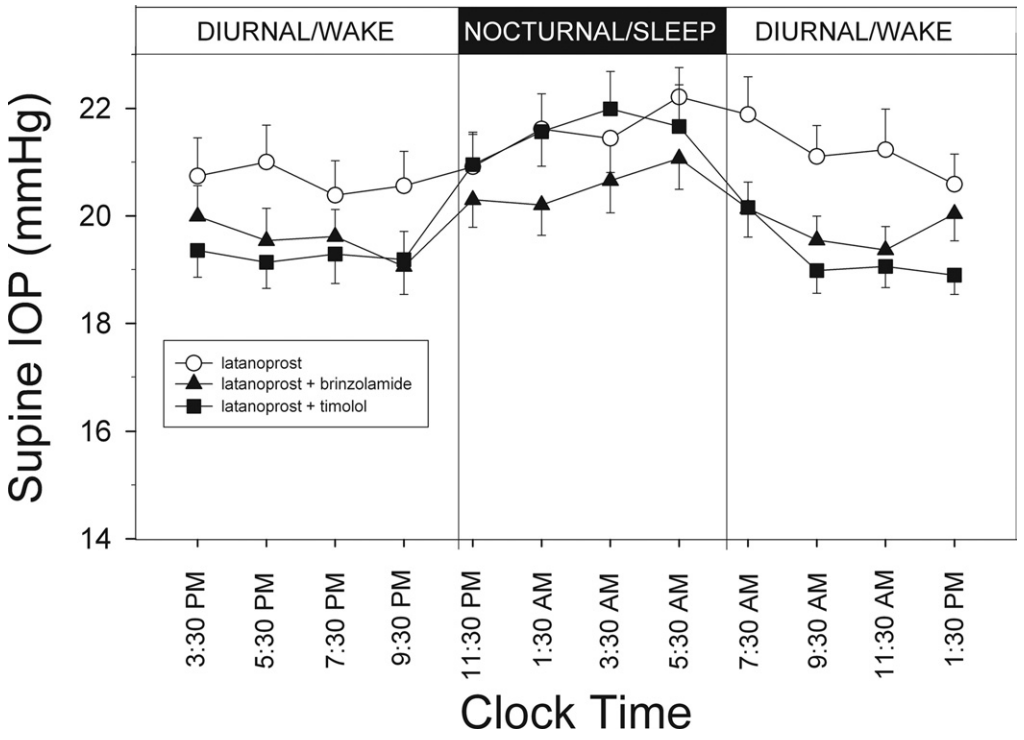

Figure 2. Profiles of 24-hour supine IOP. IOP under the latanoprost monotherapy (*open circles*), brinzolamide add-on treatment (*solid triangles*), and timolol add-on treatment (*solid squares*). Data were from the same 26 subjects. Standard error of the mean (*error bars*).

baseline was small but statistically significant. The timolol add-on treatment showed no nocturnal IOP-lowering efficacy. These observations were consistent with a previous report showing significant nocturnal efficacy of a topical carbonic anhydrase inhibitor and weaker nocturnal efficacy of a β-adrenergic antagonist, both used as monotherapy.[10] The present study was performed under strictly controlled laboratory conditions; therefore, the clinical relevance needs to be verified. In addition, the significance of nocturnal IOP reduction in glaucoma onset and progression needs to be validated.

Physiologic mechanisms for IOP regulation during the nocturnal period are not well understood.[25,26] Brinzolamide add-on treatment caused a habitual IOP reduction during the nocturnal period, but the IOP reduction was smaller than during the diurnal period. Because brinzolamide was given 3 times per day, separated approximately by 8 hours, time-related bioavailability of brinzolamide played no role in the extent of IOP reduction during the nocturnal period. Posture was also not a factor because a similar observation occurred in the supine IOP measurements taken during both the diurnal and nocturnal periods. Brinzolamide inhibits carbonic anhydrase, an important enzyme for the formation of aqueous humor, and has no effect on outflow resistance of aqueous humor.[20] Because brinzolamide causes a smaller reduction in aqueous humor formation during the nocturnal period than during the diurnal period,[19] this mechanism of action may explain the modulated IOP reduction during the nocturnal period.

Table 1. Diurnal and Nocturnal Intraocular Pressure

Treatment	Diurnal Sitting IOP	Diurnal Supine IOP	Nocturnal Supine IOP
Latanoprost only	17.3±2.8	20.9±3.1	21.6±2.9
Brinzolamide add-on	15.8±2.3*	19.7±2.3*	20.6±2.6†
Timolol add-on	15.4±2.3*	19.3±2.1*	21.5±3.3

IOP = intraocular pressure.
Values are mean ± standard deviation in mmHg (N = 26). The diurnal period was 7 AM to 11 PM, and the nocturnal period was 11 PM to 7 AM.
*$P<0.05$, different from the latanoprost monotherapy.
†$P<0.05$, different from the latanoprost monotherapy and the timolol add-on treatment; repeated-measures analysis of variance with post hoc Bonferroni test.

Timolol reduces the rate of aqueous humor formation[17,18] with no effect on aqueous outflow resistance[16] or episcleral venous pressure[27] during the diurnal period. The nocturnal aqueous humor flow is approximately half of the diurnal aqueous humor flow,[28] and timolol has no effect on the nocturnal aqueous humor flow.[21] Although diminishing IOP reduction during the nocturnal period under timolol monotherapy was frequently observed, there was no agreement on the magnitude.[10,12,29–32] The present study showed that timolol add-on treatment had no IOP-lowering efficacy during the nocturnal period, different from a report showing that the add-on treatment caused a significant IOP reduction in the early nocturnal period.[7] Timolol aqueous solution was used twice per day in the latter study,[7] and timolol gel forming solution was used once daily in the present study. The discrepancy in the nocturnal IOP-lowering efficacy is unlikely the result of different formulations or treatment

frequencies. Timolol gel forming solution used once daily can lower daytime IOP at 22 to 24 hours after an application[31,33–36] as effectively as timolol aqueous solution used twice per day.[34,36] The lack of nocturnal effect of timolol gel forming solution, occurring 16 to 22 hours after an application as add-on treatment or as monotherapy, can be well explained by the inability of a β-adrenergic antagonist to reduce the nocturnal aqueous humor formation.[12,21] In a study using timolol gel forming solution as monotherapy,[12] the pretreatment IOP values during the diurnal and nocturnal periods were 2 to 4.2 mmHg higher than the corresponding baseline IOP values under the latanoprost monotherapy in the present study.

A recent epidemiologic study indicated that ocular perfusion pressure is a significant risk factor associated with glaucoma incidence.[37] The present study examined whether the ocular perfusion pressures might have been different among the 3 treatment conditions. Because of a relatively larger variability in blood pressure (compared with IOP) and a smaller sample size (compared with an epidemiologic study), no significant difference in ocular perfusion pressure was found despite differences in the diurnal and nocturnal IOP means. On the basis of the average standard deviation of difference in ocular perfusion pressure between any 2 treatment conditions, a sample size of 26 had a statistical power (1-β) of 0.20 to 0.61 to detect 1 to 2 mmHg difference in the sitting ocular perfusion pressure during the diurnal period. The corresponding statistical power was 0.13 to 0.39 for the supine ocular perfusion pressure during the nocturnal period. To reach a generally accepted 0.80 statistical power and 0.05 type I error (α), a sample size of 49 was needed during the diurnal period and 54 was needed during the nocturnal period for detecting the largest differences observed in mean ocular perfusion pressures (using repeated-measures analysis of variance with post hoc Bonferroni test). The number of final participants was approximately half of what was minimally needed, which was a limitation for interpreting perfusion pressure data in the present study.

When considering an add-on treatment for patients already receiving latanoprost monotherapy, brinzolamide provides a more sustained lowering of IOP than timolol gel throughout the 24-hour day. Brinzolamide lowers both daytime and nighttime IOP in these patients. In contrast, timolol lowers IOP during the diurnal/wake period but has little IOP-lowering efficacy during the nocturnal/sleep period.

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Footnotes and Financial Disclosures

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