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The Effects of Bazedoxifene, Conjugated Equine Estrogens, and a Tissue Selective Estrogen Complex (TSEC) Containing Both Bazedoxifene and Conjugated Equine Estrogens on Cerebral Artery Atherosclerosis of Postmenopausal Monkeys

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Abstract

Objective—To evaluate the effects of a new selective estrogen receptor modulator (bazedoxifene acetate, BZA) and a tissue specific estrogen complex (TSEC = BZA combined with conjugated equine estrogens (CEE), on atherosclerosis extent and severity of cerebral arteries.

Methods—Ninety-eight surgically postmenopausal monkeys (*Macaca fascicularis*) were fed a moderately atherogenic diet and then randomized to receive no treatment, or women's equivalent doses of BZA (20 mg/day), CEE (0.45 mg/day) or BZA+CEE. After an experimental period of 20 months (approximately equivalent to 5 years of patient experience), the extent and severity of atherosclerosis in the common carotid artery, carotid bifurcation, internal carotid artery and the basilar artery was determined. Lesion severity was determined using the American Heart Association grading system (AHA, grades 0-5).

Results—BZA had no consistent adverse effects on the extent or severity of atherosclerosis in the cerebral arteries and did not attenuate the beneficial effects of CEE on common carotid artery atherosclerosis severity. Although CEE had only modest beneficial effects on atherosclerosis extent of the carotid bifurcation, the severity of lesions and numbers of affected cases in the

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common carotid artery were reduced with CEE treatment. As reported previously, plasma lipid profiles did not differ among the treatment groups.

Conclusions—In this long-term (equivalent to 5 human patient years) nonhuman primate trial, BZA had no consistent adverse effect on cerebral artery atherosclerosis and did not attenuate the modest beneficial effect of CEE on common carotid arteries. Furthermore, CEE inhibited the development of complicated plaques in the common carotid artery

Keywords

Cerebral atherosclerosis; menopause; estrogens; SERMS; bazedoxifene

Introduction

Postmenopausal hormone therapy (HT) is considered generally to be the most effective treatment for menopausal symptoms and osteoporosis prevention. HT includes estrogen only therapy (ET) and, for women with a uterus, estrogen + a progestogen (EPT). Prior to the publication of results from the Women's Health Initiative (WHI) trial, the most commonly prescribed EPT in the United States was the combination of conjugated equine estrogens (CEE) and medroxyprogesterone (MPA)¹. However, results of studies of both women in WHI^{2,3} and monkeys^{4,5}, have provided evidence that the progestin component of EPT increases breast cancer risk and consequently, HT use has declined from ~ 21% in 2000 to ~ 8% in 2009⁶.

Studies indicating that progestins may attenuate potential beneficial effects of estrogens (CEE) on cardiovascular risk have also contributed to recent declines in hormone use. Using the surgically postmenopausal monkey model, Adams and co-workers⁷ found that MPA antagonized the inhibitory effects of CEE on coronary artery atherosclerosis. More recently, there have been reports on subgroups from the WHI trial suggesting reduced risk for coronary heart disease associated with CEE treatment in early postmenopausal women but not with CEE+MPA⁸⁻¹⁰. In contrast to the data on coronary arteries, we reported that there were no differences between the atherosclerosis inhibitory effects of CEE alone vs. CEE +MPA on plaque extent in the common and internal carotid artery¹¹. In the WHI trial, not only were there no cerebrovascular beneficial effects of either ET or EPT but a significant increase in ischemic stroke was observed in both the ET and EPT groups^{12,13}.

Because of the aforementioned concerns about potentially adverse effects of progestins, alternative HT approaches that protect the endometrium and breast, without adversely affecting the progression of atherosclerosis are being sought. Under current investigation, is the use of a selective estrogen receptor modulator (SERM) which binds to estrogen receptors alpha and beta with high affinity and acts either as an estrogen agonist or antagonist depending on the target tissue¹⁴. The new third-generation SERM, bazedoxifene acetate (BZA) has shown considerable promise in the treatment osteoporosis when given alone and in combination with CEE (often referred to as a TSEC); it has become an effective treatment for menopausal symptoms and prevention of osteoporosis¹⁵⁻¹⁷.

In anticipation of the possible widespread use of BZA alone for the prevention and treatment of osteoporosis and the combination of BZA and CEE (TSEC) for the treatment of menopausal symptoms and osteoporosis, we have conducted a randomized, parallel-arm trial with surgically postmenopausal cynomolgus monkeys (*Macaca fascicularis*) to investigate the effects of these interventions on the breast, uterus and cardiovascular system. We have reported separately that BZA was an estrogen antagonist capable of abrogating the effects of CEE on the monkey breast¹⁸, and endometrium¹⁹. We have also reported that BZA had no adverse effects on coronary and iliac artery atherosclerosis when given alone, but did

attenuate the atheroprotective effects of CEE when given in combination²⁰. In this communication we report on the effect of these interventions on the extent and severity of cerebral artery atherosclerosis.

Methods

Details about the animals, diets they were fed and methods used to evaluate plasma lipid and lipoprotein concentrations have been published previously¹⁹. Briefly, 98 surgically postmenopausal cynomolgus monkeys (*Macaca fascicularis*) were given either no treatment (control), conjugated equine estrogens (CEE) alone at a dose comparable to a woman's daily dose of 0.45 mg/day, bazedoxifene acetate (BZA) at a woman's equivalent dose of 20 mg/day, or a combination of CEE and BZA. Monkeys were fed a diet formulated to model the high cholesterol (0.29 mg/Cal) and high fat (35% of calories from fat) diets typically consumed by postmenopausal women in the United States. All hormone treatments were administered in the diet once daily. All procedures involving animals were conducted in compliance with state and federal laws, standards of the US Department of Health and Human Services and guidelines established by the Wake Forest University Animal Care and Use Committee.

Necropsy Procedure

After 20 months of postmenopausal treatment, the monkeys were euthanized using sodium pentobarbital (100 mg/kg, intravenously), a method consistent with the recommendations of the panel on euthanasia of the American Veterinary Medical Association. The circulatory system was flushed with lactated Ringers and the left and right common carotid arteries, carotid bifurcations and internal carotid arteries, were dissected free and removed. The cranium was opened and a block of tissue containing the basilar artery was collected. All arteries were processed for histopathologic evaluation, except for the right common carotid artery, which was frozen for future studies.

Left Common Carotid Artery (LCC)

The left common carotid artery was opened longitudinally, laid flat on cardboard, and immersion fixed in 10% neutral buffered formalin. Three segments of 3 mm in length of the proximal, middle and distal portion of the artery were embedded in three separate paraffin blocks. Five- μ m sections were made and stained with Verhoeff-van Gieson's stain. Each section was captured digitally using a Nikon DS Fi1 camera mounted on an Olympus BH-2 microscope equipped with a mechanical stage. Morphometric measurements were made using Image-Pro Plus version 5.1 imaging software (Media Cybernetics, Inc., Bethesda, MD). Measurements were made blind to treatment by a single technician with more than 20 years of experience and were re-evaluated by one of us (T.B.Clarkson).

Carotid bifurcations and internal carotid arteries

The left and right carotid artery bifurcations and internal carotid arteries were immersion fixed in 10% neutral buffered formalin. One segment was collected from each artery, embedded in a paraffin block, and 5- μ m sections were stained with Verhoeff-van Gieson's stain.

Basilar arteries

The basilar arteries were collected *en bloc* with a portion of the brain and immersion fixed in 4% paraformaldehyde for 24 hours and then transferred to 70% ethanol until processing. Two segments of the artery were collected, embedded in two separate paraffin blocks, sectioned and stained with Verhoeff-van Gieson's stain (as described for previous arteries).

Plaque extent and AHA Severity Grades

Plaque extent was expressed as the cross-sectional intimal area (IA, mm²). For arteries divided in multiple sections, an average of the intimal areas (mean IA) was reported as previously described¹¹. Because plaque complications occur independently from plaque extent, a well-established system according to American Heart Association guidelines for assigning a severity grade on a 0 to V scale was used. Arteries with no lesion were given a score of 0. Intimal lesions that consisted of smooth muscle adaptive thickening were given a grade of I. If the smooth muscle adaptive thickening contained macrophage foam cells, a grade of II was given. For those cases in which there had been necrosis of macrophages and the accumulation of small pools of extracellular lipid, a grade of III was recorded. The grade of IV was recorded for those lesions in which the small pools of extracellular lipid had coalesced into a core of extracellular lipid. The most complicated plaques observed in this study were given the grade of V, based on the core of extracellular lipid being separated from the lumen by a definitive fibromuscular cap. AHA grades were determined by a single observer and corroborated by an experienced observer (T.B.C.)

Statistical Analysis

The main outcome variables for this study were plaque extent (IA, intimal area mm²) and frequency of plaque severity grades (AHA grades 0-V). For arteries in which more than one section of tissue was collected (LCC = 3 blocks and basilar artery = 2 blocks), the extent of artery atherosclerosis was evaluated from each section and the average plaque extent (mm²) across sections was calculated. There were no significant differences in plaque extent among sections within each artery ($p < 0.05$). Intimal area (IA) measurements of LCC, carotid bifurcations and internal carotids were square root transformed to improve normality of the data. One-way analysis of variance (ANOVA) was used to compare IA (mm²) between the referent control (CTL) and the three treatment groups. Data were back-transformed and are presented as mean $\pm$ SEM. Non parametric analyses (Kruskal-Wallis) of IA were also done using non-transformed data and the results did not differ from the parametric analyses.

Frequency of AHA grades was evaluated using Fisher's exact test, comparing plaque severity for each treatment group to CTL in terms of the distribution of unaffected (0,I) vs. affected (II) lesions. The p-values were adjusted for multiple comparisons using a Bonferroni correction (three comparisons, corresponding to each treatment group vs. CTL). Statistical significance was set at a p-value < 0.05 . Analyses were performed using JMP-9® (SAS Institute, Cary, NC).

Results

Plasma Lipid and Lipoprotein Concentrations

The mean plasma lipid and lipoprotein concentrations for the control and treatment groups over the experimental period were reported previously²⁰ and are presented in Table 1. There were no significant differences among the groups.

Common Carotid Artery Atherosclerosis Extent and Severity

The extent (plaque sizes) of atherosclerotic plaque in the common carotid artery for each treatment group is presented in Figure 1 (CTL: 0.17 ± 0.05 mm²; CEE: 0.07 ± 0.03 mm²; BZA: 0.31 ± 0.07 mm²; BZA+CEE: 0.13 ± 0.04 mm²). Although the overall p-value was significant ($p = 0.02$), none of the treatment groups were significantly different from control. The number of monkeys unaffected with atherosclerosis or having had either fatty streaks or complicated plaques (plaque severity) is presented in Table 2. Unlike the finding for plaque sizes, the monkeys treated with CEE had significantly more unaffected cases (11/24, $p = 0.002$), whereas the BZA treated group was indistinguishable from the control group

(BZA – 1/24 unaffected vs. CTL – 1/23, $p=1.000$) and the beneficial effect of the CEE treatment on plaque severity appeared to be modestly attenuated by the addition of BZA (CEE+BZA – 8/27 vs. CTL -1/23 unaffected cases, $p=0.028$).

Carotid Artery Bifurcation Atherosclerosis Extent and Severity

The extent (plaque sizes) of the atherosclerotic plaques in the left and right carotid bifurcations are presented in Figure 2 A and B. A significant difference was observed among the groups for both the Left (overall $p = 0.002$) and the Right (overall $p = 0.04$) arteries. The plaque sizes of the CEE treated monkeys were smaller than the control monkeys in the left carotid bifurcation (CTL: $0.81 \pm 0.12 \text{ mm}^2$ vs. CEE: $0.46 \pm 0.09 \text{ mm}^2$; $p=0.027$). However, after adjustment for multiple comparisons, the results were not significant (adjusted p -value for CEE vs. CTL, Left = 0.08). The plaque sizes in both the left and right bifurcations of the BZA and BZA+CEE groups were not different from the control group (Left, CTL: $0.81 \pm 0.12 \text{ mm}^2$ vs. BZA: $1.11 \pm 0.14 \text{ mm}^2$, $p=0.122$; CTL: $0.81 \pm 0.12 \text{ mm}^2$ vs. BZA+CEE: $0.68 \pm 0.10 \text{ mm}^2$, $p=0.444$ and Right: CTL: $0.93 \pm 0.14 \text{ mm}^2$ vs. BZA: $1.14 \pm 0.15 \text{ mm}^2$, $p=0.322$; CTL: $0.93 \pm 0.14 \text{ mm}^2$ vs. BZA+CEE: $0.94 \pm 0.13 \text{ mm}^2$). The distributions of lesion types at the carotid bifurcation are summarized in Table 3. CEE treatment resulted in more unaffected cases in the right bifurcation (CEE – 4/24 vs. CTL – 0/23 unaffected cases) but the finding did not reach significance.

Internal Carotid Artery Atherosclerosis Extent and Severity

The extent (plaque sizes) of the atherosclerotic plaques in the left and right internal carotid arteries are presented in Figure 3 A and B. A significant difference was observed among the groups for both the Left (overall $p = 0.004$) and the Right (overall $p = 0.02$) arteries. However, CEE treatment had no significant effect in either artery when compared to control (Left: CTL: $0.19 \pm 0.06 \text{ mm}^2$ vs. CEE: $0.08 \pm 0.03 \text{ mm}^2$, $p=0.136$; Right: CTL: $0.21 \pm 0.07 \text{ mm}^2$ vs. CEE: $0.03 \pm 0.04 \text{ mm}^2$, $p = 0.079$). In BZA treated monkeys, a small increase in mean plaque size was observed in the left internal carotid, but not the right internal carotid artery (Left: CTL: $0.19 \pm 0.06 \text{ mm}^2$ vs. BZA: $0.43 \pm 0.08 \text{ mm}^2$, $p=0.027$; Right: CTL: $0.21 \pm 0.07 \text{ mm}^2$ vs. BZA: $0.43 \pm 0.22 \text{ mm}^2$, $p= 0.373$). This finding did not remain significant after adjustment for multiple comparisons (BZA vs. CTL, adjusted $p = 0.08$). The mean plaque sizes of the BZA+CEE group were not different from the control group in either the left or the right internal carotid artery (Left: CTL: $0.19 \pm 0.06 \text{ mm}^2$ vs. BZA+CEE: $0.22 \pm 0.05 \text{ mm}^2$, $p=0.737$; Right: CTL: $0.21 \pm 0.07 \text{ mm}^2$ vs. BZA+CEE: $0.35 \pm 0.09 \text{ mm}^2$, $p= 0.271$). The observations on plaque severity are summarized in Table 4. CEE treated monkeys had significant increase of unaffected cases in the left internal carotid arteries (p -values = 0.049). CEE had a similar effect in the right internal carotid artery; however the finding did not reach statistical significance. The distribution of lesion types for the BZA and BZA+CEE groups was not significantly different from the control group.

Basilar Artery Atherosclerosis Severity

Atherosclerosis occurred so infrequently in the basilar artery that it was not reasonable to calculate a mean plaque extent. The occurrence of basilar lesions of those affected is presented in Table 5. CEE treated monkeys had more unaffected cases (19/23, $p=0.050$) compared to the control group. There were no significant differences for the BZA and BZA + CEE groups compared to the control group. Only 2 monkeys had complicated plaques, one in the control group and one in the BZA group.

Discussion

Stroke is the third leading cause of death in the United States and its occurrence and pathogenesis is different from that of coronary heart disease, particularly for women.

Women are more susceptible to stroke than are men. Among men and women aged 35 to 69 years, the rate of stroke is 2.9% for women compared to 1.07% for men; the difference being explained by a higher rate in women aged 45 to 54 years²¹. The evidence seems clear that there is a small risk of ischemic stroke (but not hemorrhagic stroke) associated with oral estrogen treatment of postmenopausal women^{12;13}. Ischemic stroke results from primary thrombotic mechanisms as well as from progressing atherosclerosis. The weight of the evidence seems to support that the ischemic strokes of women given oral estrogens are most likely the result of thrombotic mechanisms rather than complications of atherosclerosis of the cerebral arteries²². Never-the-less, it is important to consider the potential of exacerbated atherosclerosis when an oral estrogen is combined with a relatively new SERM.

The lack of an effect of BZA and of BZA+CEE on the plasma lipid profiles of the monkeys is in contrast to the reported effects on the plasma lipid profiles of women. BZA resulted in a 3.8% reduction in total plasma cholesterol, a 5.4% reduction in LDL-C and an increase in HDL-C of 5.1%.²³ Lobo and co-workers¹⁵ reported decreases in LDL-C of about 10% and increases of about 11% among women treated with BZA+CEE. However, beneficial effects of estrogen treatment in the monkey model, and probably among women as well, are thought to be mainly due to direct effects on the artery wall and not due to changes in plasma lipids and lipoproteins. Therefore it seems doubtful that the atherosclerosis outcomes of the monkey study would have been different had the monkey's plasma lipid responses been more like those of women, since²⁰; in the common carotid artery, there was no significant effect of BZA on plaque extent (size). There was also no significant effect of CEE on plaque size; however, the prevalence of atherosclerosis was affected beneficially (11 of 24 unaffected with CEE compared with only 1 of 23 unaffected in the control group). That beneficial effect was not significantly attenuated by the addition of BZA to the CEE treatment (8 of 27 unaffected with CEE + BZA). The lack of a significant effect of CEE on common carotid artery plaque size may relate to the dose used in this study (a woman's equivalent dose of 0.45 mg/day). In a large previous study of postmenopausal cynomolgus monkeys (56 control monkeys and 62 CEE treated monkeys) we found about a 50% ($p=0.0001$) decrease in plaque size using a CEE dose that was a woman's equivalent of 0.625 mg/day²⁴.

Atherosclerosis extent and severity at the carotid bifurcation are of high clinical importance since 40% of all clinical events in human patients are associated with atherosclerosis at this site²⁵. In the study presented here, no evidence was found to indicate exacerbation of atherosclerosis by BZA nor BZA+CEE. Somewhat unexpectedly, CEE treatment had only a small beneficial effect on carotid bifurcation atherosclerosis extent (significant for the left, $p=0.027$ but not for the right, $p=0.077$). This small effect of CEE on plaque size in the carotid bifurcation is in striking contrast to the atheroprotective effect of CEE for coronary artery atherosclerosis in these same monkeys; about 40% reduction from control in the carotid bifurcations as opposed to approximately a 70% reduction for coronary artery atherosclerosis²⁰.

There are two potential explanations for the small CEE effects at the carotid bifurcation. First, cynomolgus monkeys from the same source in Indonesia used in this study may have pre-existing plaques at the bifurcation and second, glucose intolerance rather than dyslipoproteinemia are the primary risk factors for plaque progression in the carotid bifurcations of cynomolgus monkeys²⁶.

The findings seem clear that there are no adverse effects of either, BZA or BZA+CEE on atherosclerosis extent or severity in the internal carotid arteries. The lack of significant beneficial effects of CEE was unexpected and, again, may relate to the dose of CEE (woman's equivalent of 0.45 mg/day) in this study. In two previous studies, using a

woman's equivalent dose of 0.625 mg/day, we observed robust inhibition of internal carotid artery atherosclerosis up to about 70% reductions ($p=0.0003$)¹¹.

Few nonhuman primate atherosclerosis studies have considered the intracranial arteries, specifically, the basilar arteries. In the study reported here, we found some fatty streaks and two monkeys with complicated plaques with no indication of an effect of treatment. Like atherosclerosis at the carotid bifurcation, atherosclerosis of basilar arteries may be more influenced by abnormalities in carbohydrate metabolism. For example, female cynomolgus monkeys fed a diet with 1% added cholesterol and with 31% fructose developed atherosclerosis in the basilar arteries of 3 out of 5 monkeys (60%)²⁷. Interestingly, the fructose fed monkeys also had markedly enhanced vasoconstrictor responses in the basilar arteries.

Conclusions

The results of this study have important clinical implications. It is likely that BZA alone may be used increasingly for the prevention and treatment of osteoporosis and in combination with CEE, for the treatment and prevention of postmenopausal symptoms. No consistent evidence was found in the study reported here to indicate that BZA exacerbated cerebral atherosclerosis. CEE was found to have modest beneficial effects on the severity of cerebral atherosclerosis and, importantly, BZA did not attenuate the CEE's inhibition of plaque complications in the common carotid artery.

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Figure 1.

Atherosclerosis plaque extent (intimal area, mm²) of the Left common carotid artery from monkeys treated with conjugated equine estrogens (CEE, 0.45mg women's equivalent dose/day), Bazedoxifene (20mg women's equivalent dose/day), BZA +CEE or no treatment (CTL) for 20 months. Data presented are the Mean $\pm$ SEM, estimated from the square-root of IA and then back transformed to the original scale (mm²). The overall ANOVA for any differences among the groups $p = 0.02$.

Figure 2.

Atherosclerosis plaque extent (intimal area, mm²) of the Left (A) and Right (B) carotid artery bifurcations from monkeys treated with conjugated equine estrogens (CEE, 0.45mg women's equivalent dose/day), Bazedoxifene (20mg women's equivalent dose/day), BZA +CEE or no treatment (CTL) for 20 months. Data presented are the Mean $\pm$ SEM, estimated from the square-root of IA and then back transformed to the original scale (mm²). The overall ANOVA for any differences among the groups p-values are: Left, p = 0.002, Right, p = 0.04.

Figure 3.

Atherosclerosis plaque extent (intimal area, mm²) of the Left (A) and Right (B) internal carotid arteries from monkeys treated with conjugated equine estrogens (CEE, 0.45mg women's equivalent dose/day), Bazedoxifene (20mg women's equivalent dose/day), BZA +CEE or no treatment (CTL) for 20 months. Data presented are the Mean $\pm$ SEM, estimated from the square-root of IA and then back transformed to the original scale (mm²). The overall ANOVA for any differences among the groups *p*-values are: Left, *p* = 0.004, Right, *p* = 0.02.

Table 1

Effect of Treatments on Plasma Lipid Concentrations

Groups	n	Plasma Lipid Concentrations			
		TPC	LDL + VLDL-C	HDL-C	TPC:HDL-C
Control	23	341 ± 24	291 ± 25	51 ± 3	8 ± 1
BZA	24	392 ± 24	344 ± 25	48 ± 3	9 ± 1
CEE	24	339 ± 24	287 ± 25	53 ± 3	8 ± 1
CEE + BZA	27	359 ± 22	310 ± 23	49 ± 3	9 ± 1
<i>p</i> -value		0.379	0.350	0.699	0.426

Data presented are means ± standard error of the means.

Abbreviations: TPC= total plasma cholesterol (mg/dl), VLDL+LDL-C= very low density lipoprotein cholesterol + low density lipoprotein cholesterol (mg/dl), HDL-C= high density lipoprotein cholesterol (mg/dl), TPC:HDL-C= ratio of TPC to HDL-C, BZA= Bazedoxifene acetate, CEE= conjugated equine estrogens.

Table 2
The Distribution of Left Common Carotid Artery Lesion Types by Treatment Group

Group	n	Unaffected	Affected		<i>p</i> -value versus CTL
		No Lesion (0), Adaptive Thickening (I)	Fatty Streaks (II)	Complicated Plaques (>III)	
CTL	23	1	18	4	-
CEE	24	11	10	3	0.002
BZA	24	1	17	6	1.000
BZA+CEE	27	8	12	7	0.028

p-values correspond to the pair-wise comparison of each group versus CTL in terms of the distribution of affected vs. unaffected lesions based on Fisher's exact test.

Table 3
The Distribution of Left and Right Carotid Bifurcations Artery Lesion Types by Treatment Group

Group (Left)	n	Unaffected		Affected		p-value versus CTL
		No Lesion (0), Adaptive Thickening (I)		Fatty Streaks (II)	Complicated Plaques (>III)	
CTL	23	0		16	7	-
CEE	24	2		20	2	0.489
BZA	24	0		19	5	1.000
BZA+CEE	26	0		20	6	1.000

Group (Right)	n	Unaffected		Affected		p-value versus CTL
		No Lesion (0), Adaptive Thickening (I)		Fatty Streaks (II)	Complicated Plaques (>III)	
CTL	23	0		17	6	-
CEE	24	4		19	1	0.109
BZA	24	0		19	5	1.000
BZA+CEE	27	1		18	8	1.000

p-values correspond to the pair-wise comparison of each group versus CTL in terms of the distribution of affected vs. unaffected lesions based on Fisher's exact test.

Table 4
The Distribution of Left and Right Internal Carotid Arteries Lesion Types by Treatment Group

Group (Left)	n	Unaffected		Affected		p-value versus CTL
		No Lesion (0), Adaptive Thickening (I)		Fatty Streaks (II)	Complicated Plaques (>III)	
CTL	23	3		18	2	-
CEE	24	10		12	2	0.049
BZA	24	1		21	2	0.348
BZA+CEE	27	5		21	1	0.711

Group (Right)	n	Unaffected		Affected		p-value versus CTL
		No Lesion (0), Adaptive Thickening (I)		Fatty Streaks (II)	Complicated Plaques (>III)	
CTL	23	5		16	2	-
CEE	24	11		13	0	0.125
BZA	23	3		19	1	0.699
BZA+CEE	27	6		15	6	1.000

p-values correspond to the pair-wise comparison of each group versus CTL in terms of the distribution of affected vs. unaffected lesions based on Fisher's exact test.

Table 5
The Distribution of Basilar Artery Lesion Types by Treatment Group

Group	n	Unaffected	Affected		p-value versus CTL
		No Lesion (0), Adaptive Thickening (I)	Fatty Streaks (II)	Complicated Plaques (>III)	
CTL	23	19	3	1	-
CEE	24	24	0	0	0.050
BZA	24	17	6	1	0.494
BZA+CEE	26	21	5	0	1.000

p-values correspond to the pair-wise comparison of each group versus CTL in terms of the distribution of affected vs. unaffected lesions based on Fisher's exact test.