Di.N.O.G.M.I. - Università di Genova
U.O.C. Clinica Oculistica
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Prostaglandin analogues for glaucoma

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IT-ARVO Chapter Meeting

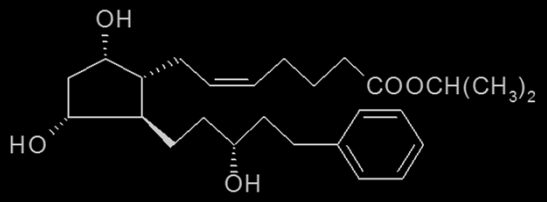
CATANIA

2-3 FEBBRAIO 2014

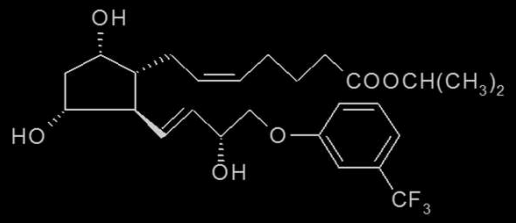
EUROPEAN GLAUCOMA SOCIETY

11th EGS Congress

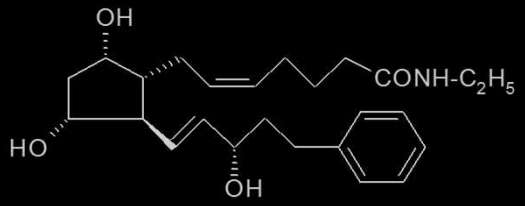
Structural formulas of prostaglandin analogues for IOP lowering



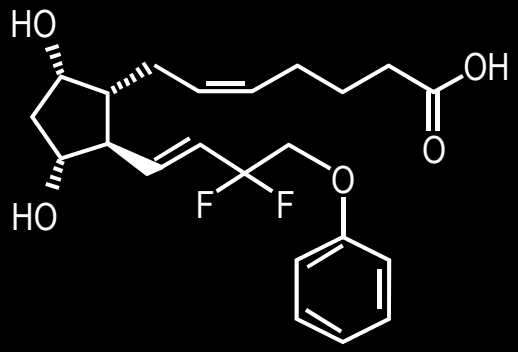
Latanoprost



Travoprost



Bimatoprost



Tafluprost

Prodrug - isopropylesther (AFP-168) facilitates penetration
Hydrolized to carboxylic active form (AFP-172)

Takagi, Nakajima et al. 2004

Pg analogues

Metabolites of arachidonic acid

Inflammatory mediators like tromboxans and leukotriens

Lower IOP ↓ **25-33** % increasing uveosceral outflow Effect starts in 2-4 h, peak 8-12 h, max effect 3-5 weeks

Very few systemic side effects

LOCAL **SIDE EFFECTS**

iris and skin hyperpigmentation, hypertrichosis,

not clear reaction to inflammatory process, allergy, cystoid macular edema

EGS. *Terminology and Guidelines for Glaucoma*, 3rd edition. 2008.

Pg ANALOGUES

Systemic effects

- Circa 80% of a topical ocular drop enters the nasolacrimal ducts immediately after instillation and is available for absorption into systemic circulation.
- SYSTEMIC peak concentration of latanoprost acid 5 minutes after topical application and reached a level of 53 pg/ml with an elimination half-life of 17 minutes.

Sjöquist B et al. Ocular and Systemic Pharmacokinetics Of Latanoprost in Humans. Survey of Ophthalmology 2002.

Pg ANALOGUES

Systemic effect, pregnancy

Numerous synthetic FP-class prostaglandin (PG) analogs stimulated the contraction of isolated non-pregnant female rat uterus in a concentration-dependent manner.

Sharif NA. Synthetic FP-prostaglandin-induced contraction of rat uterus smooth muscle in vitro. Prostaglandins Leukot Essent Fatty Acids 2008.

Bimatoprost potently contracted the rabbit isolated uterus. In contrast, bimatoprost exhibited weak excitatory activity in human myometrium from pregnant and nonpregnant donors.

Chen J et al. Studies using isolated uterine and other preparations show bimatoprost and prostanoid FP agonists have different activity profiles. British Journal of Pharmacology 2005.

Eleven cases of latanoprost exposure in pregnancy were referred to Teratology Information Service. One case was lost to follow-up, and one case was complicated by miscarriage. Nine cases had a complete follow-up without congenital anomalies.

De Santis M et al. Latanoprost exposure in pregnancy. Am J Ophthalmol 2004.

Pg ANALOGUES

Systemic effect, pregnancy

Eleven cases of latanoprost exposure in pregnancy were referred to Teratology Information Service. One case was lost to follow-up, and one case was complicated by miscarriage. Nine cases had a complete follow-up without congenital anomalies.

De Santis M et al. Latanoprost exposure in pregnancy. Am J Ophthalmol 2004.

It is not known whether the drugs or their metabolities are excreted in human milk.

European Glaucoma Society. Terminology and Guidelines for Glaucoma, 3rd edition. Savona, Italy: Dogma, 2008

Pg ANALOGUES and Uveitis

Dechallenge and rechallenge data seems strong and reproducible, making the association likely.

Up to 5% of patients treated with latanoprost can develop anterior uveitis after several month.

163 eyes of 94 patients receiving latanoprost, eight eyes (4.9%) of six patients (6.4%) developed anterior uveitis. None of these patients had a history of iritis or any medical condition associated with uveitis. Anterior uveitis resolved in all patients with discontinuation.

Warwar RE et al. Cystoid macular edema and anterior uveitis associated with latanoprost use: Experience and incidence in a retrospective review of 94 patients. Ophthalmology 1998.

Pg ANALOGUES and Uveitis

Probable breakdown of the blood–aqueous barrier, downstream stimulation of proinflammatory eicosanoids, and increased production of IL-1 and IL-6 in tears and the anterior chamber.

Lopilly Park HY et al. Effect of prostaglandin analogues on tear proteomics and expression of cytokines and matrix metalloproteinases in the conjunctiva and cornea. Exp Eye Res 2012

Controversy exists concerning their use in uveitic patients due to the theoretically higher risk of anterior uveitis. There is little evidence that PGA disrupt the blood-aqueous barrier and only anecdotal evidence suggesting an increased risk of these rare findings.

Horsley MB et al. The use of prostaglandin analogs in the uveitic patient. Semin Ophthalmol 2011.

Pg ANALOGUES and Uveitis

Four patients with complicated open-angle glaucoma who had anterior uveitis associated with the use of latanoprost. Only in the eye receiving latanoprost. 4/5 eyes had prior inflammation and/or prior incisional surgery. All rechallenged positive.

Fechtner RD et al. Anterior uveitis associated with latanoprost. American Journal of Ophthalmology 1998.

Acute uveitis in a patient using bimatoprost, after long and well-tolerated treatment with a prostaglandin analog, suggests a distinct potential pro-inflammatory action of prostamides.

Parentin F. Granulomatous anterior uveitis associated with bimatoprost. Ocul Immunol Inflamm. 2003.

Two cases of cytomegalovirus (CMV) anterior uveitis following topical prostaglandin analogue administration for glaucoma.

Babu K, Murthy GJ. Cytomegalovirus anterior uveitis in immunocompetent individuals following topical prostaglandin analogues. J Ophthalmic Inflamm Infect 2013.

Pg ANALOGUES and Uveitis

163 eyes of 84 consecutive patients with uveitis and raised IOP treated with a PG analogue at two tertiary referral uveitis clinics were identified over a 3-month period.

No significant difference in the frequency of anterior uveitis in those eyes treated with PG analogues and those treated with non-PG agents (p = 0.87).

Chang JH et al. Use of ocular hypotensive prostaglandin analogues in patients with uveitis: does their use increase anterior uveitis and cystoid macular oedema? Br J Ophthalmol 2008.

58 patients with anterior or intermediate uveitis and elevated IOP or glaucoma were randomly assigned to receive treatment either with latanoprost (30) or with dorzolamide/timolol (28).

There was no statistical difference between the two groups in respect of inflammatory relapses ($p = 0.21$).

Markomichelakis NN et al. Efficacy and safety of latanoprost in eyes with uveitic glaucoma. Graefes Arch Clin Exp Ophthalmol 2009.

Pg ANALOGUES and uveitis

Causality has not been clearly demonstrated for anterior uveitis

Caution is recommended when administering latanoprost to patients at risk for this condition. I

Some individuals may have prostaglandin receptors that are hypersensitive, with increased release of arachidonic acid and enhanced production of proinflammatory eicosanoids.

Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. Surv Ophthalmol 2008.

Pg ANALOGUES and Cystoid Macular Edema

Inflammatory mediators (including endogenous PGAs) break down the blood-aqueous and blood-retinal barriers, which leads to increased vascular permeability. Eosinophilic transudate accumulates in the outer plexiform and inner nuclear layers of the retina to create cystic spaces that coalesce to form larger pockets of fluid.

Dutra Medeiros M et al. Dexamethasone intravitreal implant for treatment of patients with recalcitrant macular edema resulting from Irvine-Gass syndrome. Invest Ophthalmol Vis Sci 2013.

Pg ANALOGUES and CME

Retrospective review

136 eyes of 94 glaucoma patients on latanoprost

clinical CME in two eyes (1.2%), one had a ruptured posterior capsule during cataract surgery and AC IOL, the other was pseudophakic with an intact posterior capsule, with a history of anterior uveitis 1 month prior to starting latanoprost.

Warwar RE. Cystoid macular edema and anterior uveitis associated with latanoprost use: Experience and incidence in a retrospective review of 94 patients. Ophthalmology 1998.

Pg ANALOGUES and blood-aqueous barrier alterations

Latanoprost therapy enhances disruption of the blood-aqueous barrier and increases the incidence of angiographic CME formation in early postoperative pseudophakias.

Miyake K et al. Latanoprost accelerates disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema in early postoperative pseudophakias. Arch Ophthalmol 1999.

Latanoprost, travoprost, and bimatoprost had no statistically significant effect on the blood-aqueous barrier of phakic patients with POAG or OHT.

Arcieri ES, Pierre Filho PTP, Wakamatsu TH, Costa VP. The effects of prostaglandin analogues on the blood aqueous barrier and corneal thickness of phakic patients with primary open-angle glaucoma and ocular hypertension. Eye 2008.

Pg ANALOGUES and CME

Published reports of the occurrence of cystoid macular edema (CME) in eyes being treated with latanoprost have led to concern regarding a possible causal relation between the two.

Schumer RA, Camras CB, Mandahl AK. Latanoprost and cystoid macular edema: is there a causal relation? Curr Opin Ophthalmol 2000.

Pg ANALOGUES and CME

Sixty-eight eyes of 38 patients with glaucoma and no risk factors for CME were studied. Latanoprost ophthalmic solution did not influence retinal thickness in the fovea at any investigated time points compared with the time before instillation.

It is unlikely that topical latanoprost induces retinal disorders, such as cystoid macular edema, in glaucomatous eyes with a normally functioning blood-ocular barrier.

Furuichi M et al. Cystoid macular edema associated with topical latanoprost in glaucomatous eyes with a normally functioning blood-ocular barrier. J Glaucoma 2001.

Pg ANALOGUES and CME

All cases described to date had other risk factors for the development of CME.

There is no evidence for CME developing in a phakic eye without risk factors for CME.

Digiuni M, Fogagnolo P, Rossetti L. A review of the use of latanoprost for glaucoma since its launch. Expert Opin Pharmacother 2012.

It would appear, therefore, that the risk of CME is extremely low to non-existent in low-risk eyes (no intraocular surgery or uveitis) and that even in high-risk eyes the incidence is relatively low.

Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. Surv Ophthalmol 2008.

Pg ANALOGUES and CME

A PGA may not be the first drug of choice in patients that are at high risk for CME (aphakia, pseudophakia with a ruptured posterior capsule during surgery, history of uveitis, or retinal inflammatory or vascular disease), the incidence of CME associated with PGA therapy is low even in these patients and it is not felt to constitute an absolute contraindication to PGA therapy.

Wand M, Shields BM. Cystoid macular edema in the era of ocular hypotensive lipids. Am J Ophthalmol 2002.

Bimatoprost,latanoprost, tafluprost, travoprost and unoprostone should be used with caution in these patiens although concourrent administration of nonsteroidal ant-inflammatory agents, such as diclofenac, might decrease the side effects.

European Glaucoma Society. Terminology and Guidelines for Glaucoma, 3rd edition. Savona, Italy: Dogma, 2008

Pg ANALOGUES

Recurrence HSV keratitis, case reports

Three cases of HSV K after initiation of latanoprost therapy. In one cleared with discontinuation of latanoprost but recurred when rechallenged. Another patient with bilateral recurrence, could not be eradicated with antiviral therapy until latanoprost was discontinued.

Wand M, Gilbert CM, Liesegang TJ. Latanoprost and herpes simplex keratitis. American Journal of Ophthalmology 1999.

Two patients treated with latanoprost for primary open angle glaucoma developed herpes keratitis.

EKATOMATIS P. Herpes simplex dendritic keratitis after treatment with latanoprost for primary open angle glaucoma. Br J Ophthalmol 2001.

Pg ANALOGUES

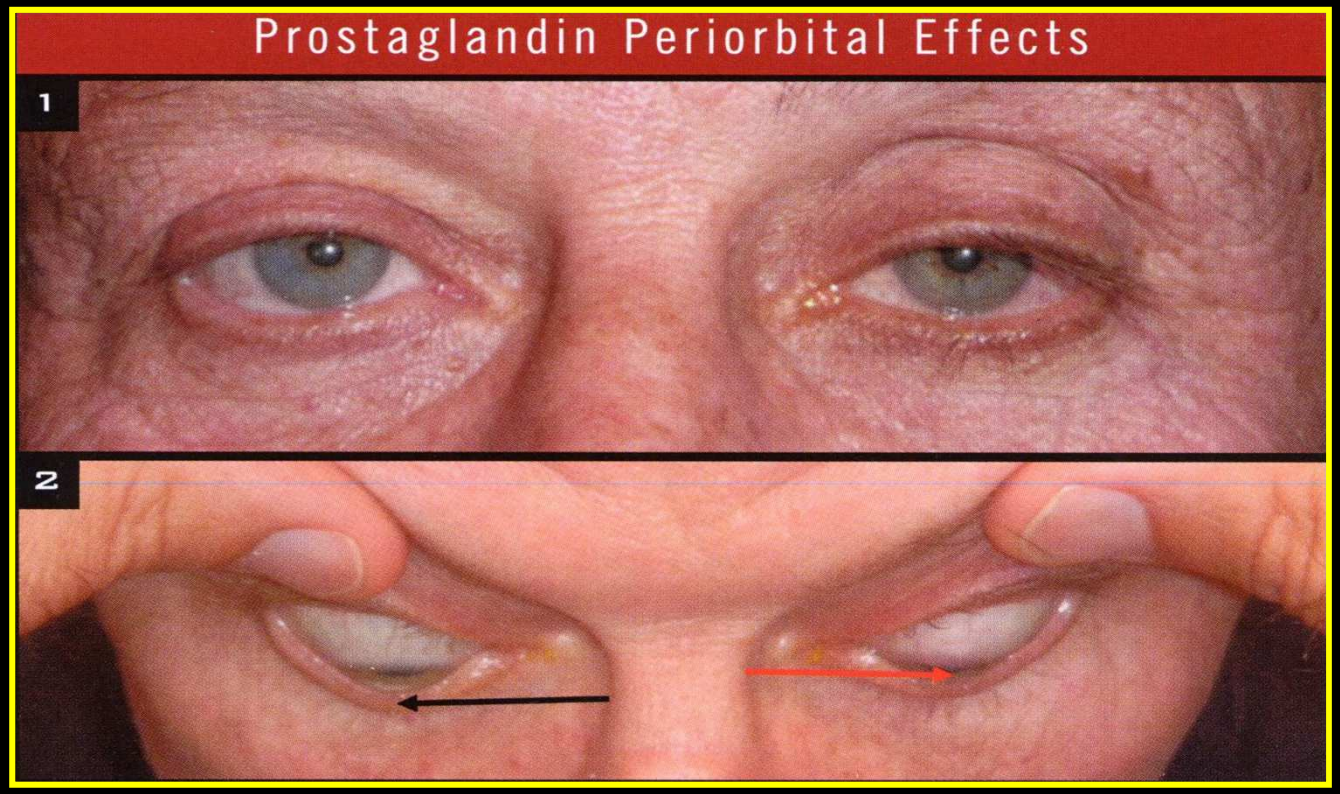
and HSV keratitis: population-based, retrospective, cohort study

A total of 93,869 eligible glaucoma patients, 21 different ocular hypotensive agents, and 192,840 agent-utilizing patient combinations were identified. In all, 411 patients had an OHSV event.

Ocular herpes simplex virus is extremely rare in patients treated with ocular hypotensive therapies, and its prevalence is similar to that found in the general population. The current analysis revealed no association between the use of particular topical ocular hypotensive therapies and OHSV.

Bean G, Reardon G, Zimmerman TJ. Association between ocular herpes simplex virus and topical ocular hypotensive therapy. J Glaucoma 2004.

LONG-TERM SIDE EFFECTS



PGA - ASSOCIATED PERIOBITOPATHY

Berke SJ , Pasquale L 2012

PATIENTS FIRST

PGA - ASSOCIATED PERIOBITOPATHY

DEEP SUPERIOR SULCUS

Pg ANALOGUES

Upper eyelid sulcus

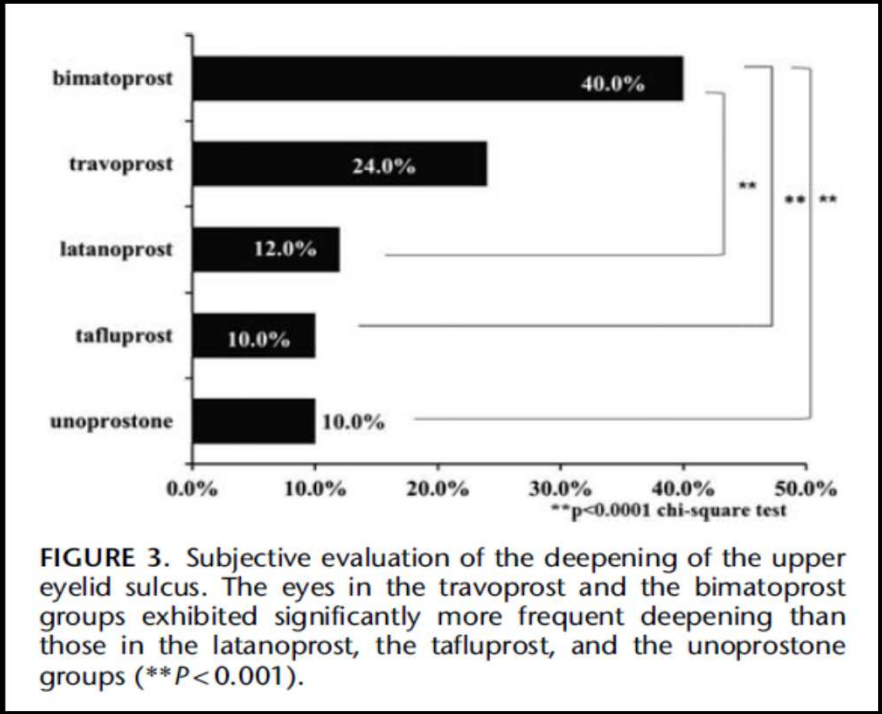


FIGURE 3. Subjective evaluation of the deepening of the upper eyelid sulcus. The eyes in the travoprost and the bimatoprost groups exhibited significantly more frequent deepening than those in the latanoprost, the tafluprost, and the unoprostone groups (**$P < 0.001$).

Upper eyelid sulcus deepening frequently occurred with bimatoprost usage, and this effect should be sufficiently elucidated before starting bimatoprost treatment.

Inoue K, Shiokawa M, Wakakura M, Tomita G. Deepening of the upper eyelid sulcus caused by 5 types of prostaglandin analogs. J Glaucoma 2013.

Pg ANALOGUES and trabeculectomy

- Long-term glaucoma medication has been suspected to be a risk factor for bleb failure following trabeculectomy.

Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Arch Ophthalmol 1994.

- It has been proposed that in patients exposed to excessive preoperative topical medication, postoperative fibroblast proliferation occurs secondary to a cascade of cellular events induced by subclinical inflammation.

Broadway DC, Chang LP. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. J Glaucoma 2001.

Pg ANALOGUES and metalloproteinase

- Levels of MMP-3 and TIMP-2 increase after treatment with latanoprost. Tenon fibroblasts may be the target cells for attempts to influence the tissue levels of MMPs and TIMPs in the context of conjunctival wound healing after glaucoma surgery.

Mietz H et al. Latanoprost stimulates secretion of matrix metalloproteinases in tenon fibroblasts both in vitro and in vivo. Invest Ophthalmol Vis Sci 2003.

- Latanoprost induced collagen gel contraction mediated by human Tenon fibroblasts. This action of latanoprost appeared to depend on the formation of stress fibers and the activation of mitogen-activated protein kinases , focal adhesion kinase, Rho-associated kinase, phospholipase C, and myosin light chain kinase in human Tenon fibroblasts. Latanoprost may therefore influence subconjunctival wound healing by affecting the contractility of Tenon fibroblasts.

Liu Y, Ko J-A, Yanai R, et al. Induction by latanoprost of collagen gel contraction mediated by human tenon fibroblasts: role of intracellular signaling molecules. Invest Ophthalmol Vis Sci 2008.

Pg ANALOGUES and trabeculectomy

The preservative, especially benzalkonium chloride, has consistently demonstrated its toxic effects in laboratory, experimental, and clinical studies, could induce or enhance inflammatory changes.

Broadway DC, Chang LP. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. J Glaucoma 2001.

Subclinical inflammatory changes preoperatively may lead to a higher rate of trabeculectomy failure.

Increased preoperative exposure to ophthalmic solutions preserved with BAK is a risk factor for earlier surgical failure, independent of the number of medications used.

Boimer C, Birt CM. Preservative exposure and surgical outcomes in glaucoma patients: The PESO study. J Glaucoma 2013.

Pg ANALOGUES and trabeculectomy

However, latanoprost-treated conjunctival specimens showed a decreased stromal collagen density and a less pronounced inflammatory infiltration. The upregulation of MMP-1 and MMP-3 in latanoprost-treated eyes might explain the reduced extracellular matrix accumulation in the conjunctival stroma.

Therefore, latanoprost therapy might have a more favourable effect on the outcome of glaucoma filtering surgery.

Terai N et al. Effect of latanoprost and timolol on the histopathology of the human conjunctiva. Br J Ophthalmol 2009.

latanoprost and unoprostone, may inhibit postoperative wound healing after glaucoma surgery.

Wu K-Y et al. Novel usage of intraocular pressure-lowering drugs as wound-healing inhibitors after trabeculectomy with cell culture and animal models. The Kaohsiung Journal of Medical Sciences 2013.

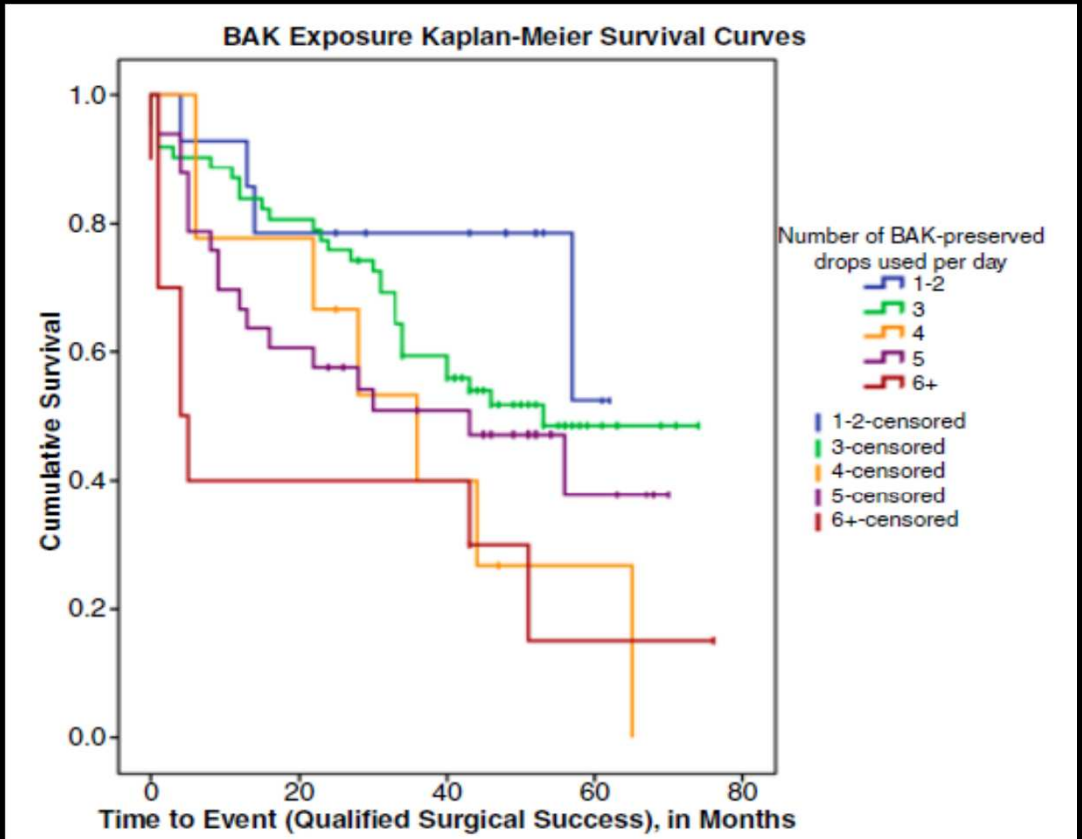
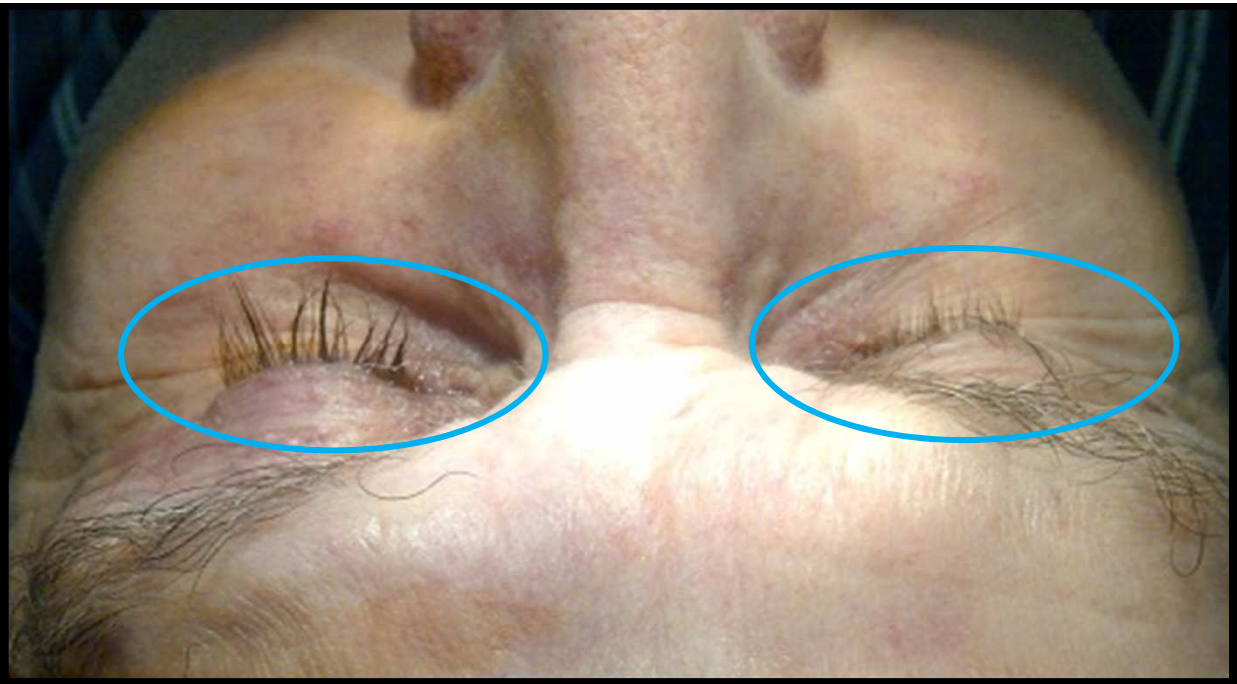
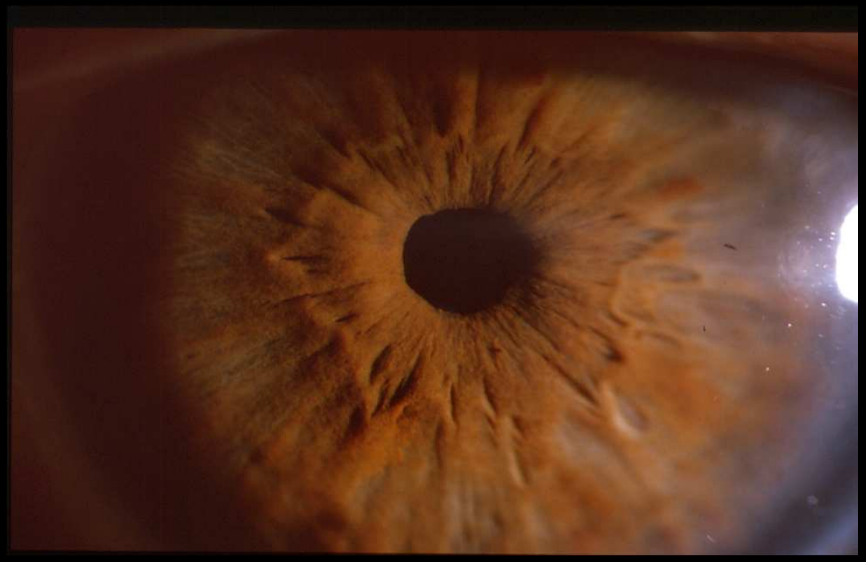
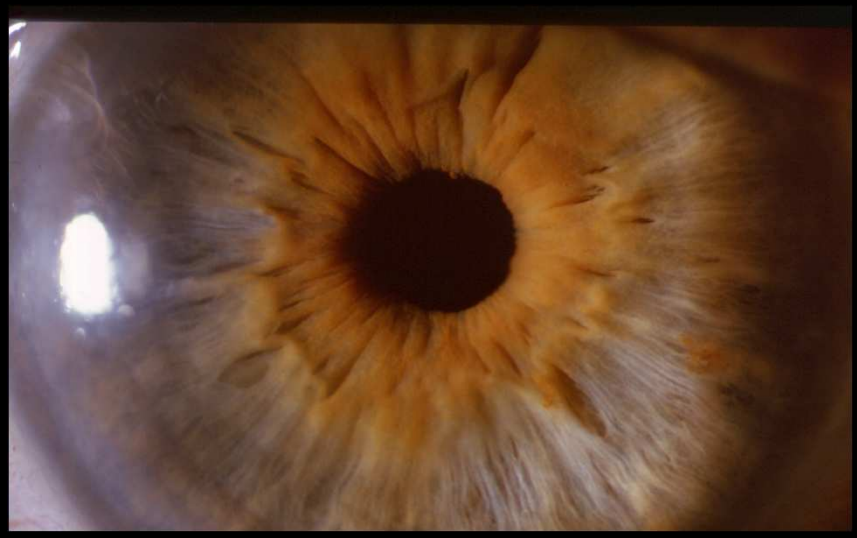


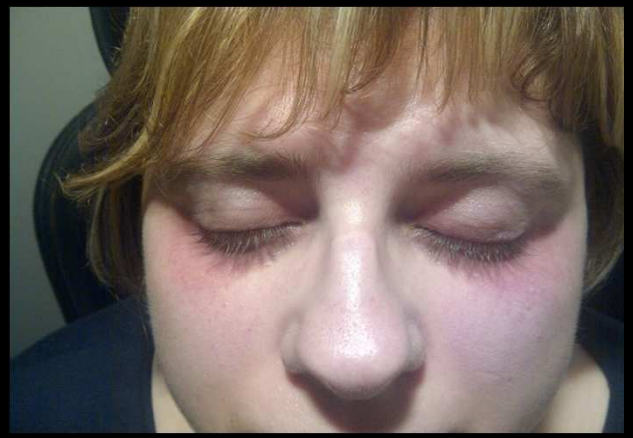
FIGURE 1. Kaplan-Meier survival analysis for glaucoma surgery outcome stratified by exposure to benzalkonium chloride (BAK) ($P = 0.008$).

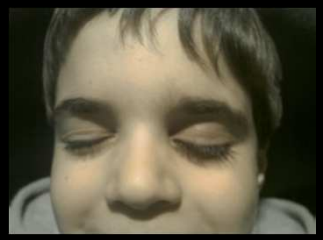
Boimer C, Birt CM. Preservative exposure and surgical outcomes in glaucoma patients: The PESO study. J Glaucoma 2013.

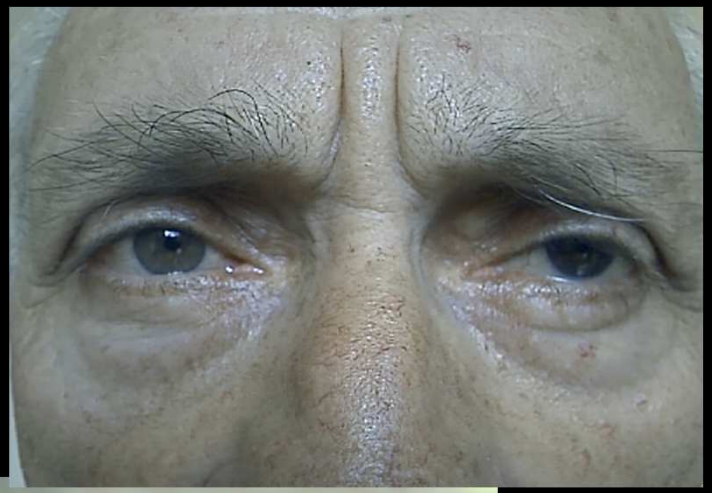


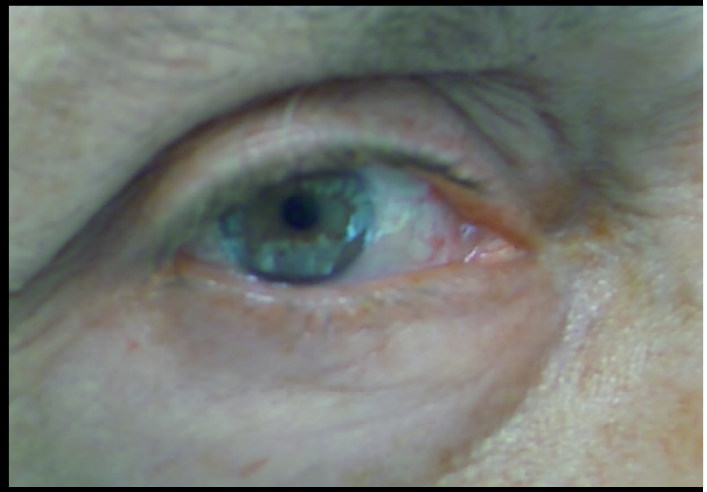


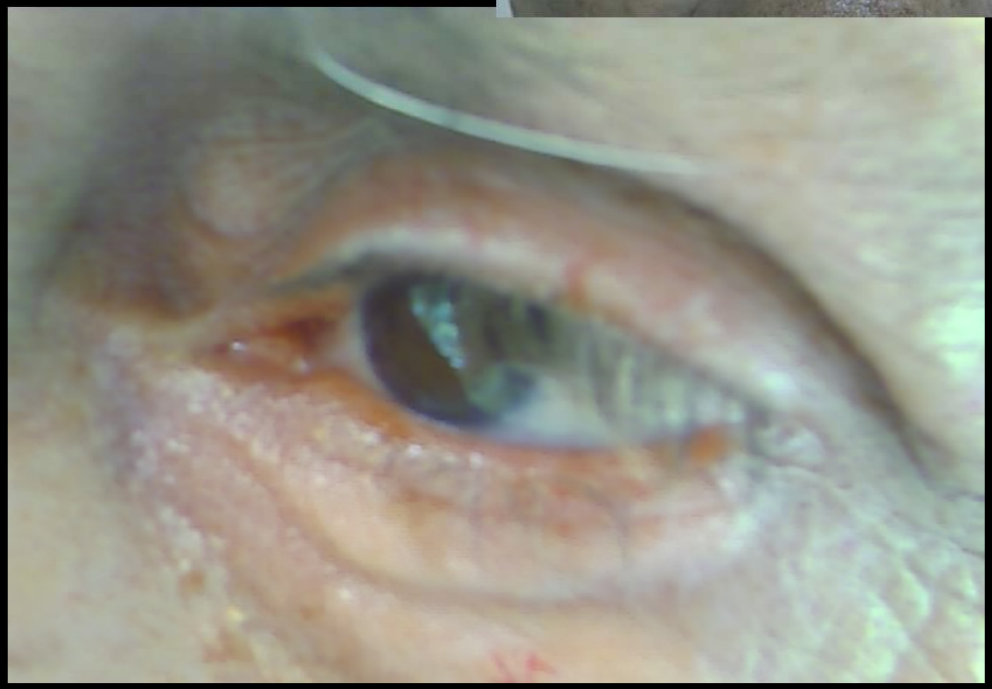


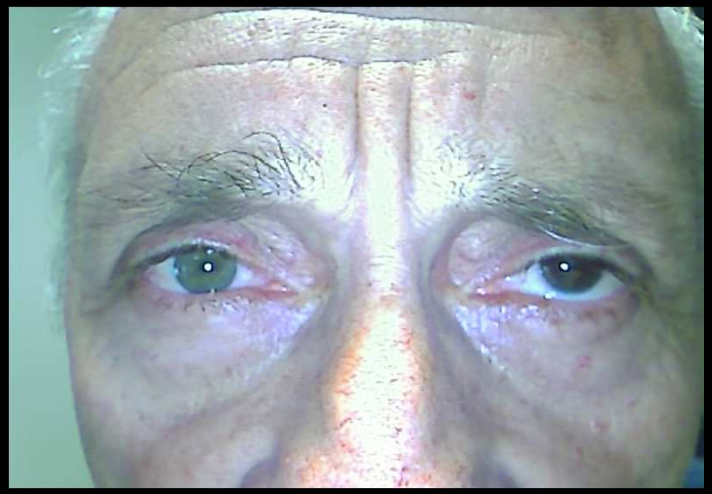












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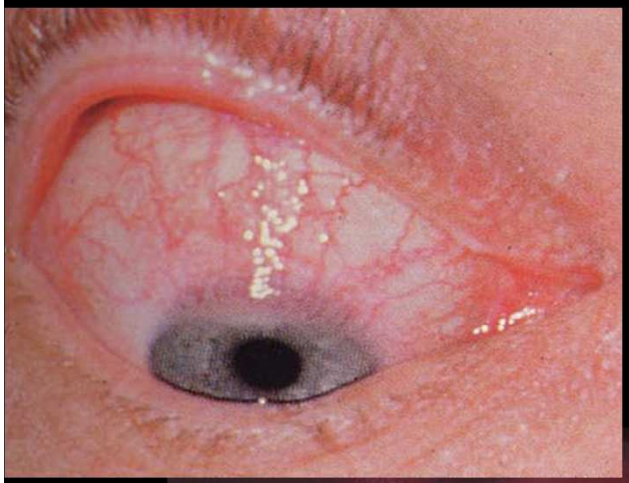

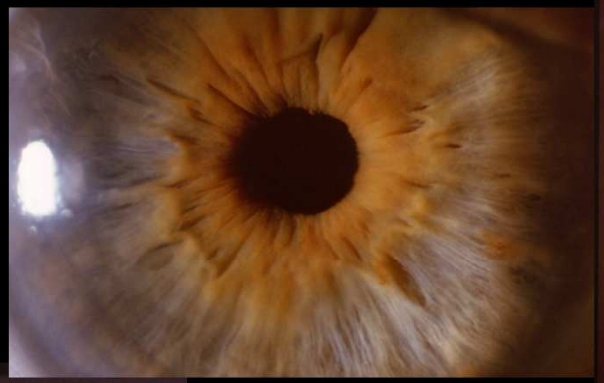

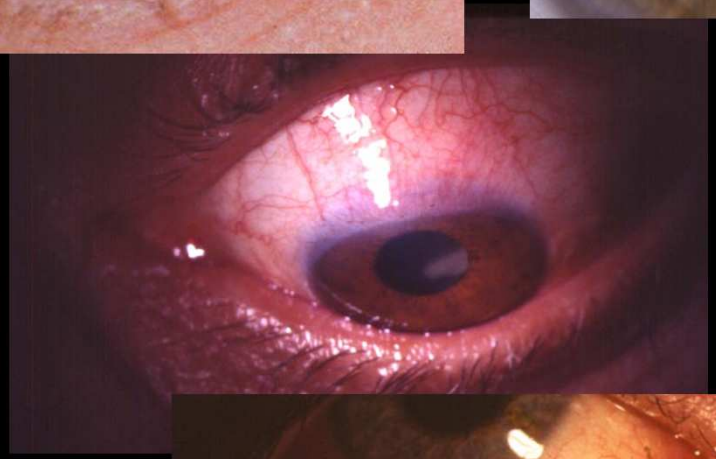

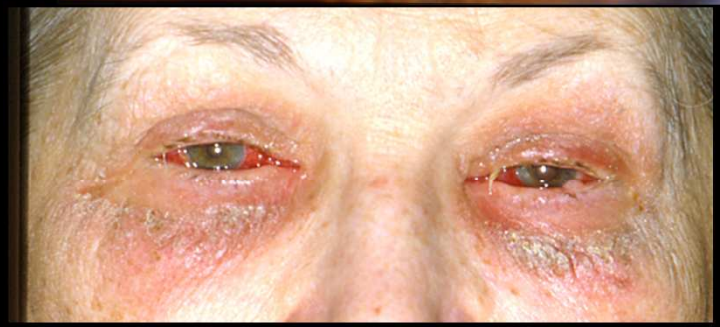

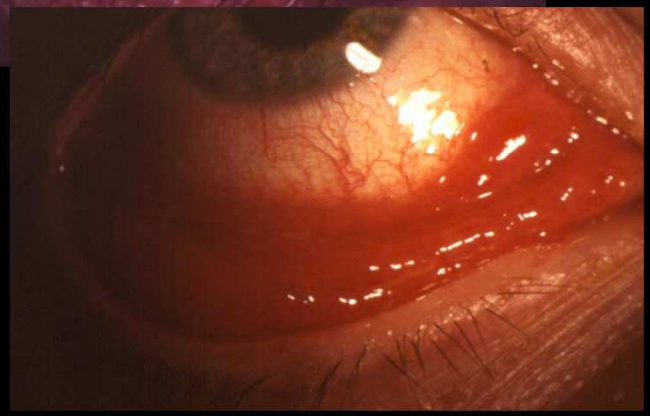

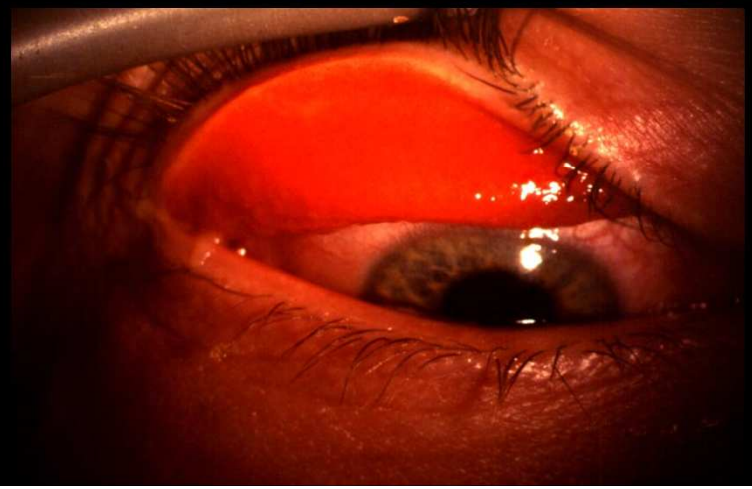

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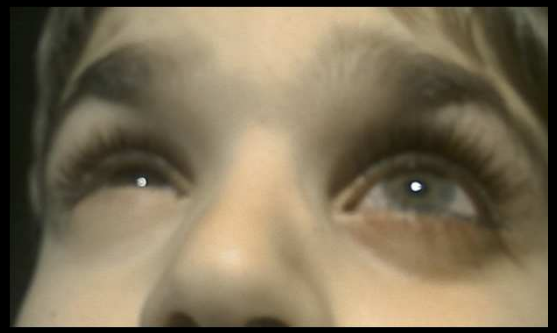
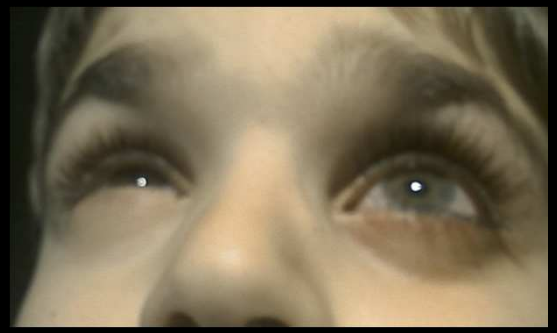


8 YO BOY
Dx: congenital glaucoma
Initial IOP 25
On topical meds for 2 years
Treated IOP IOP 20 – 22

Second opinion for surgery
“very sad case, severe daily life difficulties, family devastatingly worried”

PATIENTS FIRST



PROFOUND DIFFICULTIES AT SCHOOL, SUPPORT TEACHERS NEEDED, UNDER PSYCHO HELP

NORMAL VA / ONH / FIELD ?

WOULD FALL ASLEEP AT SCHOOL AND IN THE AFTERNOONS
BETABLOCKER BID PROSTAGLANDIN HS
BRIMONIDINE TID
CCT 720

TREATMENT UNNECESSARY, CONTRAINDICATED, CAUSING HANDICAP

THE PRESCRIPTION OF TOPICAL TREATMENT: A COOKBOOK FORMULA

DATA: POPULATION >40 in MIL

PREVALENCE OF POAG

DIAGNOSED CASES/MISSED CASES

NUMBER OF UNITS-BOTTLES/MONTH

28 MIL >40 YO - 2% OAG is 560k

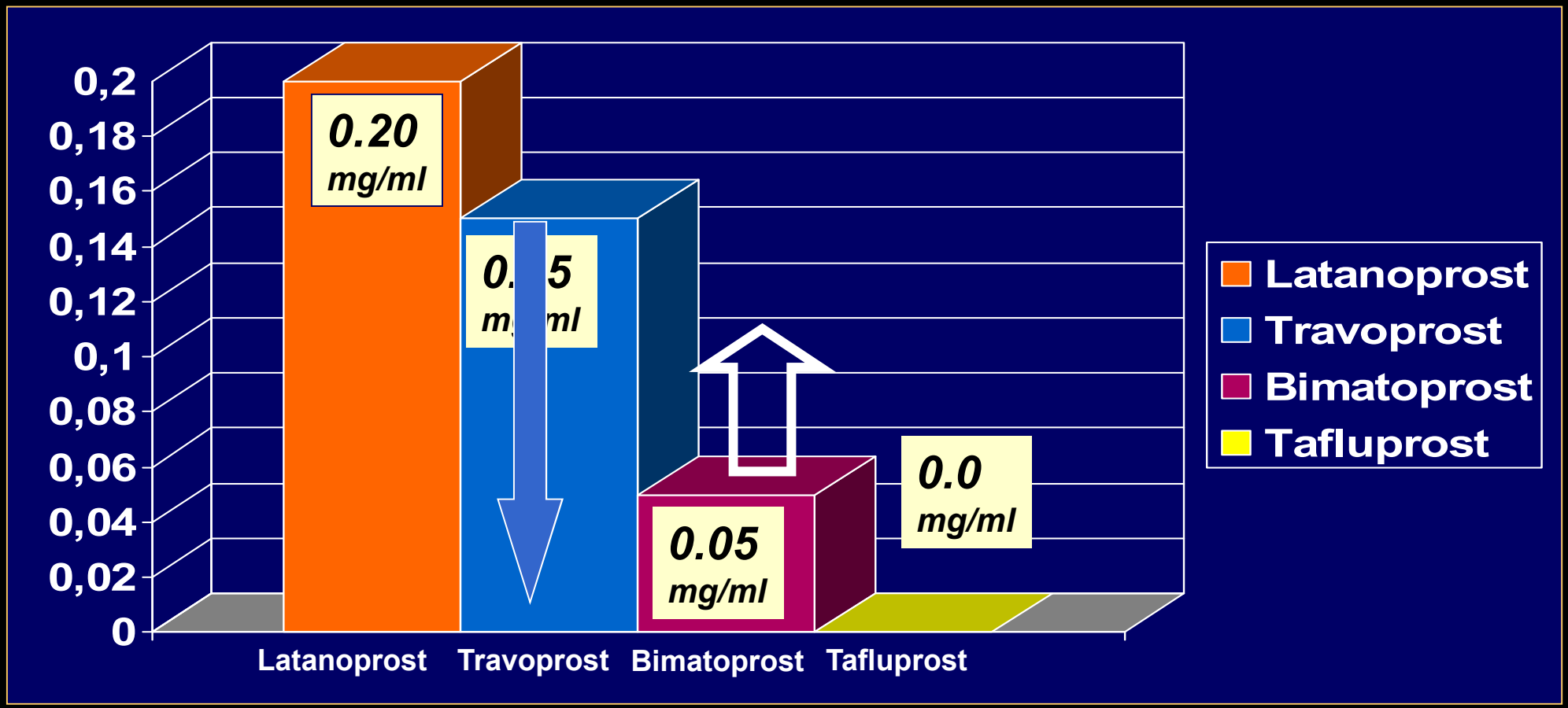
50% DIAGNOSED is 280k

UNITS/YEAR are 17 MIL

THEORETICAL BOTTLES PER TRUE GLAUCOMA

Pt PER MONTH = 5

BAC MG/ML as PRESERVATIVE



Pg ANALOGUES combined formulations PRESERVATIVE FREE

Preservative-free tafluprost/timolol fixed dose combination: A 6-month double-masked, randomised, multicenter P-III study comparing efficacy and safety to its individual preservative-free components in patients with glaucoma or ocular hypertension

Norbert Pfeiffer, Carlo E. Traverso, Yury Astakhov, Ernest Boiko and Auli Ropo

Purposes: Efficacy, tolerability and safety of the preservative-free (PF) fixed dose combination (FDC) of tafluprost 0.0015% and timolol 0.5% (once daily) were compared to those of the individual components (PF tafluprost 0.0015% once daily and PF timolol 0.5% twice daily) in patients inadequately controlled with prior timolol or prostaglandin monotherapy.

Methods: A total of 189 prior timolol users were randomised within the timolol stratum (TS) to receive FDC (n=95) or timolol (TIM; n= 94). In the stratum of prior prostaglandin users (PS) a total of 375 patients were randomised to receive FDC (n=188) or tafluprost (TAF; n=187). Study visits included baseline-visit, 2 and 6 weeks, 3 and 6 months. IOP was measured at 8 a.m., 10 a.m., 4 p.m. and 8 p.m. Primary efficacy variable was the change in average IOP from baseline at month 3.

Results: In the TS a significant reduction from baseline IOP was seen with FDC and TIM throughout the study. Average diurnal IOP change from baseline at month 3 was
-8.55 mmHg (32%) for FDC and -7.35 mmHg (28%) for TIM.The estimated overall treatment difference (FDC–TIM) was -0.885 mmHg (95% CI: -1.745 to -0.024; p=0.044) demonstrating superiority of FDC over TIM. In the PS a significant reduction in IOP was seen with both FDC and TAF throughout the study. Average diurnal IOP change from baseline at month 3 was -8.61 mmHg (33%) for FDC and -7.23 mmHg (28%) for TAF. The estimated overall treatment difference (FDC–TAF) was -1.516 mmHg (95% CI: -2.044 to -0.988; p< 0.001) demonstrating superiority of FDC over TAF. In the TS related ocular adverse events (AEs) were more frequent for patients treated with FDC compared to TIM (16.8 vs 6.4%) whereas related non-ocular AE's were more frequent with TIM compared to FDC (2.1% vs 0.0%). In the PS related AE's were similarly distributed between FDC and TAF.

Conclusions: The preservative-free FC of tafluprost and timolol provided a significant IOP reduction in both strata. The IOP reduction was superior to both, tafluprost and timolol given as monotherapies. The study treatments were safe and well tolerated.

Poster at WGA 2013

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PARADIGM SHIFT IN TREATMENT PATTERNS

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- WORK IN ANGLE CLOSURE AND IN SECONDARY FORMS
- PRESERVATIVE FREE AVAILABLE
- GENERIC LATANOPROST AVAILABLE
- NEUROPROTECTION SUSPECTED
- IN EUROPE Rx NUMBERS ARE SURPASSING BETABLOCKERS

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