Xalatan and Xalatan /betablocker fixed combination : role in glaucoma therapy

- Grant McLaren
- St John Eye Hospital
- Division of Ophthalmology
- University of Witwatersrand
- Johannesburg
- South Africa

Goals of this presentation

- **1.Background** of prostaglandins/amides
- **2.Efficacy and safety** of Xalatan and its rivals
-
- **3.Efficacy and safety of Xalacom** and fixed combination (FC) competitors
- **4.Xalatan** versus FC carbonic anhydrase inhibitors (CAI)/beta blockers
- **5.Treatment Guidelines**: therapeutic algorithm in Glaucoma topical therapy

Carl Camras

- Yale graduate
- Discovered new class of glaucoma drugs - prostaglandin analogues.
- He helped develope latanoprost (Xalatan)
- Most widely used glaucoma medication.[1]

Carl Camras

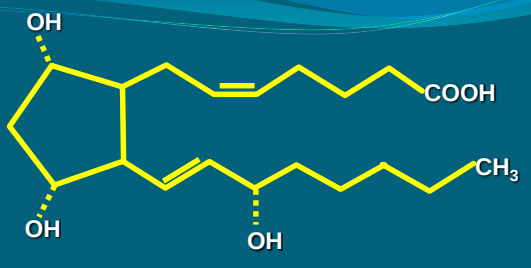
- Son of the engineer and inventor Marvin Camras who held over 550 patents.
- Father invented magnetic recording which was later used on **VCR tapes and computer disks.**

László Z. Bitó and Johan Sternschantz joint 2000 recipients:

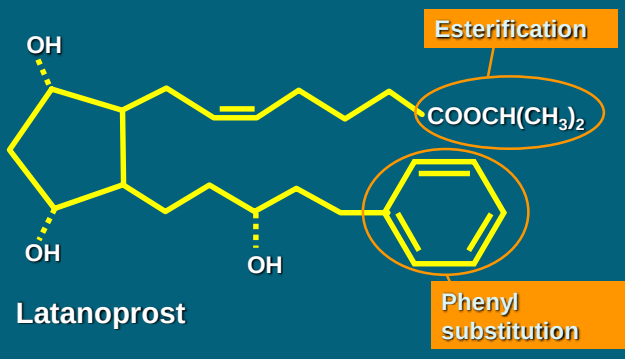
Lecture by Carl Camras

- **Proctor Medal**.... the highest recognition in the field of eye research, collaborated with Prof Carl B Camras
- Dr Anders Bill : "PG project **5% chance of success**"

The chemical structure of PhXA41 – latanoprost



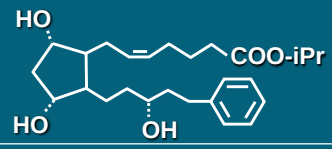
$PGF_{2\alpha}$



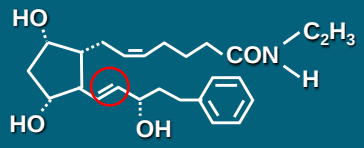
Latanoprost

Prostaglandin $F_{2\alpha}$ derivatives

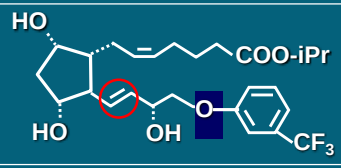
XALATAN
Isopropyl ester
($PGF_{2\alpha}$ derivative)



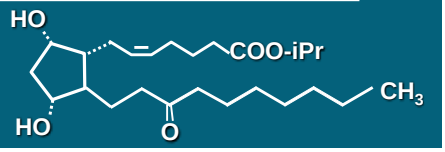
Bimatoprost
N-ethyl amide
(prostamide;
structural derivative
of $PGF_{2\alpha}$)



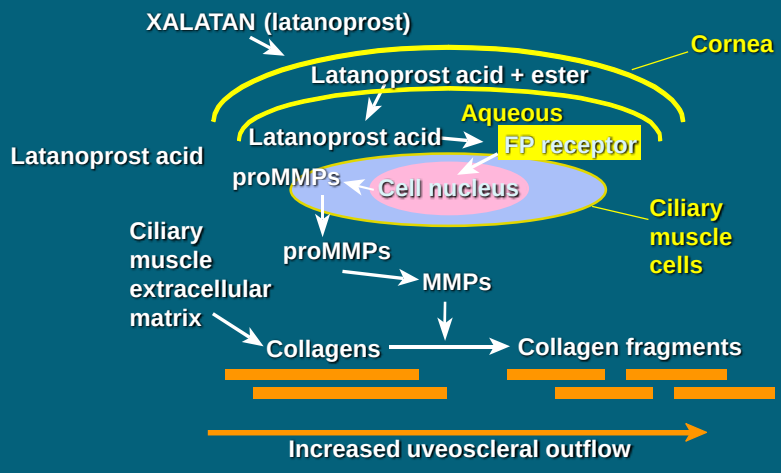
Travoprost
Isopropyl ester
($PGF_{2\alpha}$ derivative)



Unoprostone
Isopropyl ester
(docosanoid)



Mechanism of action of XALATAN

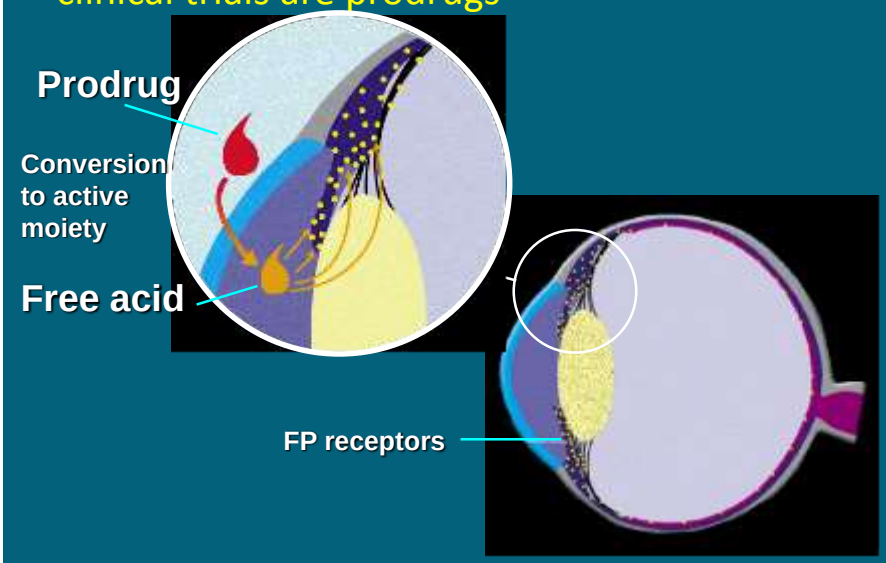


Adapted from Lindsey and Weinreb (2000)

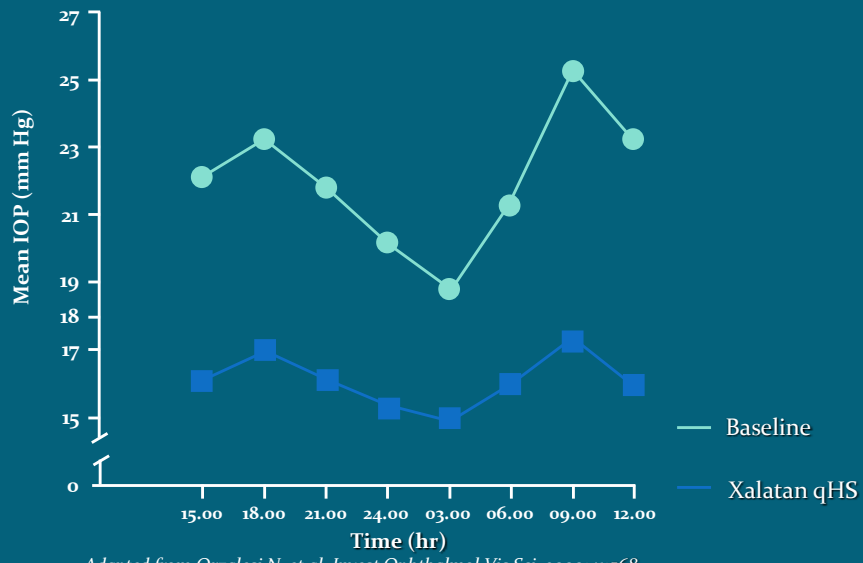
PROSTAGLANDIN RECEPTORS

- Widespread in the eye: **iris and ciliary body**
- Increased post cataract surgery (Miyake)
- **NSAIDs inhibit PG Production** by blocking cox cycle
- (Solomon,1995 ,JCRS)
  (Bressler,1999,OPHTHALMOLOGY)

All prostaglandin derivatives evaluated in clinical trials are prodrugs



Diurnal IOP Curve for Latanoprost



Adapted from Orzalesi N, et al. Invest Ophthalmol Vis Sci. 2000;41:568.

Xalatan® (latanoprost ophthalmic solution) vs Lumigan®† (bimatoprost ophthalmic solution) vs Travatan®† (travoprost ophthalmic solution)

A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients With Elevated Intraocular Pressure:

A 12-Week, Randomized, Masked-Evaluator, Multicenter Study[1]

†Trademarks are the property of their respective owners.

1. Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.

Primary Study Objective[1]

To compare the efficacy of

- Latanoprost
- Bimatoprost
- Travoprost

in patients with elevated IOP

1. Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.

Primary Study End Point[1]

The mean change from baseline to week 12 in IOP measured at the time of peak drug effect (8.00)

1. **Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.**

Secondary Study Objective[1]

To study safety within and between treatment groups over 12 weeks

- **Ocular and systemic adverse events**
- **Visual acuity**
- **Lid and slit lamp examinations**
- **Ophthalmoscopy**
- **Conjunctival hyperaemia (grading scale & patient reports)**

1. **Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.**

Secondary Study End Points[1]

- **Mean change from baseline to week 12 in IOP measured at 12.00, 16.00, and 20.00 (time of trough)**
- **Mean change from baseline to week 12 in diurnal IOP (mean of 8.00, 12.00, 16.00, and 20.00 IOP values)**
- **Mean change from baseline to week 12 in IOP measured at peak and trough evaluated by race**

1. **Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.**

Stephano Gandolfi:Noecker vs Parrish

- POAG most prevalent in Parrish
- **OH** more prevalent in Noecker study
- Baselines comparable?
- Washout required.
- **Central corneal thickness**-no data in either study.
- Netland did 64%(TPT)vs 68%(XLT) in POAG gp

Stephano Gandolfi:Noecker vs Parrish

- **IOP levels comparable in both studies**
- Statistical methods different
- **Parrish sized to detect 1.5mmHg diff in mean IOP;**
- p value=0.05

Stephano Gandolfi:Noecker vs Parrish

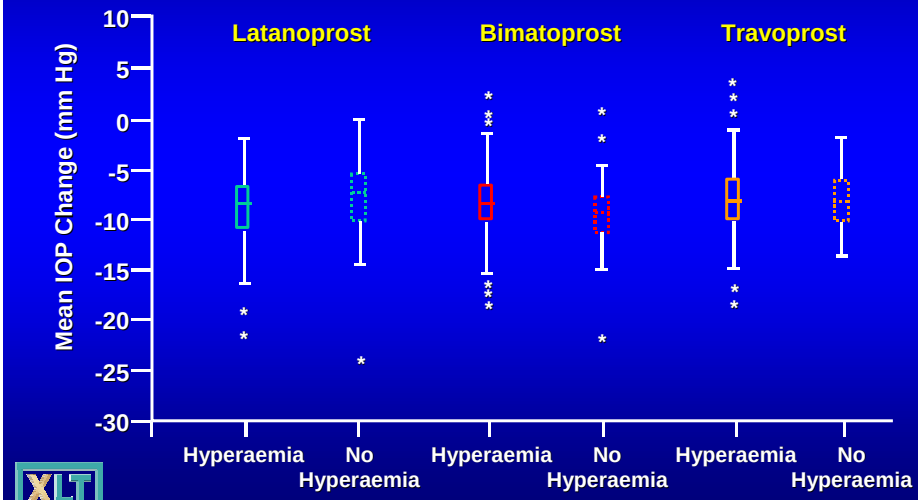
- Previous exposure to PG analogues does not negatively affect outcome
- Pre-study **IOP on PG higher than observed IOP** in same eyes after Rx **three hypotensive lipids**

Stephano Gandolfi:Noecker vs Parrish

- **Bimatoprost** associated with more ocular side effects
- More patients and **more severe hyperaemia**
- Degree of hyperaemia associated with each medication **remained consistent for the 12 weeks***

Distributions of Reductions From Baseline to Week 12 in 8.00 Mean IOP Levels by Treatment and Occurrence of Hyperaemia

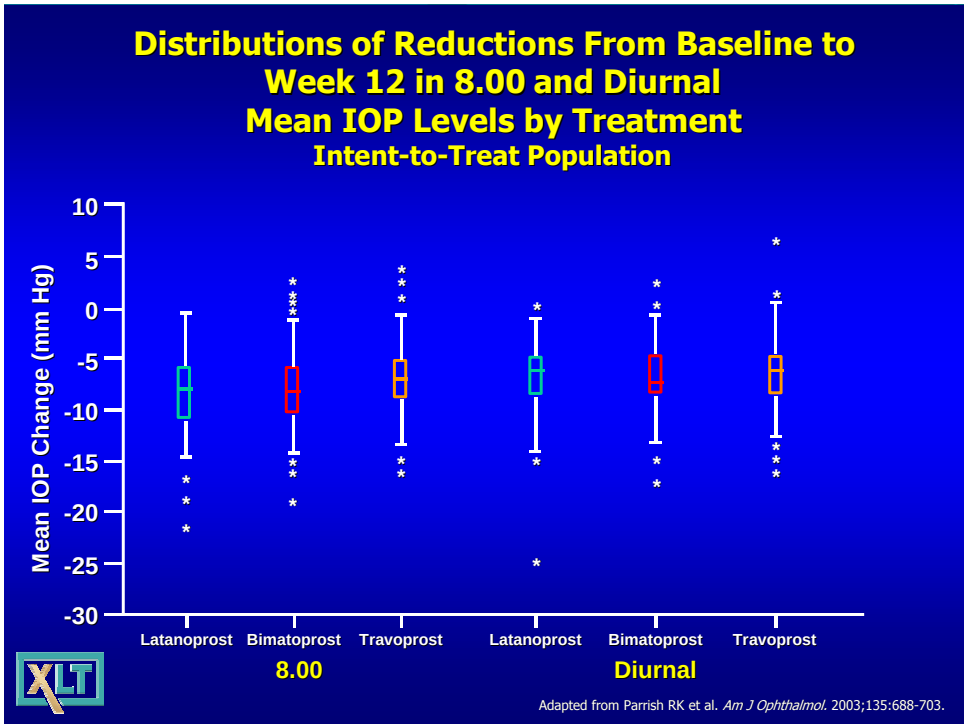
Intent-to-Treat Population; Post Hoc Analysis



Adapted from Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.

Stephano Gandolfi:Noecker vs Parrish

- Comments:
- **Data presentation**: percentage reaching target IOPs
- **Boxplots** with 90% ci in Parrish group dissects out the **outliers better***



Stephano Gandolfi

	Noecker		Parrish	
	Latanoprost	Bimatoprost	Latanoprost	Bimatoprost
Completed	**125**	**124**	**126**	**127**
POAG	78(57.4%)	72(54.1%)	105(77.2%)	103(75.7%)
OH	**47(34.6%)***	**46(34.6%)***	29(21.3%)*	31(22.8%)*
Washout	62%	68%	100%	100%
Previous PG	28.6%	28.6%	52.9%	50%
Baseline IOP-8am	24.9	25	25.7	25.7
Baseline IOP-12pm	**23.3**	24	23.7	23.8

Anne Coleman

- Similar study design but **different conclusions= concern**
- Differences in Baseline characteristics Parrish vs Noecker:
- **65 vs 61 yrs.**
- Caucasians: 53% vs 82.5%
- Brown eyes:66 vs **47%**
- POAG: 77% vs **56%**

Anne Coleman

- Parrish includes **baseline IOP as a covariate** and not Noecker.
- Without controlling IOP at baseline ranges of **22-34 mmHg differences between Rx arms can be misleading**

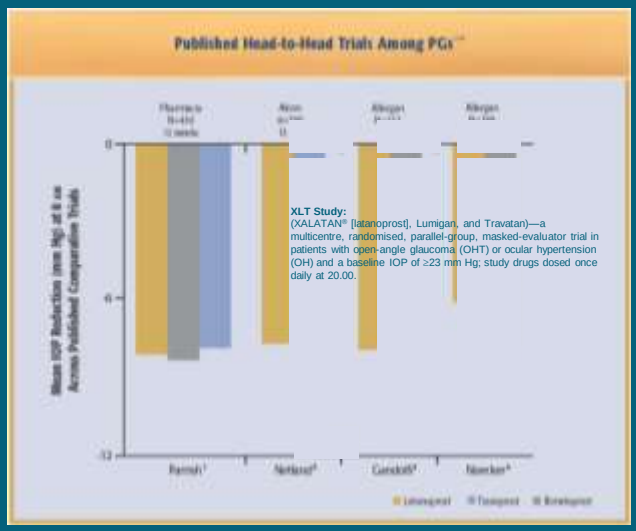
Anne Coleman

- Higher IOP at baseline can yield **higher IOP reduction on Rx**

Carl Camras

- **Three out of 4 studies** demonstrated equivalent efficacy:
- Noecker is the **outlier.**
- Reasons:
- **3 statistical flukes**
- **Outlier**: not double masked
- **Hyperaemia** source of unmasking
- **Chance** alone in single study

IOP Reduction as Demonstrated in Head-to-Head Trials of PG Analogues



[1]Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703. [2]Netland PA et al. *Am J Ophthalmol.* 2001;132:472-484.
[3]Gandolfi S et al. *Advances in Therapy.* 2001;18:110-121. [4]Noecker RS et al. *Am J Ophthalmol.* 2003;135:55-63.

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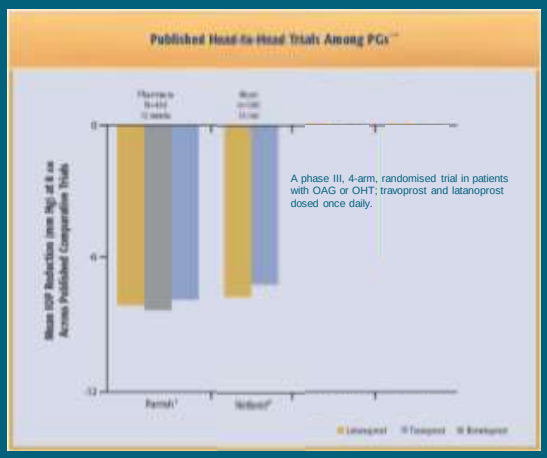

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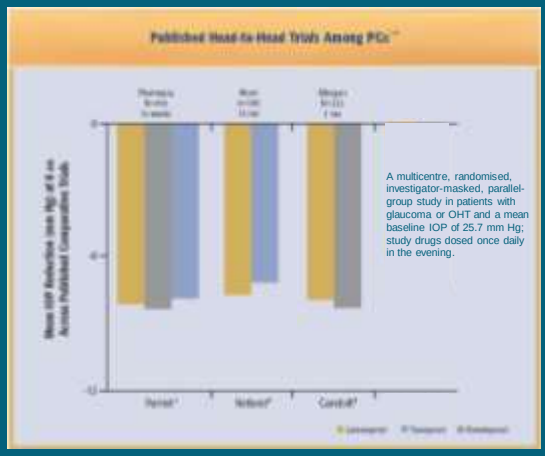

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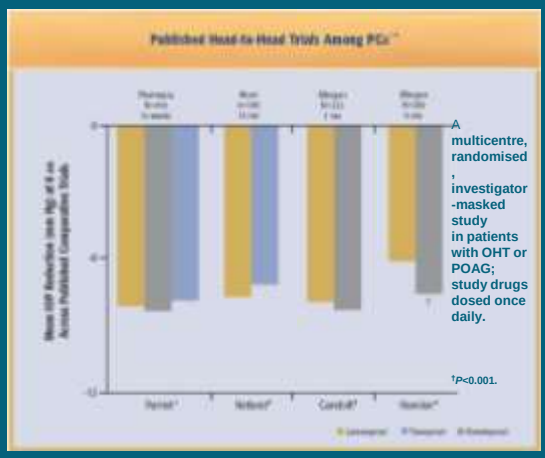

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Carl Camras

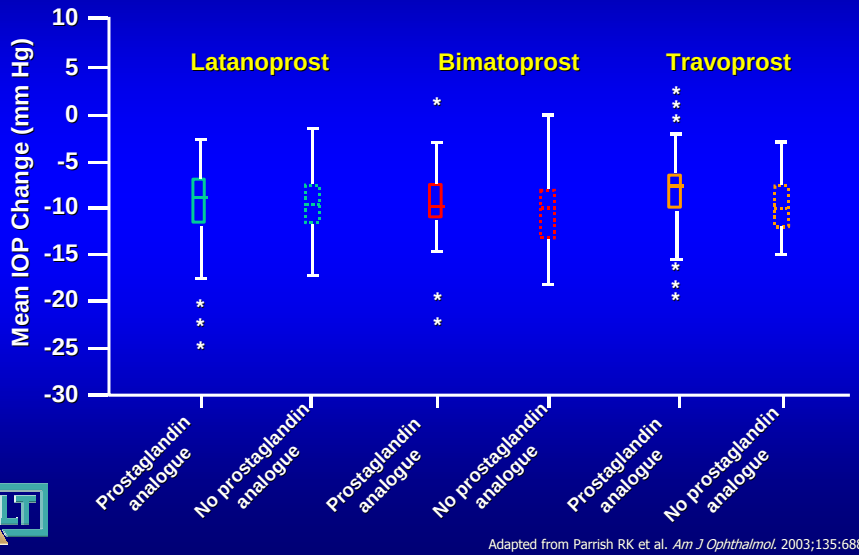
- **Efficacy of Latanoprost only 24% in Noecker**
- versus 33.5% and 30.4% in other studies

Carl Camras

- Marketing spin versus Science
- FDA reviewers are the final judges of claims made by Corporates

Distributions of Reductions From Baseline to Week 12 in 8.00 Mean IOP Levels by Treatment and Prostaglandin Therapy at Screening

Intent-to-Treat Population; Post Hoc Analysis



Adapted from Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.

PG Side Effects:B.Shields

- No convincing evidence of **superiority in IOP lowering**
- Stewart study:
- Latanoprost advantage **less hyperaemia**
- Important to many patients*

PG Side Effects : B.Shields

- Patient **persistency** with ocular PG Rx:
- Population based study: **4356** pts
- Who is likely to stop?
- 3 different prostaglandins

Gail Schwartz et Al

PG Side Effects : B.Shields

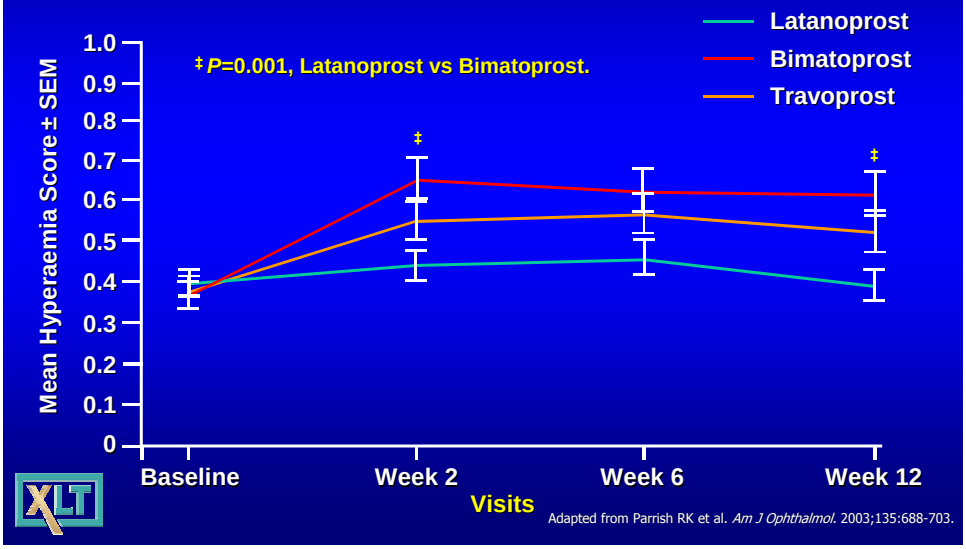
- Latanoprost (Xalatan) patients' persistence:
- Compared to those on
- 1. Lumigan **38%** more likely to stop treatment
- 2. Travatan patients **36%** more likely to stop Rx

Gail Schwartz et Al

Kuldev Singh: Stewart Study

- Volunteers on latanoprost
- less likely to be told by others that eyes red.
- Subjects : themselves noted more redness when receiving BMT/TPT than Latanoprost
- Data from all long term studies: Hyperaemia constant for duration of therapy

Mean Hyperaemia Score by Treatment and Visit
Investigators' Assessments



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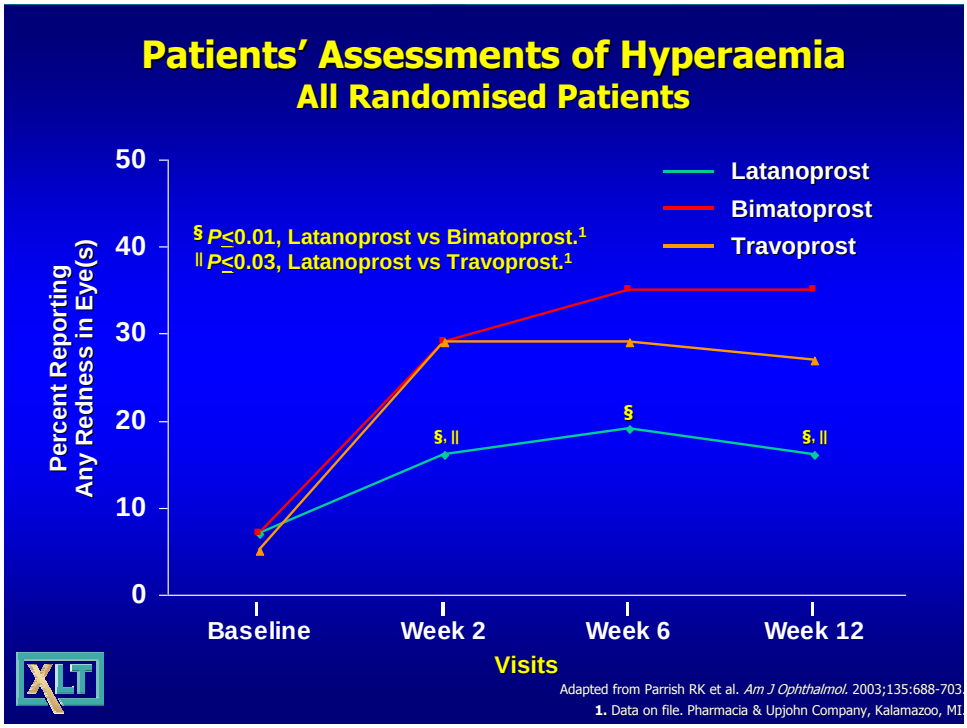
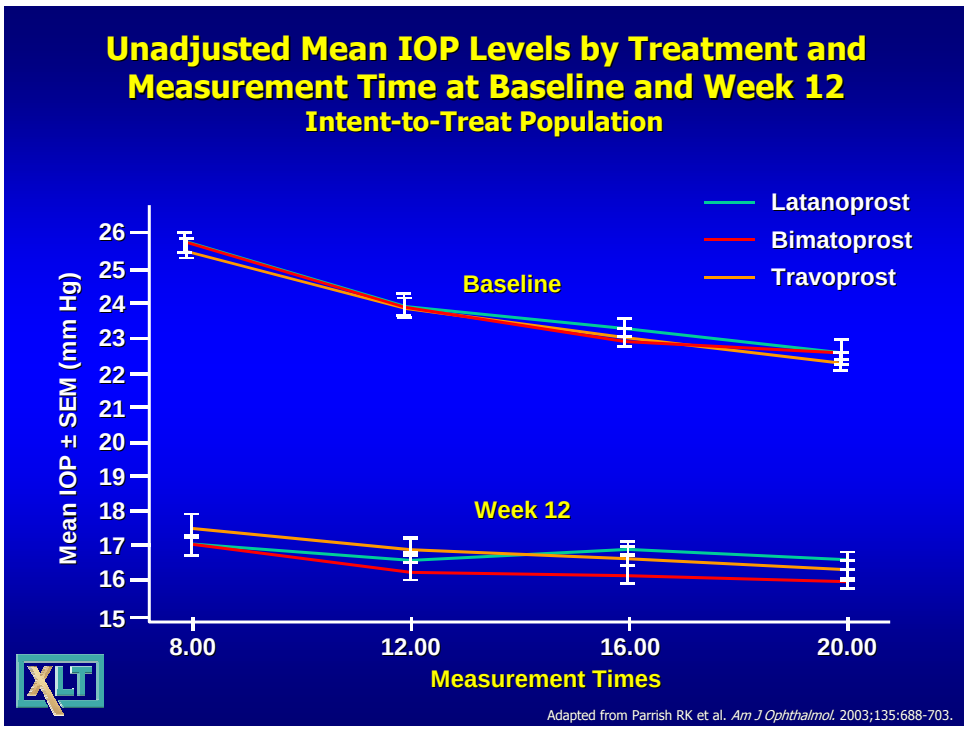
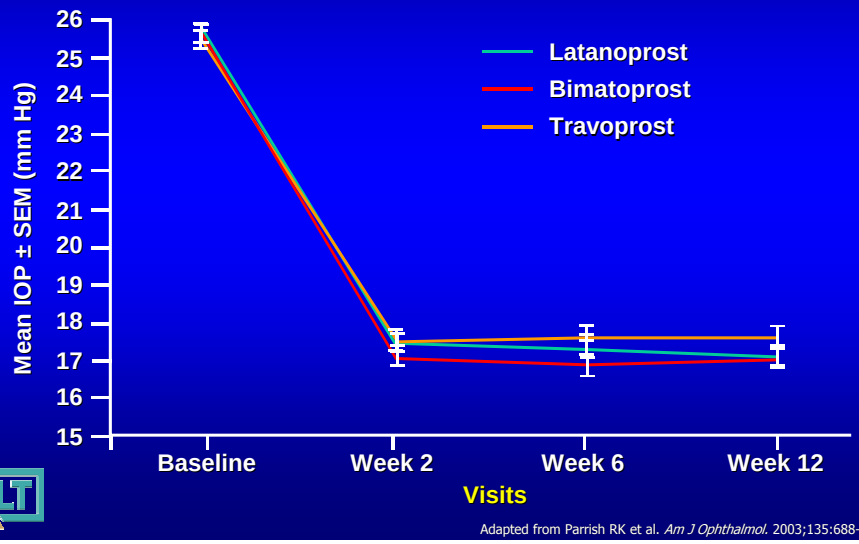

Patients' Assessments of Hyperaemia
All Randomised Patients
Percent Reporting Any Redness in Eye(s)
50
40
30
20
10
0
§ P≤0.01, Latanoprost vs Bimatoprost.1
‖ P≤0.03, Latanoprost vs Travoprost.1
Latanoprost
Bimatoprost
Travoprost
§, ‖
§
§, ‖
Baseline
Week 2
Week 6
Week 12
Visits
XLT
Adapted from Parrish RK et al. Am J Ophthalmol. 2003;135:688-703.
1. Data on file. Pharmacia & Upjohn Company, Kalamazoo, MI


Unadjusted Mean IOP Levels by Treatment and Measurement Time at Baseline and Week 12
Intent-to-Treat Population
Mean IOP ± SEM (mm Hg)
26
25
24
23
22
21
20
19
18
17
16
15
Latanoprost
Bimatoprost
Travoprost
Baseline
Week 12
8.00
12.00
16.00
20.00
Measurement Times
XLT
Adapted from Parrish RK et al. Am J Ophthalmol. 2003;135:688-703.

Unadjusted 8.00 Mean IOP Levels by Treatment and Visit
Intent-to-Treat Population



Adapted from Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.

Summary of Efficacy Results[1]

- Mean IOP levels at baseline were not significantly different
- Mean IOP levels at 8.00 at week 12 were not significantly different
-
- Mean IOP levels at week 12 were not significantly different at any time point
- Mean diurnal IOP levels at week 12 were not significantly different
- **No racial differences in response to treatments were observed (exploratory analysis)**

1. Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.

CLINICAL TRIALS

SECTION EDITOR: ROY BECK, MD, PhD

A 5-Year, Multicenter, Open-Label, Safety Study of Adjunctive Latanoprost Therapy for Glaucoma

Albert Alm, MD; John Schoenfelder, PhD; Jacquie McDermott, PhD

Objective: To evaluate the 5-year safety and efficacy of adjunctive 0.005% latanoprost once daily.

Methods: Patients with primary open-angle or exfoliation glaucoma who completed a 3-year, open-label, uncontrolled, prospective trial could enter a 2-year extension phase. High-resolution color photographs of irides were taken at baseline and at 14 subsequent visits. Photographs were assessed for change in iris pigmentation compared with baseline. Intraocular pressures and adverse events were recorded.

Main Outcome Measure: Development and progression of increased iris pigmentation over 5 years.

Results: Of the 519 original patients, 380 enrolled in the extension phase with approximately 89% having an eye color known to be susceptible to color change. After 5 years, most patients had no increase in iris pigmentation, but certain colored irides exhibited notably greater susceptibility than others. For those whose irides did change, onset occurred during the first 8 months in 74% and during the first 24 months in 94%. No patient developed an increase in pigmentation after month 36; the rate of progression decreased over time. Adverse event profiles were similar for patients with and without increased pigmentation. The overall mean intraocular pressure reduction from baseline of 25% was sustained with no need for change in intraocular pressure–lowering treatment in 70% of the eyes.

Conclusion: Latanoprost therapy is safe and well tolerated for long-term treatment of open-angle glaucoma.

Arch Ophthalmol. 2004;122:957-965

Fixed Combination : Rationale

- Pharmacology of Components
- Timolol facts
- Hyperaemia management
- Summary

RATIONALE FOR LATANOPROST AND TIMOLOL FIXED COMBINATION (FC)

- Many patients need more than one drug to reach target IOP
- Xalatan and timolol is the most commonly prescribed unfixed combination
- Issues: Multiple bottles
  - Multiple dosing regimes
  - Confusion
  - Dosing error potential
  - Compliance
  - Exposure to preservative

XALATAN

- t_{max} aqueous humour 2-3 hours
- Maximal intraocular pressure reducing effect 8-12 hours*
- 0.005% solution applied once daily

Timolol maleate

- Lowers IOP by decreasing **ciliary aqueous humour formation** ; blocking mainly **beta 2 receptors**
- Maximal intraocular pressure reducing effect
- **2-3 hours**
- **0.5% solution** applied twice daily
- **is in excess of necessary dose**

XALATAN COMBINATION

- **Ocular pharmacokinetics**
  - Absorption into aqueous humour **similar for FC, latanoprost and timolol**
  - Concentration of **latanoprost acid higher** with **FC** vs monotherapy
  - Latanoprost did not affect **PK of timolol**

XALATAN COMBINATION

- Pharmacodynamics:
-
  - Single dose administration

    Time of onset within **1 hour**

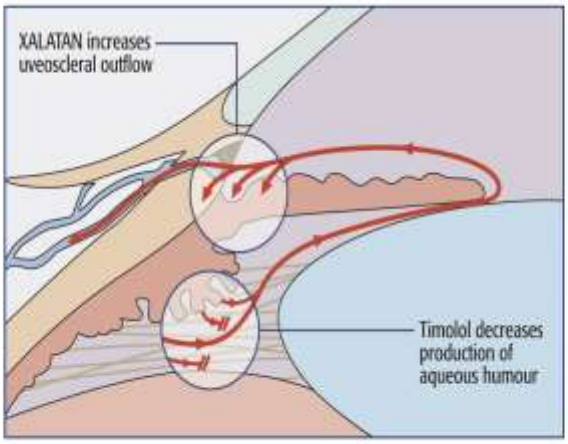
    Maximal reduction of 12.4 mmHg at 6.4 hours
    -

    IOP reduction still seen after 24 and 48 hours

XALATAN COMBINATION

- **Systemic pharmacokinetics**
  - **Less rapid absorption of timolol with FC**
  - **t_{max} reached later with FC**
  - **No significant interaction administered as a FC**

XALACOM Provides Complementary Modes of Action to Lower IOP



WHY TIMOLOL ?

- Most common combination in use
- **Aqueous suppressant**; most effective combination with Xalatan
- **Data show fixed combination more**
- **effective in IOP reduction** than individual components

Is Once Daily Timolol Enough?

- **70% patients controlled with 0.25% once daily**
- 30% require 0.5%
- or BD 0.25%, especially black patients
- **Conclusion**: once daily sufficient for most *
- [T Zimmerman 1976, J Wilensky, Ophth 1993, many m

Do Our Black Patients Need More ?

Melanocyte storage/saturation 2-4weeks*

Monitor 1 month for stabilization

0.5% conc. sufficient once daily

Therapeutic Drift:Myth or Reality?

"Short – term escape",partial loss efficacy in weeks

possibly upregulation Beta receptors in ciliary body

"Long –term drift" loss over months /years : progression and real loss

(slightly higher aqueous flow after 1 year vs 1 week, Brubaker 1982)

Therapeutic Drift:Myth or Reality?

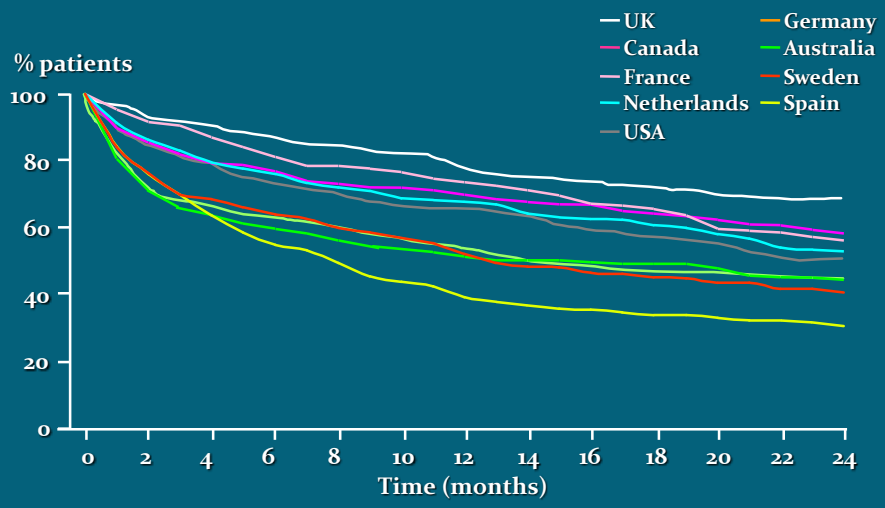
1.Compliance Issue?
SE's from o/d/ BD regimen

2.**Senescence of TM;** decreased facility outflow*

3.**Switch** : more IOP lowering needed

4.**Doubt;** ONE EYE TRIAL** (P.Palmberg)

Patients remaining on initial β-blocker monotherapy over 2 years



Adapted from Jönsson et al (1998)

Non selective Beta Blocker Side Effects

- Exercise tolerance decreased
- **Males comply poorly**: impotence(BES)
- Asthma (FEV1 reduced)
- **Central nervous side effects** :
- depression management intractable, precipitate migraines in sufferers

WHY NOT A.M. DOSING ?

Daytime Aqueous Flow **2x nocturnal flow;**

BB's no effect at night *

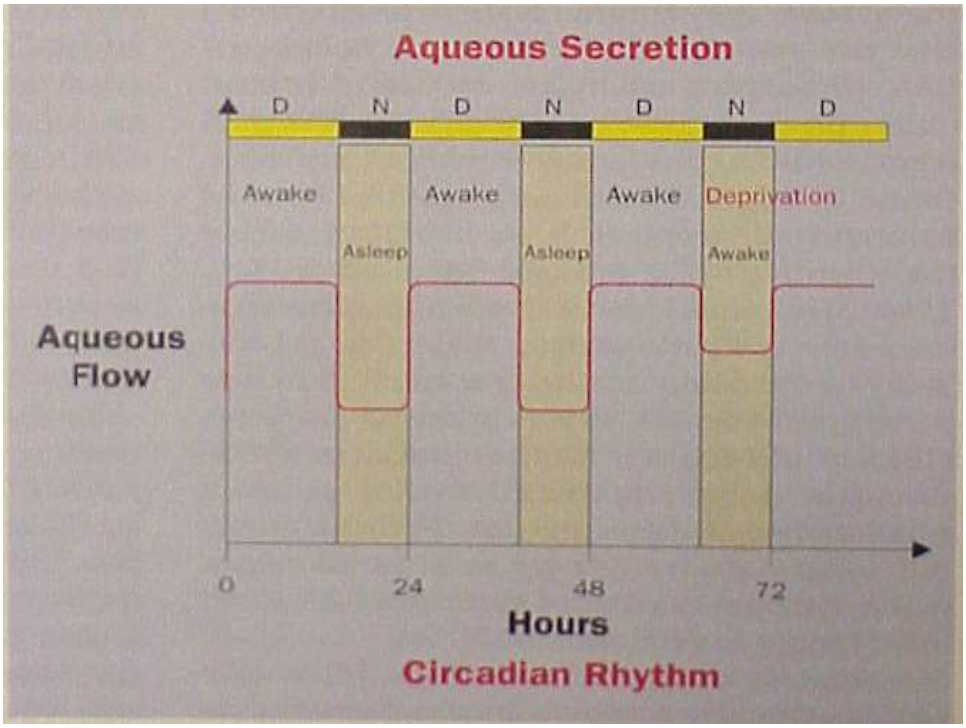
BB's antagonize Beta adrenergic tone
= smoothes out diurnal curve

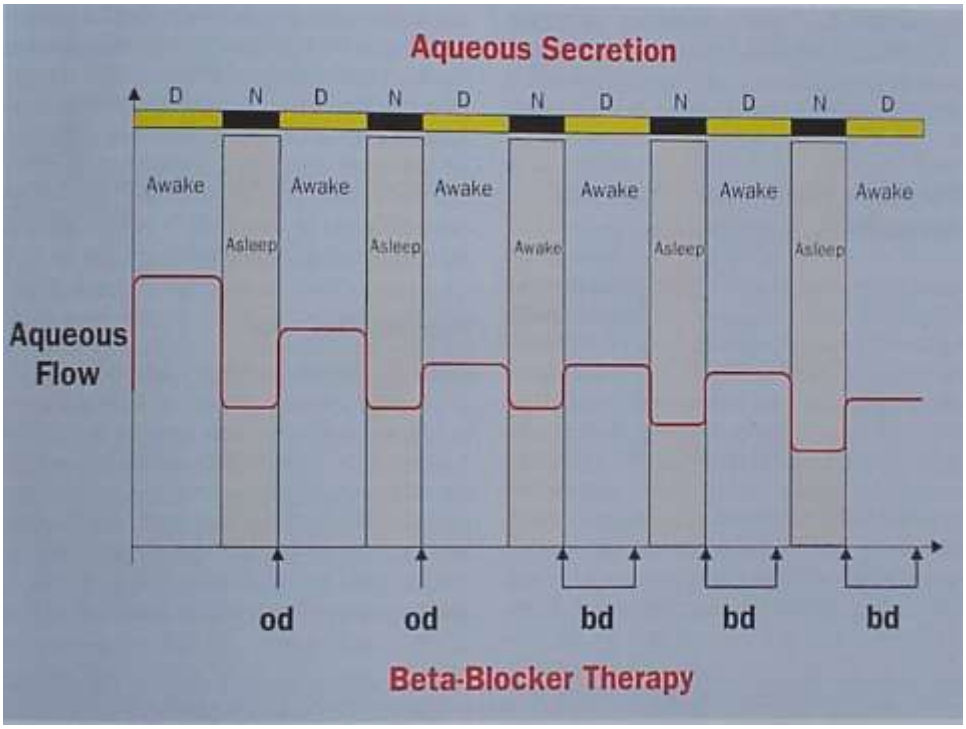
Patient preference

Long duration action BB's

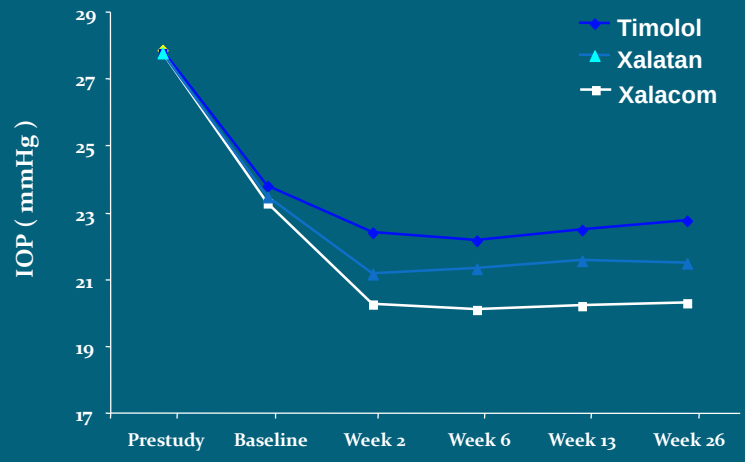
No peak or trough effects

so evening dose adequate choice


Aqueous Secretion
D
N
D
N
D
N
D
Awake
Asleep
Awake
Asleep
Awake
Deprivation
Awake
Aqueous Flow
0
24
48
72
Hours
Circadian Rhythm


Aqueous Secretion
D
N
D
N
D
N
D
N
D
N
D
Awake
Asleep
Awake
Asleep
Awake
Awake
Asleep
Awake
Asleep
Awake
Aqueous Flow
od
od
bd
bd
bd
Beta-Blocker Therapy

Overall IOP Lowering Effect
European and US at 8 am IOP



Xalacom: Indications

- **Target IOP not reached :**
- **1. Monotherapy using** Prostaglandin(Lipid receptor agonist)
- 2. Fixed combination
- 3.Other Dual therapies

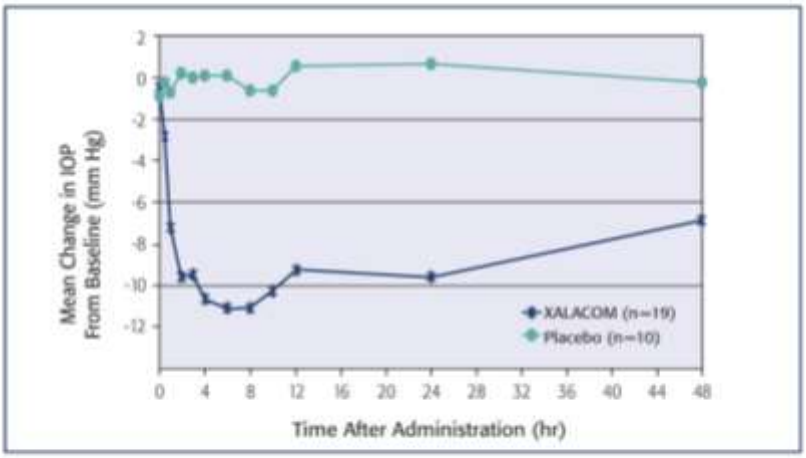
Xalacom:Indications

1.Drug intolerance
allergies,
BAK o/load
stinging

2. Compliance failure
on BD dosing

XALACOM Maintains IOP Reduction at 24 and 48 Hours[6,7]

- XALACOM demonstrated a clinically and statistically significant reduction in IOP (compared with placebo) that was evident at 24 hours and even at 48 hours[6,7]

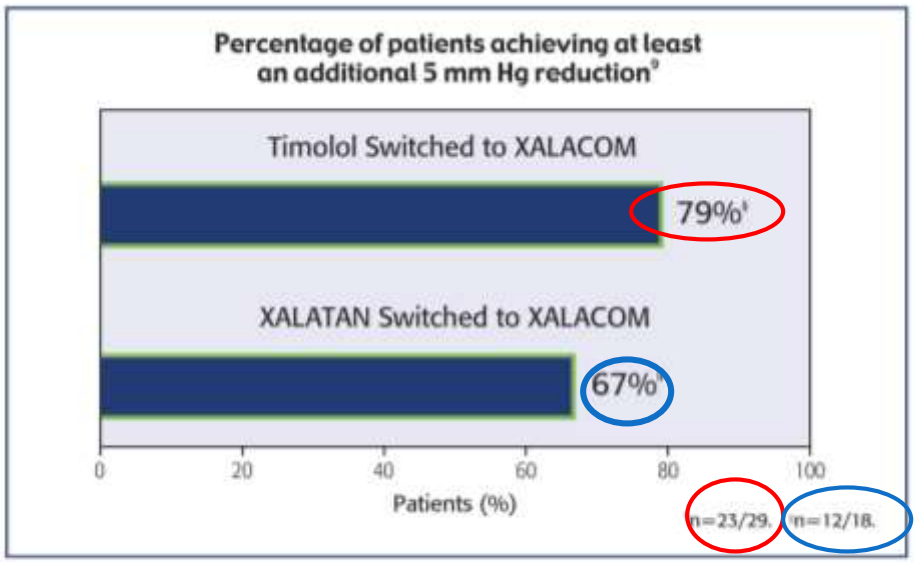


These data are from a randomised, double-masked trial including patients (per-protocol population) with ocular hypertension who were treatment naive. The primary objective was 12-hour IOP reduction following a single-dose administration of XALACOM or placebo. The secondary objectives were IOP reduction at 24 and 48 hours.[6,7]

Experience the Additional Power in 1 Daily Drop

XALACOM Provides Additional IOP Reductions in Patients Inadequately Controlled on Monotherapy[9]

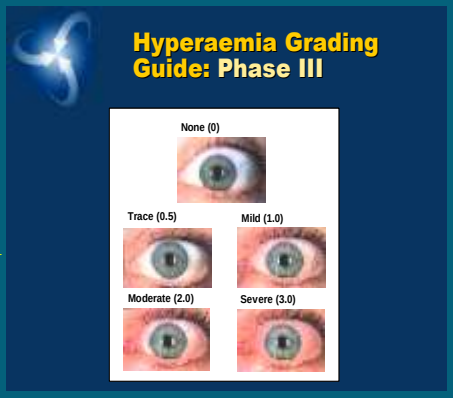
- In the study of 418 patients and in a second study of similar design (N=436),[10] a retrospective subanalysis looked at patients whose IOP was inadequately controlled on 1 of the 3 monotherapies and were switched to open-label XALACOM (patients completing 52 weeks of study are shown below)[9]



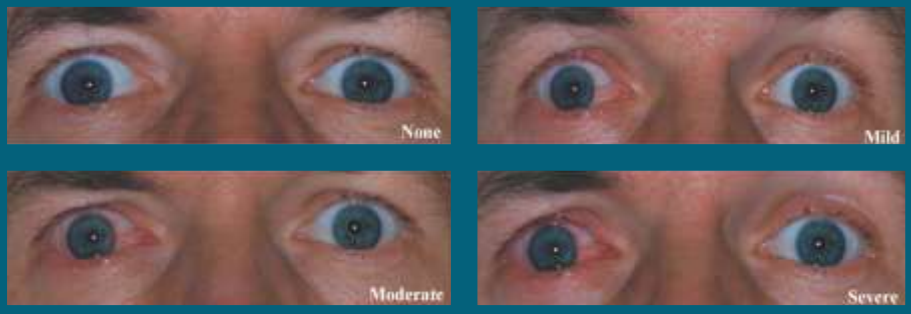
During the double-masked portion of these trials, patients whose IOP was inadequately controlled were switched to open-label XALACOM and were continued on that therapy for the 52-week study period if they responded adequately (n=72). Of those, 68 patients switched from either latanoprost or timolol, 47 completed the entire study period, and a retrospective analysis of their results is shown above. The remaining patients withdrew due to inadequate IOP control (n=17), adverse events (n=1), or for other reasons (n=3).[9]

HYPERAEMIA:Management

- Educate (Gross, Palmberg)
- Fluoromethalone
- Alternate days
- Non-preserved tears 5 mins prior to instilling
- Total BAK load eg dry eye meds



Hyperaemia Grading Scale



Adapted from Parrish RK et al. *Am J Ophthalmol.* 2003;135:688-703.

BAK LOAD

Product	BAK(%)
Xalacom(80 drops)	0.02
Xalatan	0.02
Travatan	0.015
Cosopt	0.015
Lumigan	0.004
Timoptol	0.01

Clinical Ophthalmology

Dovepress

ORIGINAL RESEARCH

Randomized trial comparing three fixed combinations of prostaglandins/prostamide with timolol maleate

This article was published in the following Dove Press journal:
Clinical Ophthalmology
9 February 2011
Number of times this article has been viewed

Jaime Pablo Kelly Rigollet
Joan Anton Ondategui
Angels Pasto
Laura Lop

Institut Català de la Salut, Centre de Atenció Primaria MANSO, Eixample esquerra, Barcelona, Spain

The results of this were first presented in the World Glaucoma Congress, Boston (8–11 July 2009)

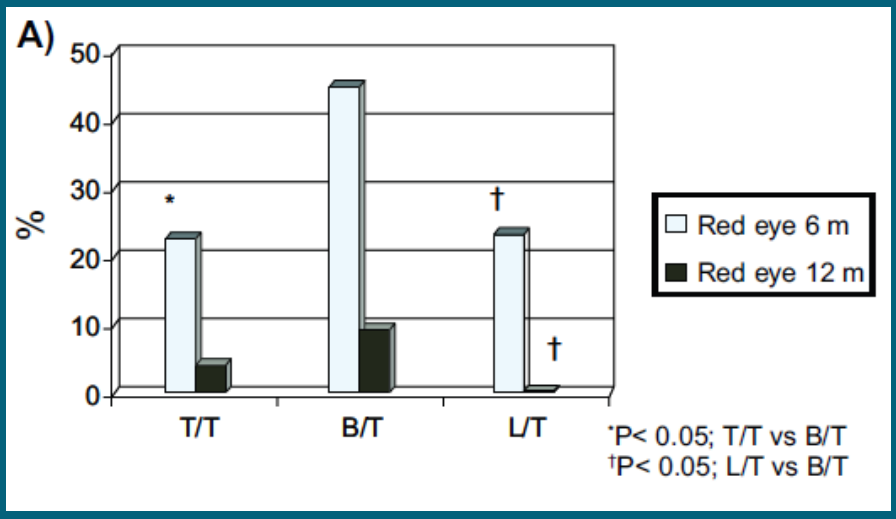
Introduction: To evaluate the long-term efficacy and safety of 3 commercially available fixed combinations of prostaglandin analogs or a prostamide with timolol maleate in patients with primary open angle glaucoma or ocular hypertension.

Methods: In this randomized, prospective, single-blind study, intraocular pressure (IOP) was measured after a 1-month washout period and pachymetry was performed before randomizing patients to latanoprost 50 μg/timolol 5 mg/1 mL (L/T), bimatoprost 300 μg/timolol 5 mg/1 mL (B/T), or travoprost 40 μg/timolol 5 mg/1 mL (T/T). IOP was measured monthly for 6 months and then at 12 months by an investigator blinded to the study drug. Adverse reactions were recorded.

Results: 128 cases were included in the study. The 3 treatment groups had similar baseline characteristics and comparable IOP. All 3 combinations decreased IOP by at least 6 mmHg and IOP remained below 21 mmHg throughout the study. At 12 months L/T achieved greater reduction in IOP than the other 2 fixed combinations, but the difference between L/T and B/T was not statistically significant. At 6 months, more B/T-treated patients reported red eye ($P < 0.05$ vs L/T and T/T). At 12 months, fewer adverse reactions were reported, with no cases of red eye reported for L/T ($P = 0.03$ vs B/T).

Conclusions: All 3 combinations are effective at lowering IOP but at 12 months L/T and B/T were found to be more effective than T/T. Treatments were well tolerated after 12 months but L/T showed less hyperemia than B/T throughout the study ($P < 0.05$).

Hyperaemia (Red Eyes)



IOP Reduction

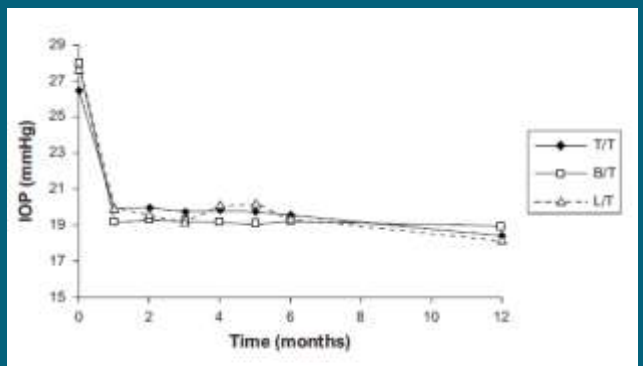
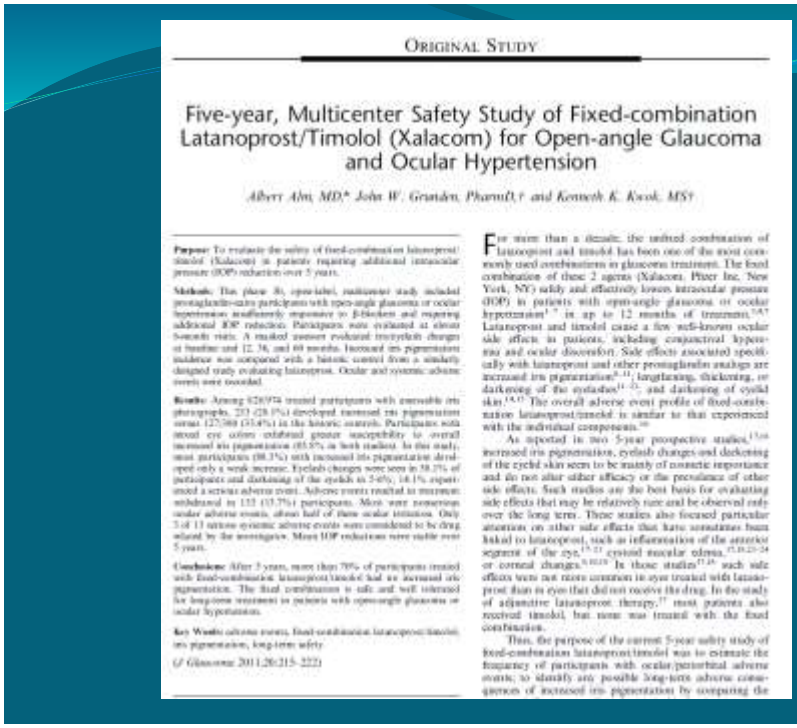


Figure 1 Changes in intraocular pressure (IOP) from baseline.
Abbreviations: B/T, bimatoprost/timolol fixed combination; L/T, latanoprost/timolol fixed combination; T/T, travoprost/timolol fixed combination; IOP, intraocular pressure.

Dark Eye rings

	6 months	12 months
B/T	14.3%	14.3%
T/T	4.5%	13.6%
L/T	0%	15%

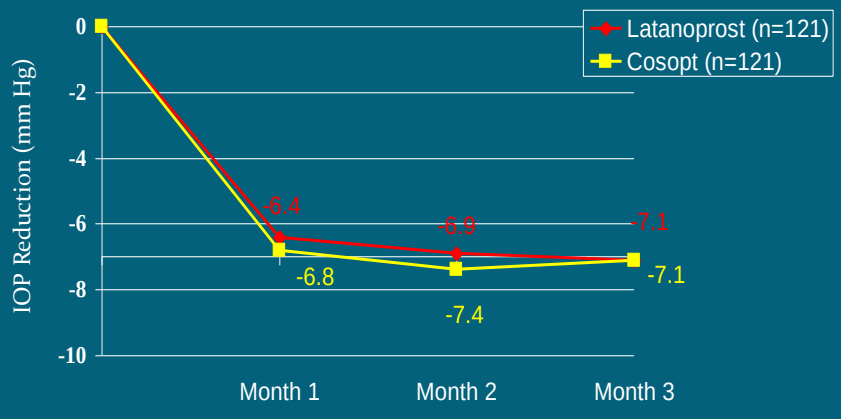


ORIGINAL STUDY

Five-year, Multicenter Safety Study of Fixed-combination Latanoprost/Timolol (Xalacom) for Open-angle Glaucoma and Ocular Hypertension

Albert Alm, MD, John W. Grierson, PharmD,† and Kenneth K. Kwok, MS†*

Cosopt® vs. Latanoprost



24 IOP : Cosopt better 10pm

Presented at ARVO, 1999

Xalacom vs Cosopt

Mean IOP reduction at month 3 (ANCOVA)

	Xalacom	Cosopt	Difference	95% Confidence Interval
8 AM	9.6	8.4	1.2 *	0.33 - 2.12
12 Noon	9.1	8.8	0.3	-0.49 - 1.03
4 PM	9.6	8.2	1.4 *	0.67 - 2.15
Diurnal	**9.5**	**8.5**	**1.0 ***	**0.31 - 1.69**

* p<0.05 t-test

Dong H. Shin, MD
Kresge Eye Institute, Wayne State University, Detroit, US

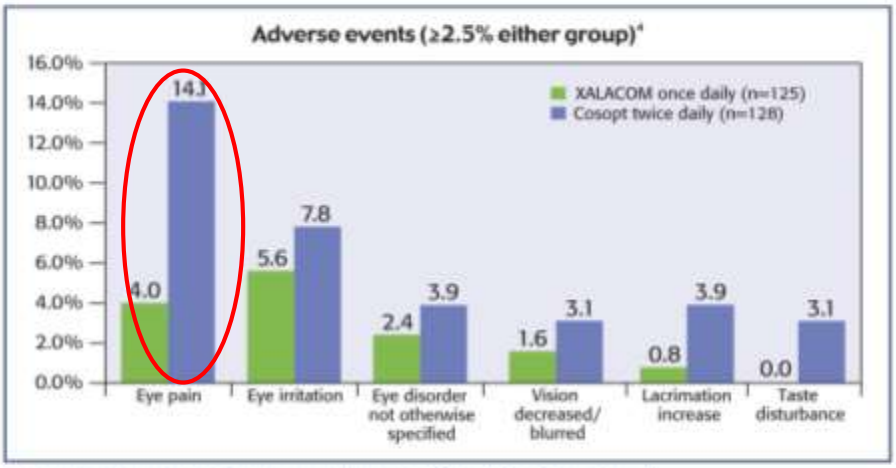
Experience the Greater Power in 1 Daily Drop

XALACOM Once Daily Was Significantly More Effective in Reducing Mean Diurnal IOP Than Cosopt Twice Daily[4]

- XALACOM achieved a 33.5% mean reduction in diurnal IOP vs 30.3% for Cosopt[†*] (dorzolamide hydrochloride and timolol maleate) (*P*=0.017) at month 3[4†]

Experience Well-Tolerated Therapy

- Compared with Cosopt



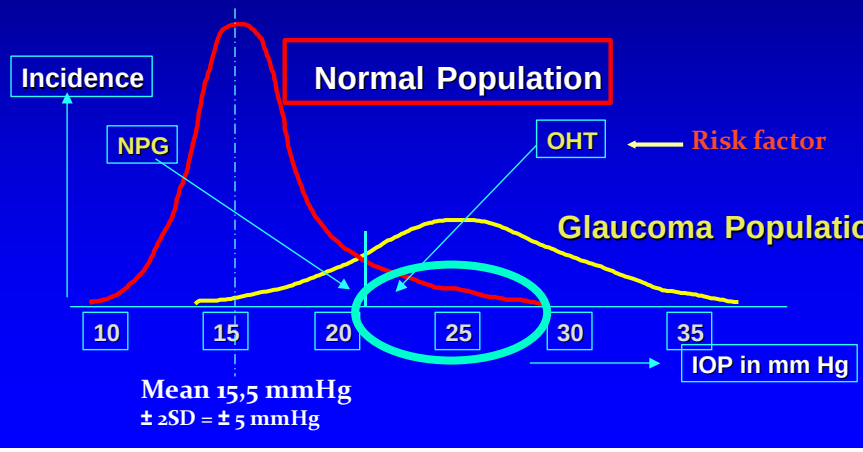
Adapted from Feldman RM et al. Poster presented at: ICO; 21-25 April 2002; Sydney, Australia.

[1]In a 3-month, randomised, parallel-group, masked-evaluator, multicentre study, patients with POAG or ocular hypertension that was insufficiently responsive to monotherapy were placed on either once-daily XALACOM (n=125) or twice-daily Cosopt (n=128).[4]

Elephant scratching post with a difference

IOP and Glaucoma

IOP curves of Normal- and Glaucoma Population



Treatment Principles and Options

Antiglaucoma drugs have been available since 1875. The following diagram shows the chronology of the introduction of topical intraocular pressure-lowering medications (Fig. 3.3).

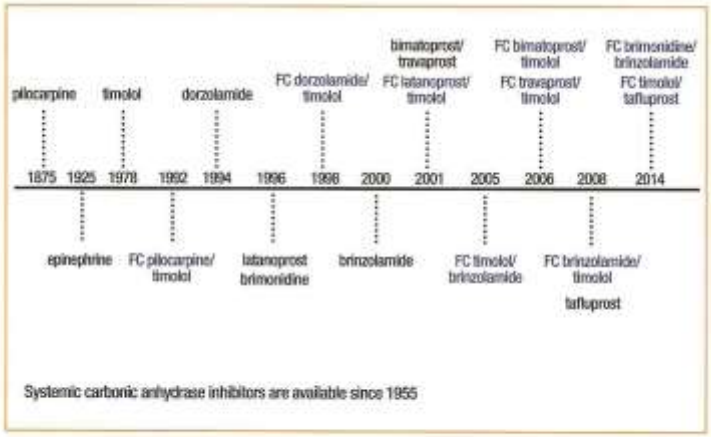
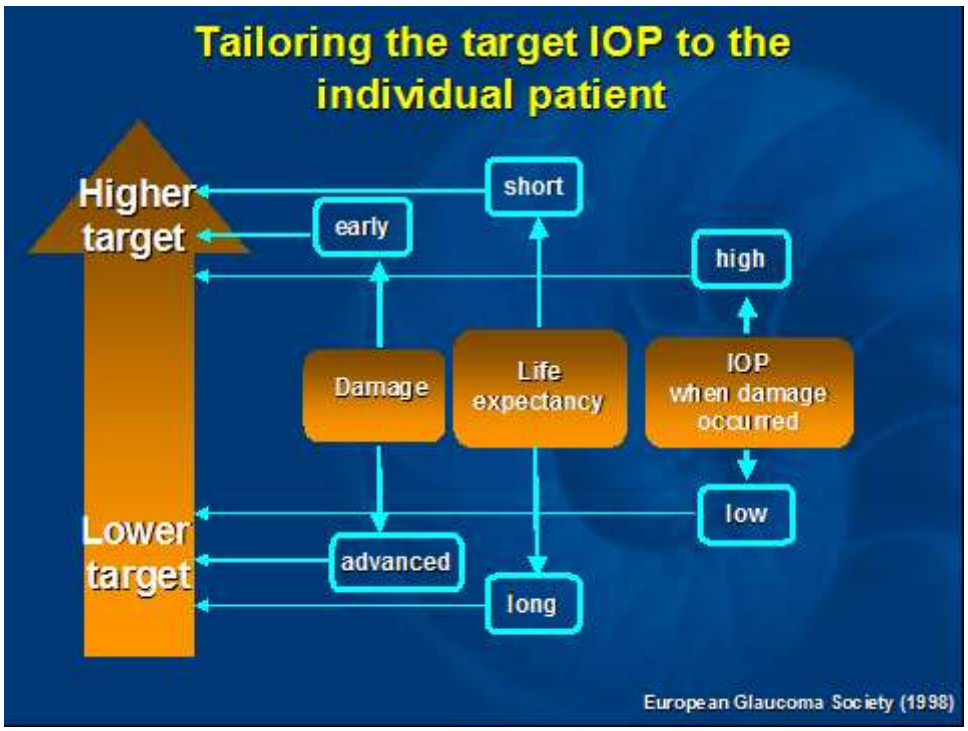
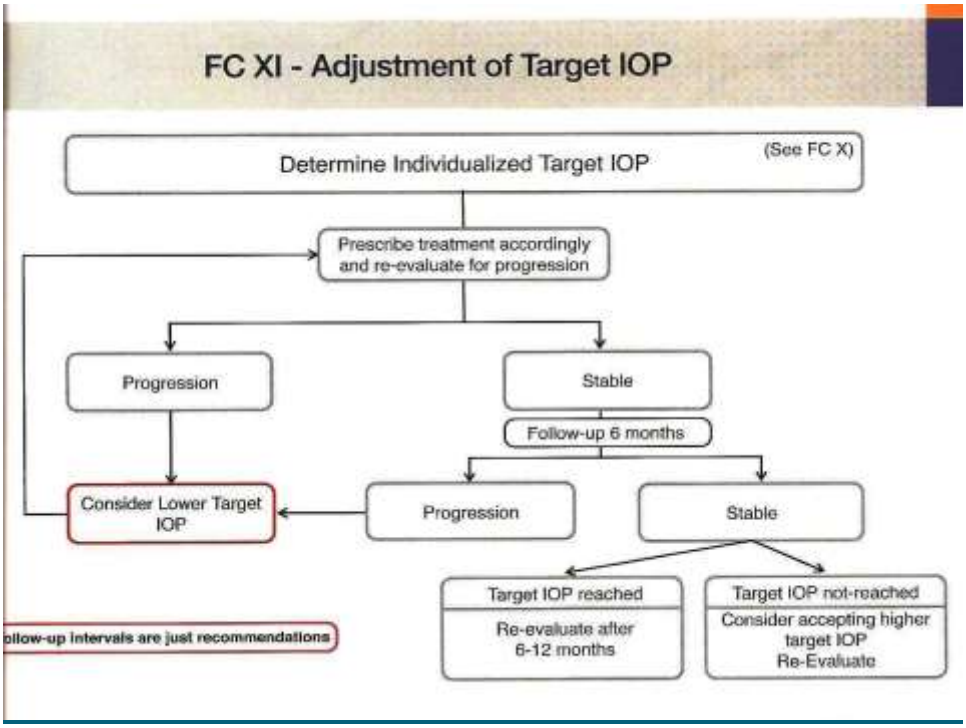


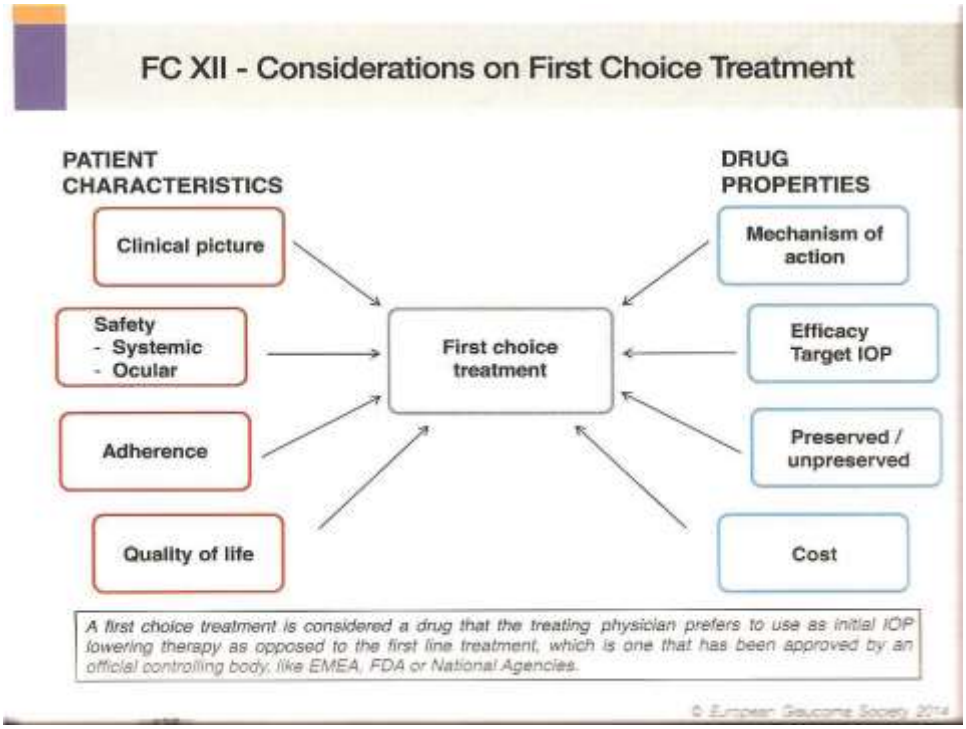
Figure 3.3. IOP lowering molecules and year of first clinical use. FC: fixed combination. In black: monotherapy.

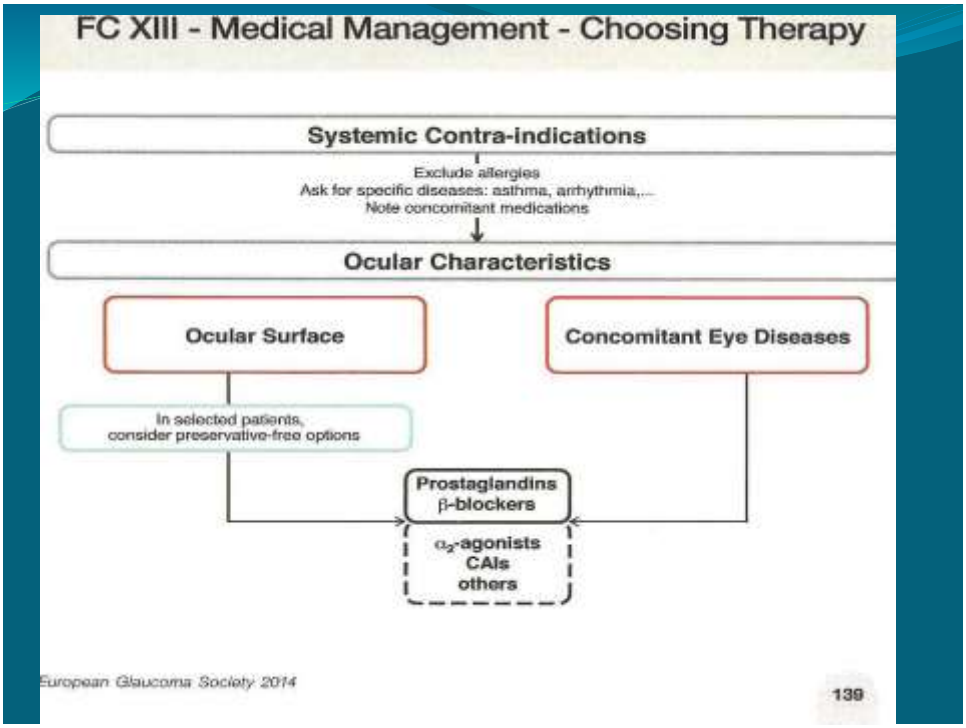
Target pressure

- IOP highest at night and supine position
- Perfusion pressure is lowest while sleeping
- Aqueous production: 10pm to 6am : =1.2µl/min
- and 6am to 12 noon = 3.0µl/min
- Why is IOP highest when aqueous production is lowest?
- Outflow facility is lowest at night




FC XI - Adjustment of Target IOP
Determine Individualized Target IOP
(See FC X)
Prescribe treatment accordingly and re-evaluate for progression
Progression
Stable
Follow-up 6 months
Consider Lower Target IOP
Progression
Stable
Target IOP reached
Re-evaluate after 6-12 months
Target IOP not-reached
Consider accepting higher target IOP
Re-Evaluate
ollow-up intervals are just recommendations

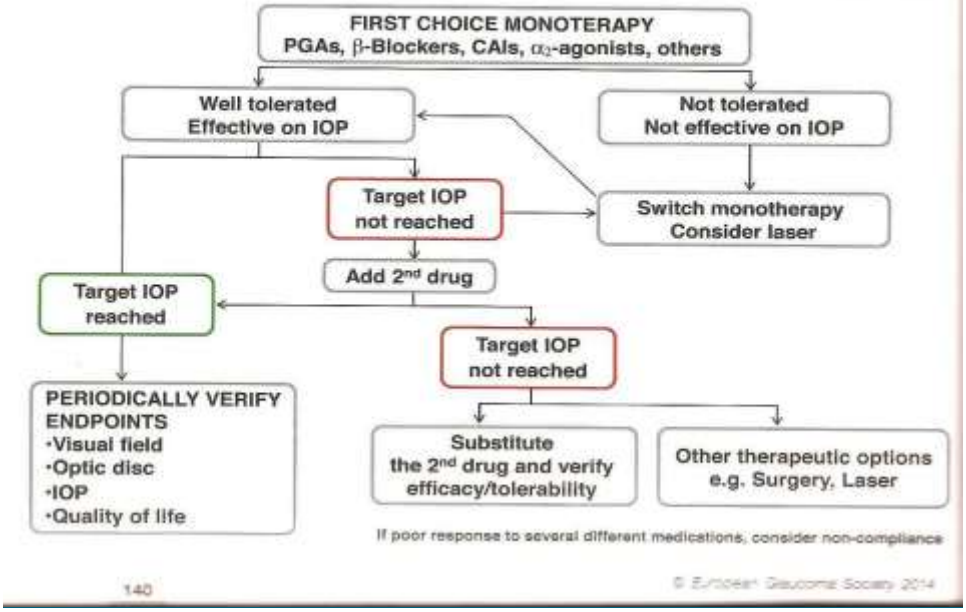

FC XII - Considerations on First Choice Treatment
PATIENT CHARACTERISTICS
DRUG PROPERTIES
Clinical picture
Safety
- Systemic
- Ocular
Adherence
Quality of life
First choice treatment
Mechanism of action
Efficacy Target IOP
Preserved / unpreserved
Cost
A first choice treatment is considered a drug that the treating physician prefers to use as initial IOP lowering therapy as opposed to the first line treatment, which is one that has been approved by an official controlling body, like EMEA, FDA or National Agencies.
© European Glaucoma Society 2014



First choice : Monotherapy

- **Meta-analysis** randomised controlled trials
- **Highest** reduction in IOP : **Prostaglandins**
- **Next most effective : Non selective Beta blockers**
- **Followed by Alpha –adrenergic agonists**
- **Topical CAI (carbonic anhydrase inhibitors)**

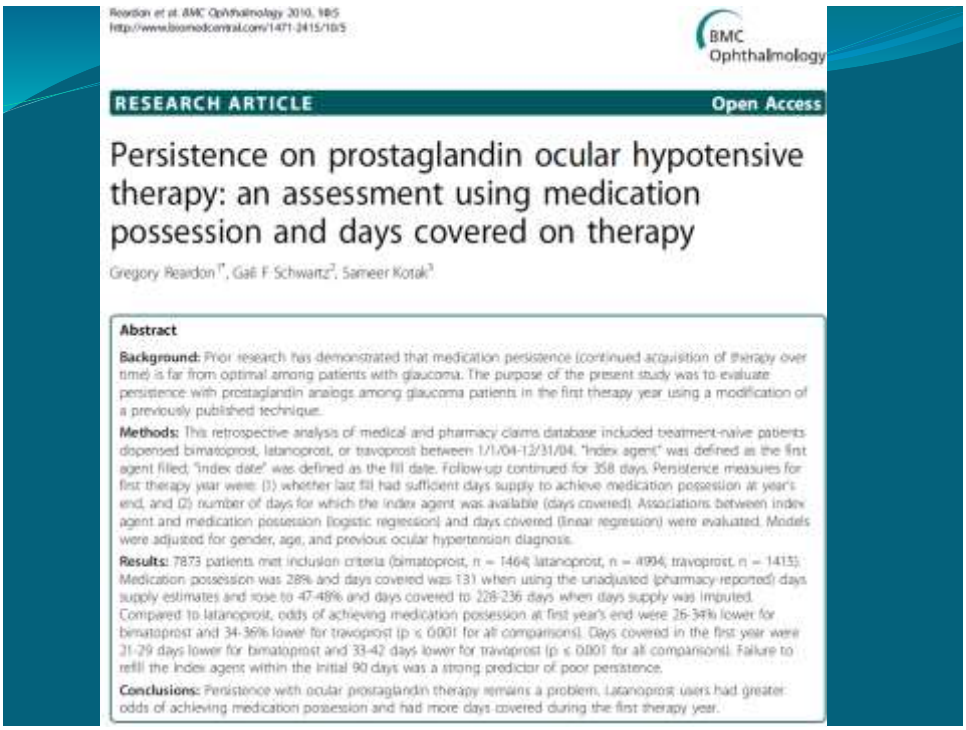
FC XIV - Therapeutical Algorithm in Glaucoma Topical Therapy



Breakfast surprise in Kruger Park

Compliance and persistency

- **Are patients taking meds correctly ?: compliance adherence**
- **Are they continuing long term: persistence**
- **Convenience linked to compliance**
- **Once a day has advantage over BD (twice daily)**



Reardon et al. BMC Ophthalmology 2010, 10:5
http://www.biomedcentral.com/1471-2415/10/5

BMC Ophthalmology

RESEARCH ARTICLE Open Access

Persistence on prostaglandin ocular hypotensive therapy: an assessment using medication possession and days covered on therapy

Gregory Reardon[1*], Gail F Schwartz[2], Sameer Kotak[3]

Abstract

Background: Prior research has demonstrated that medication persistence (continued acquisition of therapy over time) is far from optimal among patients with glaucoma. The purpose of the present study was to evaluate persistence with prostaglandin analogs among glaucoma patients in the first therapy year using a modification of a previously published technique.

Methods: This retrospective analysis of medical and pharmacy claims database included treatment-naive patients dispensed bimatoprost, latanoprost, or travoprost between 1/1/04-12/31/04. "Index agent" was defined as the first agent filled; "index date" was defined as the fill date. Follow-up continued for 358 days. Persistence measures for first therapy year were: (1) whether last fill had sufficient days supply to achieve medication possession at year's end, and (2) number of days for which the index agent was available (days covered). Associations between index agent and medication possession (logistic regression) and days covered (linear regression) were evaluated. Models were adjusted for gender, age, and previous ocular hypertension diagnosis.

Results: 7873 patients met inclusion criteria (bimatoprost, n = 1464; latanoprost, n = 4994; travoprost, n = 1415). Medication possession was 28% and days covered was 131 when using the unadjusted (pharmacy-reported) days supply estimates and rose to 47-48% and days covered to 228-236 days when days supply was imputed. Compared to latanoprost, odds of achieving medication possession at first year's end were 26-34% lower for bimatoprost and 34-36% lower for travoprost ($p \leq 0.001$ for all comparisons). Days covered in the first year were 21-29 days lower for bimatoprost and 33-42 days lower for travoprost ($p \leq 0.001$ for all comparisons). Failure to refill the index agent within the initial 90 days was a strong predictor of poor persistence.

Conclusions: Persistence with ocular prostaglandin therapy remains a problem. Latanoprost users had greater odds of achieving medication possession and had more days covered during the first therapy year.

Convenience - compliance

Kass et al	1987
Weinreb	1992
Patel & Spaeth	1995

Compliance - washout effect

- 30 second interval
  - 45% washout loss of first drug effect
- 2 min interval
  - 17% washout loss of first drug effect
- 5 min interval
  - almost no washout effect on first drug

Mauger et al.1996

Method of Instillation (I .Goldberg)

- Witness patient in action
- High altitude bombing
- Cluster bombing
- Pinball method
- Finger tip bounce
- Punctal occlusion
- Voluntary closure x1 min

Take Home message

- **Monotherapy : compliance and persistence**
- **Xalatan and Xalatan/ beta-blocker FC**
- **lowest side effect profile**
- Xalatan proven **long term safety record** :
- **5 year studies**
- Xalatan IOP lowering **equivalent** to other Prostaglandins
- **First choice** in terms of **European Glaucoma Society Treatment Guidelines**