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Effects of Hormone Therapy on Intraocular Pressure: The Women's Health Initiative-Sight Exam Study

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Abstract

Purpose—Previous studies suggest that hormone therapy favorably affects intraocular pressure (IOP). Here, we examined the association between hormone therapy use and IOP in the context of a large randomized trial.

Design—Secondary data analysis from a randomized-control trial

Methods—We used data from the Women's Health Initiative-Sight Exam (WHISE). Women with prior hysterectomy received oral conjugated equine estrogen (0.625 mg/day) or placebo. Women with a uterus received estrogen plus progestin (medroxyprogesterone acetate 2.5 mg/day) or placebo. IOP was measured five years after randomization. Adjusted linear regression models were used to assess the association between hormone therapy and IOP.

Results—The WHISE included 1,668 women in the estrogen-alone trial (aged 63–86, mean 72 years) and 2,679 women in the estrogen-plus-progestin trial (aged 63–87, mean 72 years). In

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multivariate analyses, compared to placebo treatment, treatment with estrogen alone was associated with a 0.5-mmHg reduction of the IOP in the right eye (95% CI; −0.8, −0.1, p = 0.005) and a 0.6 mmHg (95% CI; −0.9, −0.3, p < 0.001) reduction of the IOP in the left eye. In the estrogen-plus-progestin trial, there was no significant difference in IOP between the treatment and placebo groups (p = 0.30 right eye and p = 0.43 left eye).

Conclusions—This study represents an IOP analysis in the largest hormone trial available. Estrogen-alone therapy in postmenopausal women is associated with a small but significant IOP reduction of 0.5 mmHg. The clinical significance of this small decrease remains to be determined.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide, and the global burden is increasing as the population ages.[1-3] Based on a recent meta-analysis of 50 population-based studies, glaucoma was estimated to affect 64.3 million people aged 40–80 years in 2013, and that number is predicted to increase to 76 million in 2020 and to 111.8 million in 2040.[3] Women comprise the majority of glaucoma cases worldwide[1] and in the United States (U.S.).[2,4-6] In certain regions, women have less access to eye care than do men; even in developed nations such as the U.S., women are 24% less likely than are men to receive treatment for glaucoma.[2,4] Primary open-angle glaucoma (POAG) is the most common type of glaucoma in the U.S., and although a recent meta-analysis suggested that men have a 36% greater risk of POAG than do women, women comprise the majority of POAG cases in the U.S., perhaps as a result of their longer lifespans.[3] At present, POAG affects 1.44 million women in the U.S., and that number is projected to increase to 3.66 million by 2050.[5,6] Thus, from a public health perspective, glaucoma screening and prevention in women is vital.

The risk of POAG in women is affected not only by chronological age but also by advancing reproductive age.[2,7,8] For example, in a Mayo Clinic study of 1044 women, early menopause as a result of bilateral oophorectomy before the age of 43 years was associated with a 1.6-fold increase in the risk for POAG.[9] Menopausal stage and sex steroid hormones influence the level of intraocular pressure (IOP), the major risk factor for glaucoma and is the only one that is modifiable. The Early Manifest Glaucoma Treatment Trial (EMGT) suggested that each 1-mmHg reduction in IOP decreases the risk of glaucoma progression by 10% in patients with early POAG, normal-tension glaucoma, and exfoliation glaucoma.[10] Compared to age-matched premenopausal women, postmenopausal women exhibited 1.5–2 mmHg greater IOP.[11,12] Small randomized trials and observational studies have shown that IOP decreased by 1–5 mmHg following treatment with hormone therapy in postmenopausal women with and without POAG.[12-22] Based on these findings and those of the EMGT, the observed IOP reduction, though small in magnitude, may be clinically significant in postmenopausal women with glaucoma.

Notably, prior studies also suggest that medroxyprogesterone acetate can minimize the beneficial effects of estrogen in the central nervous system.[23] Similarly, a large claims database of 152,163 enrollees aged >50 years showed that each additional month of

hormone therapy containing estrogen, but not a combination of estrogen and progesterone, was associated with a 0.4% reduced risk for POAG.[24]

To date, however, there has been no large, randomized, placebo-controlled trial with longitudinal follow-up designed to assess the effect of postmenopausal hormone therapy on IOP. To examine the effect of estrogen and estrogen plus progestin on IOP in the context of a large randomized clinical trial, we performed a secondary data analysis of IOP outcomes on data collected during the Women's Health Initiative Sight Exam (WHISE) study, an ancillary study of the Women's Health Initiative (WHI) randomized hormone trial that focused on age-related macular degeneration (AMD).

IOP was measured 5 years after baseline in two groups: 1) women with prior hysterectomy who were randomized to receive either conjugated equine estrogens (estrogen-alone trial) or placebo; and 2) women with a uterus who were randomized to receive conjugated equine estrogens combined with medroxyprogesterone acetate (estrogen-plus-progestin trial) or placebo. Based on previous findings, we hypothesized that women who had been randomized to receive conjugated equine estrogens would have lower IOP compared to women randomized to receive placebo. In contrast, we hypothesized that this association would not be observed in women randomized to receive conjugated equine estrogens and medroxyprogesterone acetate.

METHODS

Study design and population

The WHI (the parent study) was a 15-year research program initiated in 1991 by the National Institutes of Health consisting of a set of clinical trials and an observational study, which together involved 161,808 generally healthy postmenopausal women aged 50–79 years.[25,26] The clinical trials were designed to test the effects of hormone therapy, diet modification, and calcium and vitamin D supplementation on the incidence of heart disease, fractures, and breast and colorectal cancer. The hormone trial was stratified by hysterectomy status: the estrogen-plus-progestin study of women with a uterus and the estrogen-alone study of women without a uterus (i.e., those who had undergone hysterectomy). Of note, women with a uterus received progestin in combination with estrogen, a practice known to prevent endometrial cancer. Within each stratum, the women were randomly assigned to either a hormone or a placebo arm. The WHI trial has been registered at clinicaltrials.gov (identifier is NCT00000611).

The present study was a secondary analysis of IOP data from the WHISE, an ancillary study to the WHI randomized hormone therapy trial.[27] The WHISE study was conducted between 2000 and 2002 to examine the association between prior randomization to hormone therapy and AMD, where early or late AMD was assessed based on fundus photography in women 65 years and older an average of 5 years after randomization to hormone therapy or placebo.[28] WHISE recruited 4,347 women who underwent fundus photography of at least one eye at 21 WHI clinics. A flow diagram of the WHISE study is presented in Figure 1. Overall, the WHISE study reached 96.6% of its enrollment goal of 4,500 eligible and consenting participants (15.9% of the WHI hormone trial, n = 27,347) before termination of

the estrogen plus progestin study arm due to an adverse risk-benefit profile after an average follow-up period of 5.2 years.[29] The WHISE protocol was approved by Institutional Review Boards at each clinic site, and all participants provided written informed consent to participate. The Institutional Review Board at the University of Illinois at Chicago waived the need for approval of this secondary data analysis. The study was conducted in accordance with HIPAA regulations and adhered to the tenets of the Declaration of Helsinki.

Participant randomization to hormone therapy and adherence

Randomized treatment assignment was performed in the WHI hormone trial.[28] In the WHI, the women who had previously undergone hysterectomy were randomized to receive either conjugated equine estrogens (0.625 mg/day) or placebo; women with a uterus were randomized to receive oral conjugated equine estrogens and medroxyprogesterone acetate (0.625 mg/day + 2.5 mg/day) or placebo. As reported previously, there were no differences within each randomized trial with respect to patient age, age at menarche or menopause, education, race, annual income, smoking, alcohol consumption, history of hormone use, or the incidence of diabetes mellitus, stroke, myocardial infarction, peripheral artery disease, glaucoma, and cataracts in the WHI hormone trial.[28] For the WHISE study, women aged 65 years and older were recruited from the WHI hormone trial. Participants in the WHISE study were recruited an average of 5.1 (median, 5.0; range, 1–10) years after randomization to the WHI hormone trial.

In the WHI hormone trial, non-adherence to treatment was defined by the parent trial as any of the following: discontinuation of study medications, crossover to the placebo or other hormone group, or <80% adherence based on pill counts from a six-month supply at any time during follow-up. In the estrogen-alone trial, 53.8% had discontinued study medications by the end of study,[29] and the rates were equal in the treatment and placebo groups. In the estrogen-plus-progestin trial, 42% of the active estrogen-plus-progestin group and 38% of the placebo group had discontinued treatment by the end of study.[30] Accordingly, the WHISE study followed the definition of non-adherence for consistency.[28]

Eye health and general health assessment

At the WHISE clinics, participants completed a questionnaire on ocular conditions, including cataracts, glaucoma, early and late AMD, retinal detachment, trauma, previous treatment or ocular surgery, and other eye conditions.[28] During each visit to the WHI or WHISE clinics, participants completed a questionnaire assessing medical history, medical conditions, and lifestyle factors.

Ophthalmic assessment

Eye examinations were performed at the time of WHISE study recruitment. The examination included visual acuity testing with refraction, anterior segment examination, bilateral standard stereoscopic fundus photography, and IOP measurements. After pupillary dilation to at least 6 mm, the photographer took 30° or 35° stereoscopic fundus photographs. Fundus photography followed a specified protocol that was adapted for the study by photography consultants at the University of Wisconsin.[31] A single IOP measurement was performed by a Goldmann applanation tonometer in each eye if the participant reported no

known allergy to anesthetic eye drops or fluorescein. If the IOP reading was >30 mmHg in either eye, the participant was advised to seek further evaluation by her ophthalmologist. As a double-masked trial, examiners and participants did not know the patient's treatment assignment.

Selection criteria and statistical analysis

The final analysis in the current study included all WHISE participants who had IOP data for both eyes. Demographic and clinical characteristics were compared between participants in the treatment and placebo groups. T-tests were used for continuous variables, and chi-squared tests were used for categorical variables. Multiple linear regression models were conducted to determine the effect of estrogen alone or estrogen plus progestin on IOP compared to that for placebo treatment. Covariates included age, duration of hormone therapy, race, body mass index (BMI), lens status (pseudophakia yes/no, excluding aphakia), adherence, and history of any of the following: diabetes mellitus, hypertension, smoking (never, past, current), and alcohol use (>12 drinks ever). Data from the right and left eyes were analyzed and reported separately. For the primary outcome, an intention-to-treat analysis was performed, and the model included all women with available IOP data (Model 1). To minimize the potential effect of glaucoma treatment on IOP, we excluded women who reported glaucoma or glaucoma treatment (Model 2). For the secondary outcome, analyses adjusted for adherence were performed for all women (Model 3) and for all women except those with self-reported glaucoma or glaucoma treatment (Model 4). All analyses were conducted using SAS statistical software, version 9.0 (SAS Institute Inc., Cary, NC). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Study sample

All 4,347 women enrolled in the original WHISE study had IOP data; 1,668 were enrolled in the estrogen-alone trial and 2,679 were enrolled in the estrogen-plus-progestin trial (Figure 1). In the estrogen-alone trial, 808 women (48.4%) received active treatment and 860 women (51.6%) received the placebo. In the estrogen-plus-progestin trial, 1,397 women (52.1%) received active treatment and 1,282 women (47.9%) received the placebo. Demographic and clinical characteristics of the participants included in the WHISE study are presented in Table 1. In the estrogen-alone trial, the demographic and clinical characteristics of the treatment vs. placebo group were balanced, except that the rate of cigarette smokers was higher in the treatment group. Likewise, in the estrogen-plus-progestin trial, the demographic and clinical characteristics of the treatment versus placebo group were balanced, except that the duration of hormone therapy was higher in the treatment group, whereas the rates of adherence and of lens implants were lower in the treatment group.

Effects of hormone therapy on IOP

IOP was measured approximately 5 years after randomization to treatment. In the estrogen-alone trial, for right eyes, the IOP mean ± standard deviation (SD) was 15.4 ± 3.2 mmHg in the active treatment group and 15.8 ± 3.3 mmHg in the placebo group. For left eyes, the mean IOP ± SD was 15.3 ± 3.1 mmHg in the active treatment group and 15.9 ± 3.2 mmHg

in the placebo group (Table 1). In the estrogen-plus-progestin trial, the mean IOP ± SD of the right eye was 15.6 ± 3 mmHg in the treatment group and 15.7 ± 3.1 mmHg in the placebo group; the mean IOP ± SD of the left eye was 15.7 ± 3.0 mmHg in the treatment group and 15.7 ± 3.0 in the placebo group (Table 1).

In Table 2, the final adjusted analysis included women with available covariates. In the primary models (1 and 3), the final analysis included 4,105 women for the right eyes and 4,098 women for the left eyes. The secondary models (2 and 4) excluded 328 women who reported glaucoma or history of glaucoma treatment at the WHI baseline examination and/or the WHISE examination. The 328 women who were excluded consisted of 71 women in the estrogen-alone arm and 65 in the placebo arm of the estrogen-alone trial and 98 women in the estrogen-plus-progestin arm and 94 in the placebo arm of the estrogen-plus-progestin trial. In the secondary models (models 2 and 4), the final analysis included 3,798 women for the right eyes and 3,7985 women for the left eyes. After adjusting for covariates, the intention-to-treat analysis (Model 1) showed that estrogen-alone treatment was associated with a 0.5-mmHg lower IOP in the right eye (95% confidence interval (CI); −0.8, −0.1, $p = 0.005$) and a 0.6 mmHg lower IOP in the left eye (95% CI; −0.9, −0.3, $p < 0.001$) when compared to the IOP in the placebo group (Table 2). In the estrogen-plus-progestin trial, there was no significant difference in IOP between the active treatment and placebo groups ($p = 0.30$ in the right eye and $p = 0.43$ in the left eye, Table 2). Similar findings were observed in Model 2, which excluded 328 women with either self-reported glaucoma or glaucoma treatment at the WHI baseline examination and/or the WHISE examinations. The IOP was significantly lower in the estrogen-alone treatment group compared to that in the placebo group for both the right and left eyes, and there was no significant effect of estrogen-plus-progestin treatment on IOP (Table 2). Compared to the IOP in the placebo group, estrogen-alone treatment was associated with a 0.5-mmHg lower IOP in the right eye (95% CI; −0.8, −0.2, $p = 0.005$) and a 0.6-mmHg lower IOP in the left eye (95% CI; −0.9, −0.3, $p < 0.001$) (Table 2). In the estrogen-plus-progestin trial, there was no significant difference in IOP between the active treatment and placebo groups ($p = 0.54$ in the right eye and $p = 0.62$ in the left eye, Table 2). Similar findings were observed in the adherence-adjusted analyses (Models 3 and 4, Table 2).

DISCUSSION

In this study, postmenopausal women aged 65 years and older with a history of hysterectomy who were randomized to receive estrogen-alone treatment had slightly but significantly lower IOP than did women randomized to receive placebo 5 years after initiation of estrogen treatment. In contrast, treatment with estrogen plus progestin had no effect on IOP. Similar findings were obtained after excluding women who reported glaucoma or who had undergone previous glaucoma treatment.

The present findings are consistent with findings from five interventional studies showing that hormone therapy significantly reduced IOP by 1 to 5 mmHg.[12,15,19,22,32] The sample sizes in those studies ranged from 15 to 50 women. Of the five interventional studies, none except for one small trial ($n = 45$)[32] was placebo-controlled. In addition, the route of hormone therapy administration varied between oral and transdermal forms, the formula was

either estrogen alone or a combination of estrogen and progesterone, and the treatment duration ranged from 3 to 12 months. In four observational studies of hormone therapy and IOP in women without glaucoma, only the largest study[16] found an effect of hormone therapy on IOP.[16-18,20] Specifically, among 263 non-glaucomatous women with an average age of 53 years, IOP was 1.3 mmHg lower for current hormone therapy users than for non-users.[16] Table 3 summarizes findings from previous studies.

The role of progestogens in reducing IOP is unclear. Progestogens, particularly medroxyprogesterone acetate, may minimize the effects of estrogen on IOP. This observation is consistent with the findings from a non-randomized active-controlled trial showing a significant IOP reduction in women treated with transdermal estradiol but not in women treated with oral conjugated equine estrogens and medroxyprogesterone acetate.[22] Similarly, prior studies suggest that progestogens antagonize the beneficial effects of estrogens on cognitive function and POAG.[23, 24] In contrast, other non-placebo-controlled clinical trials showed that a combination of estrogen and progesterone significantly decreased IOP.[12,15,19] Of note, two of the three interventional trials[12,15,19] that showed an IOP-reducing effect used a higher dose of estrogen and progesterone than that used in our trial and in the transdermal estradiol trial.[22]

The IOP-reducing effect of hormone therapy is likely driven by estrogen. Estrogen can influence IOP via multiple mechanisms, including by reducing aqueous humor production, improving outflow facility, and reducing venous pressure through estrogen receptors in the ciliary epithelium, trabecular meshwork, and blood vessels.[12, 13] This explanation is supported by an early randomized, placebo-controlled clinical trial in 45 healthy women who had previously undergone hysterectomy and with no glaucoma on clinical examination where estrogen (mestranol) treatment for 6 months significantly decreased IOP and improved outflow facility, whereas the addition of progestin ethynodiol diacetate did not lead to a significant change in the magnitude of those outcomes.[32]

Natural fluctuations in sex steroid hormones have also been shown to influence IOP. Compared to age-matched pre-menopausal women, postmenopausal women have been reported to have a 1.5–2.0-mmHg higher IOP.[12,16] IOP in postmenopausal women correlates with serum testosterone levels, but not with serum estrogen or follicular stimulating hormone levels.[17,33] Although the effects of the menstrual cycle on IOP are variable,[34-36] During pregnancy IOP decreases by 10% and is lowest during the third trimester, when the levels of estrogen and progesterone are particularly high.[36,37] This pregnancy-related change in IOP is notable given that the central corneal thickness (CCT), which can falsely elevate or reduce IOP depending on the level of corneal hydration, also increases during pregnancy.[38] It has been postulated that the pregnancy-related reduction in IOP results from increased outflow facility and decreased venous pressure.[35-37,39,40]

Consistent with the timing hypothesis of hormone therapy on cognitive and cardiovascular function,[23,41] one factor that might influence the effect of hormone therapy on IOP is the point at which treatment is initiated. There might be a greater IOP-reducing effect of hormone therapy in younger postmenopausal women than in older postmenopausal women. Consistent with this hypothesis, a study of 263 women with an average age of 53 years

showed a significant effect of hormone therapy on IOP, whereas a study of 214 women with an average age of 66 years showed no effect.[16,18] Similarly, in our study, even with a very large sample (n = 4347), there was only a 0.5–0.6-mmHg reduction in IOP among older women (average age, 72 years). The magnitude of the IOP reduction in our study may reflect the declining number of estrogen receptors in ocular tissues with aging,[13] potentially less compliant aged tissue (trabecular meshwork and vessels), or a decreased responsiveness to hormone therapy. In light of this observation, the timing of hormone therapy (based on the timing theory) may be important for maximizing the IOP-reducing benefits of hormone therapy in postmenopausal women.

Our study has several strengths. It is the first and largest investigation of the effects of hormone therapy on IOP and exposure to hormone therapy was in a randomized, double-masked, placebo-controlled trial. Treatment groups were similar with respect to baseline medical conditions and potential IOP-associated factors, and the duration of hormone therapy use was appreciably long (a median of 5 years; range, 1–10 years).

The study has several notable limitations. First, results derived from a secondary analysis of data from a randomized trial that was not originally designed for IOP outcomes. Hence, IOP data prior to the initiation of hormone therapy were not available. The WHISE study was designed to assess early and late AMD in participants an average of 5 years after randomization in the main WHI trial.[28] There was no pre-randomization assessment of AMD in the WHISE study, or in this study.[28] In our analysis, it was assumed based on the large sample size, but not demonstrated objectively, that treatment groups were matched for IOP at baseline. In addition, our results were based on a single measurement of IOP, and the analysis did not adjust for the time of day at which the IOP was measured. Furthermore, information on CCT, an ocular parameter that can affect IOP measurements, was not available, although a previous prospective non-placebo-controlled clinical trial showed that CCT did not change after the initiation of hormone therapy.[19] Second, while our analysis was adjusted for available covariates that might affect the IOP, possible confounders that were not measured in the study, such as beta-blocker use and coffee consumption, were likewise not included in our statistical models. Third, our analysis focused on older postmenopausal women. Recruitment to the WHISE study was limited to postmenopausal women aged 65 years and older, and our findings cannot be generalized to younger women. Further investigation of the timing hypothesis in younger women is warranted. It is worthwhile to note that women with no uterus in the estrogen-alone trial entered menopause at a much younger age (due to hysterectomy) compared to those with an intact uterus (for whom menopause occurred naturally) in the estrogen-plus-progestin trial (43 years vs. 50 years, respectively). Finally, although adherence to treatment in the WHISE study was similar to that in the parent study (the WHI), we were unable to analyze our data for adherents alone (those with >80% compliance based on pill counts) because of a lack of statistical power. A sample size of 566 for each treatment group would be needed to detect a 0.5-mmHg IOP difference given the standard deviation of 3 mmHg, but the estrogen arm in this study had 288 adherents in the treated group and 352 adherents in the placebo group in the estrogen-alone trial. Hence, our analysis was adjusted for adherence (Models 3 and 4), and we found that the results for the adherence-adjusted analysis were similar to those for the intention-to-treat analysis (Models 1 and 2).

The effects of hormone therapy on ophthalmologic outcomes should be considered in the context of the broader effects of hormone therapy on general health. The most recent long-term follow-up data from the WHI do not support the use of either estrogen alone or estrogen plus progestin for chronic disease prevention.[42] Neither regimen affected the overall all-cause mortality, but both regimens were associated with increased risks for stroke, venous thrombosis, gall stones, and urinary incontinence. The WHI study group concluded that the risks of estrogen plus progestin outweighed the benefits, irrespective of a woman's age. However, the risk-to-benefit ratio of estrogen-alone treatment was more balanced. Estrogen alone in younger women (aged 50–59 years) had more favorable trends for all-cause mortality, myocardial infarction, and the global index, including stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture, and death (nominal $p < 0.05$ for trends by age).

In conclusion, our findings suggest that treatment with estrogen alone, but not estrogen plus progestin, leads to small but statistically significant declines in IOP in postmenopausal women aged 65 years and older. The clinical significance of this observed small-magnitude IOP decrease (0.5 mmHg IOP) remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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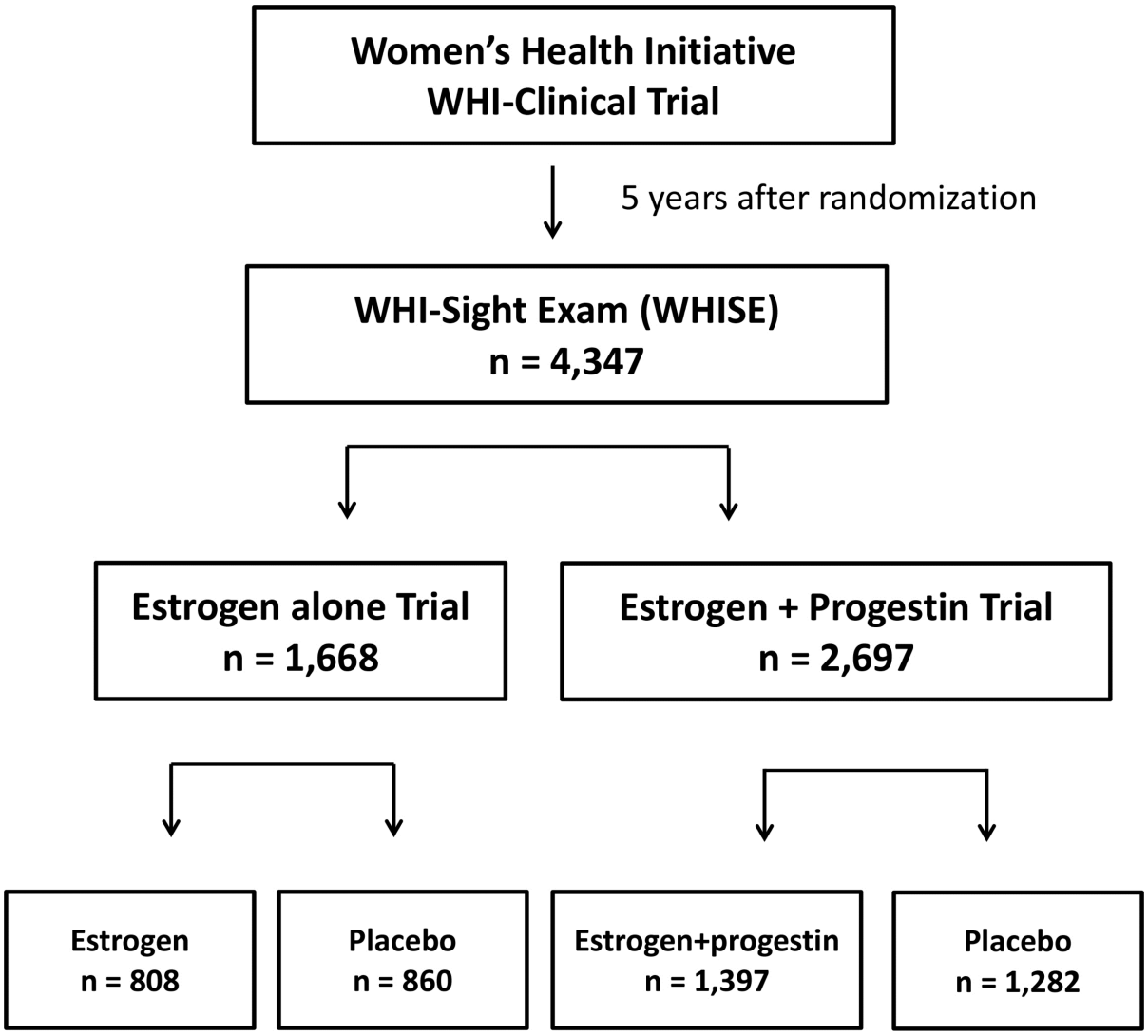

Figure 1.
A flow chart for the Women's Health Initiative-Sight Exam

Table 1

Demographic and clinical characteristics of participants in the Women's Health Initiative Sight Exam Study

Variables	Estrogen-alone (n = 1,668)			Estrogen-plus-progestin (n = 2,679)		
	Estrogen (n = 808)	Placebo (n = 860)	p-value	Estrogen+ Progestin (n = 1,397)	Placebo (n = 1,282)	p-value
Age at eye exam (years; mean ± SD)	72.0 ± 5	72.2 ± 5	0.23	71.6 ± 5	71.7 ± 5	0.46
Duration of hormone use (years; mean ± SD)	5.0 ± 1	5.1 ± 1	0.34	5.1 ± 1	5.0 ± 1	0.009
Race (%)						
Caucasian	84.8%	83.5%	0.06	90.1%	91.9%	0.67
African-American	10.3%	12.1%		5.6%	4.4%	
Hispanic	3.5%	2.1%		2.7%	2.3%	
Diabetes mellitus,[a] N (%)	108 (13.4)	129 (15.0)	0.34	133 (9.5)	113 (8.8)	0.53
Hypertension,[b] N (%)	313 (39.4)	334 (39.2)	0.94	460 (33.0)	420 (33.1)	0.97
Alcohol consumption,[c] N (%)	697 (86.6)	736 (86.1)	0.77	1,248 (89.7)	1,119 (88.1)	0.20
Cigarette smoking,[d] N (%)						
Never smoked	479 (60.0)	454 (53.5)	0.03	741 (53.6)	651 (51.6)	0.53
Past smoker	270 (33.8)	330 (38.9)		542 (39.2)	522 (41.4)	
Current smoker	50 (6.3)	65 (7.7)		99 (7.16)	89 (7.05)	
BMI (kg/m^2; mean ± SD)	29.6 ± 5.9	29.7 ± 5.7	0.71	28.5 ± 5.6	28.6 ± 6.0	0.58
Self-reported glaucoma,[e] N (%)	71 (8.8)	65 (7.6)	0.36	98 (7.0)	94 (7.3)	0.75
Adherence to intervention,[f] N (%)	298 (36.9)	352 (40.9)	0.09	645 (46.2)	736 (57.4)	<0.001
IOP (mean ± SD, in mmHg)						
Right eye	15.4 ± 3.2	15.8 ± 3.3	0.009	15.6 ± 3.0	15.7 ± 3.1	0.34
Left eye	15.3 ± 3.1	15.9 ± 3.2	<0.001	15.7 ± 3.0	15.7 ± 3.0	0.54
Pseudophakia[g] N (%)						
Right eye	150 (18.8%)	147 (17.3%)	0.45	190 (13.9%)	210 (16.7%)	0.05
Left eye	143 (17.8%)	136 (16.0%)	0.33	187 (13.7%)	209 (16.6%)	0.04

BMI, body mass index; IOP, intraocular pressure; SD, standard deviation.

p-values were based on comparisons between treatment vs. placebo groups (t-tests for continuous variables and chi-squared tests for categorical variables).

[a]The presence of diabetes mellitus was self-reported from the Women's Health Initiative (WHI) questionnaire and/or the Women's Health Initiative Sight Exam (WHISE) questionnaire.

[b]Hypertension was self-reported from the WHI questionnaire.

[c]Alcohol consumption, determined from the WHI questionnaire, was evaluated using a yes or no response to the following question: “have drunk 12 alcoholic beverages ever”.

[d]Smoking status was determined from the WHI categorization.

[e]Self-reported glaucoma or glaucoma treatment was determined from the WHI baseline examination or the WHISE visits.

[f]Non-adherence was defined as any of the following: discontinued use of study medications, converted to the placebo group or treatment with another, or <80% compliance based on pill counts at any time during follow-up.

[g]Pseudophakia (yes/no).

Table 2

The effect of active hormone therapy compared to placebo on intraocular pressure from linear regression models in the Women's Health Initiative Sight Exam study

Trials	Estrogen-alone		Estrogen-plus-progestin	
	Right Eye	Left Eye	Right Eye	Left Eye
Primary outcome: Intention-to-treat analysis				
Model 1: all women				
All	N = 1,584	N = 1,582	N = 2,521	N = 2,516
β (95% CI)	−0.46 (−0.78,−0.14)	−0.60 (−0.91, −0.29)	−0.13 (−0.37, 0.11)	−0.09 (−0.32, 0.14)
p-value[a]	p = 0.005	p < 0.001	p = 0.30	p = 0.43
Model 2: excluded women with self-reported glaucoma or glaucoma treatment[b]				
All	N = 1,454	N = 1,453	N = 2,344	N = 2,342
β (95% CI)	−0.47 (−0.80,−0.15)	−0.57 (−0.89, −0.25)	−0.08 (−0.32,0.17)	−0.06 (−0.30,0.18)
p-value[a]	p = 0.005	p < 0.001	p = 0.54	p = 0.62
Secondary outcome: Adherence-adjusted analysis				
Model 3: all women				
All	N = 1,584	N = 1,582	N = 2,521	N = 2,516
β (95% CI)	−0.45 (−0.77,−0.13)	−0.60 (−0.91, −0.28)	−0.14 (−0.38, 0.10)	−0.11 (−0.35, 0.13)
p-value[a]	p = 0.006	p < 0.001	p = 0.26	p = 0.36
Model 4: excluded women with self-reported glaucoma or glaucoma treatment[b]				
All	N = 1,454	N = 1,453	N = 2,344	N = 2,342
β (95% CI)	−0.46 (−0.79,−0.13)	−0.57 (−0.89, −0.24)	−0.08 (−0.33,0.16)	−0.07 (−0.31,0.17)
p-value[a]	p = 0.006	p < 0.001	p = 0.50	p = 0.57

CI, confidence interval; β, coefficient represents a comparison of IOP in the treatment group relative to that in the placebo group (negative values indicate that the treatment group had a lower IOP compared to that in the placebo group).

[a]Adjusted for age at eye exam, duration of hormone therapy, race, body mass index, treatment adherence, lens status (pseudophakia, yes/no, excluding aphakia), and history of diabetes mellitus, hypertension, smoking, or alcohol use.

[b]Reported glaucoma or glaucoma treatment at the Women's Health Initiative baseline examination or the Women's Health Initiative Sight Exam study visits.

Table 3

Summary of previous studies investigating the effects of hormone therapy on intraocular pressure

Study	Average Age	Population Demographics and Sample Size	Hormone(s) Administered	Main Findings
Interventional studies				
Treister, 1970	37–55 yrs (average age not available)	45 non-glaucomatous women	Mestranol 0.1 mg (n = 15) vs. mestranol and progestin ethynodiol diacetate 1 mg (n = 15) vs. placebo (n = 15)	Significantly lower IOP (2 mmHg) at 6 mos in mestranol group. Combining ethynodiol had no additional effect on IOP.
Sator, 1997	56 yrs	25 non-glaucomatous women	2 mg oral estradiol valerate + 10 mg medroxyprogesterone acetate	Significantly lower IOP (1.3–2.2 mmHg) after hormone therapy for 12 wks
Affinito, 2003	53 yrs	50 non-glaucomatous women; 25 women with hormone therapy vs. 25 without hormone therapy (randomized, non-placebo controlled)	Transdermal 17β estradiol (50 μg/day) + medroxyprogesterone acetate (10 mg/day)	Significantly lower IOP (2 mmHg) after hormone therapy at 12 wks and 24 wks No significant change in CCT
Altintas, 2004	47 yrs	15 non-glaucomatous women	0.625 mg of oral conjugated equine estrogens + 2.5 mg of medroxyprogesterone acetate (n = 17) or 2 mg of estradiol hemihydrate (n = 3); 5 women discontinued hormone therapy due to undesirable side effects	Significantly lower IOP (3–4 mmHg) after hormone therapy at 24 wks
Uncu, 2006	48 yrs (Group 1) 52 yrs (Group 2) 51 yrs (Group 3)	30 women Glaucoma status not specified	Group 1 (n = 19): 0.625 mg of oral conjugated equine estrogens + 2.5 mg medroxyprogesterone Group 2 (n = 6): oral tibolone Group 3 (n = 5): 3.9 mg/12 cm^2 of transdermal estrogen	Groups 1 and 2: No significant difference in IOP pre- and post-hormone therapy at 6 and 12 mos Group 3: Significantly lower IOP (2 mmHg) after hormone therapy at 12 mos
The present study	72 yrs in estrogen-alone trial vs. 72 in estrogen-plus-progestin trial	Final analysis included 4,105 of 4,347 women in the Women's Health Initiative Sight Exam (7% self-reported glaucoma) (randomized, active-controlled)	Estrogen-alone trial: 0.625 mg conjugated equine estrogens Estrogen-plus-progestin trial: 0.625 mg of conjugated equine estrogens + 2.5 mg of medroxyprogesterone acetate	Significantly lower IOP (0.5–0.6 mmHg) in estrogen-alone group compared to placebo after 5 yrs of hormone therapy No difference in IOP in the estrogen-plus-progestin group compared to placebo after 5 yrs
Observational studies				
Toker, 2003	53 yrs with hormone therapy vs. 52 yrs without hormone therapy	62 women; 30 with hormone therapy vs. 32 without hormone therapy Glaucoma status not specified	0.625 mg of oral conjugated equine estrogens + 2.5 mg of medroxyprogesterone acetate	No difference in IOP after mean of 4 yrs on hormone therapy Higher serum testosterone associated with higher IOP No significant association between IOP and serum estradiol (E_2) and follicle-stimulating hormone (FSH)
Abramov, 2005	66 yrs with hormone therapy vs. 67 yrs without	214 non-glaucomatous women 107 with hormone therapy vs. 107 without hormone therapy	Oral hormone therapy; 89% with combination of estrogen and progesterone and 11% with estrogen alone	No difference in IOP after mean duration of 7 yrs

Study	Average Age	Population Demographics and Sample Size	Hormone(s) Administered	Main Findings
	hormone therapy	15% of women had IOP higher than 21 mmHg		No associations between IOP and estrogen and progesterone exposure as measured by number of pregnancies, number of deliveries, duration of menstruation, or duration of hormone therapy and oral contraceptive use
Deschenes, 2010	57 yrs	64 women; 35 with hormone therapy vs. 29 without hormone therapy Glaucoma status not specified	Oral hormone therapy (mixed types, not specified)	No significant difference in IOP after mean duration of 8 yrs
Tint, 2010	53 yrs	263 non-glaucomatous women 96 with hormone therapy (33 estrogen alone and 58 a combination of estrogen and progesterone) vs.172 without hormone therapy	Oral hormone therapy (mixed types and duration, not specified)	Significantly lower IOP in hormone therapy group (1.4 mmHg) compared to non-hormone therapy group, adjusted for age, use of beta blockers, and time of IOP measurements No significant difference in IOP between estrogen-alone group vs. a combination of estrogen and progesterone group

CCT, central corneal thickness; IOP, intraocular pressure; mos, months; wks, weeks; Yrs, years.