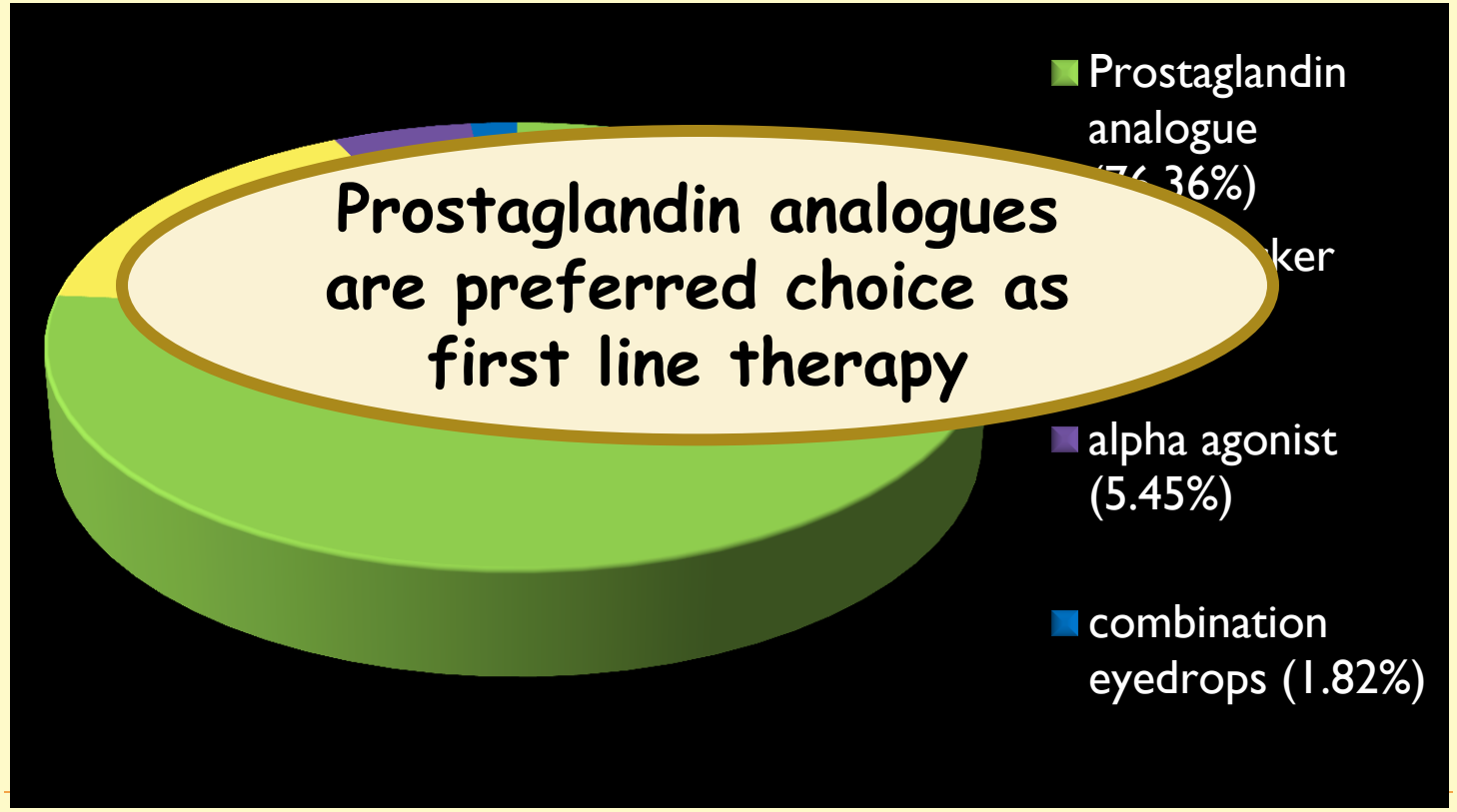
PG analogues

First-Line therapy for Glaucoma management

A Question poll was conducted at one of the well known ophthalmology website

In treating primary open angle glaucoma, you are most likely to initiate therapy with a topical:



http://www.healio.com/optometry/glaucoma/news/print/primary-care-optometry-news/%7BE241BEEC-4D3F-45E6-9A24-E715F594371C%7D/Clinicians-prostaglandins-are-the-clear-choice-for-first-line-glaucoma-therapy last accessed 21st August 2012.

Place in therapy

Step 4-Surgery

Insufficient fall of IOP
Progression of visual field defects

Step 3-Adjunctive/ Add-On Therapy:
Combining anti-glaucoma drugs.
β-bl… / PGA/ α_2-agonist

Thus PGA are widely being used at all stages of glaucoma treatment

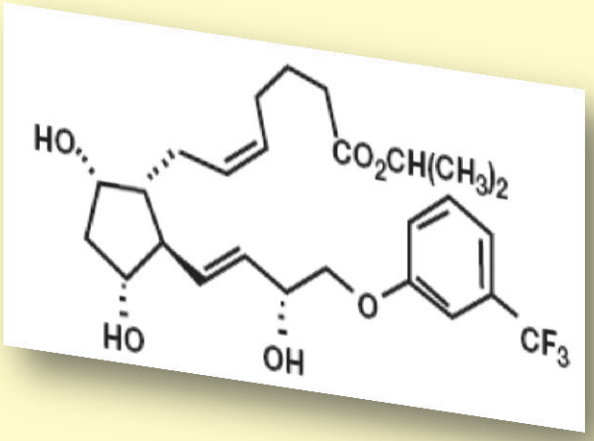
Step 2-Re… …notherapy :
Topical carbonic anhydrase inhibitors (CAIs), prostaglandin analogues (PGA), α_2-agonist

Insufficient fall of IOP
Adverse effects

Step 1-Monotherapy : β-blockers/ prostaglandin analogues (PGA)

What are Prostaglandins?

- Prostaglandins (PGs) constitute a group of naturally occurring hydroxylated fatty acids.
- Biosynthesised from free arachidonic acid, and are released by variety of physiological stimuli.
- Many tissues secrete prostaglandins for various functions, and have important functions in the body.



Ref: Drugs and Ageing 1999; 14(5): 387-398

Prostaglandins: Types & their receptors

Naturally occurring prostaglandins/ prostanoids	Prostanoid receptors
PGD_2	DP
Thromboxane (TXA_2)	TP
$PGF_{2\alpha}$	FP

FP receptor has a widespread distribution in ciliary muscle & ciliary processes.

Ref: *Drugs and Ageing 1999; 14(5): 387-398*

Prostaglandins

- In 1981, Camras and Dito demonstrated that topically applied $PGF_{2\alpha}$ reduces intraocular pressure (IOP) in monkeys with no or minimal intraocular side effects.

- **Synthetic prostaglandin analogues (PGAs)** are molecules which are manufactured to bind to a prostaglandin receptor.

- **Uses** -Prostaglandin analogues such as misoprostol are used in treatment of duodenal and gastric ulcers.
- Prostaglandin analogues can also be used in the management of open-angle glaucoma.

Ref: 1. Drugs and Ageing 1999; 14(5): 387-398
2. *IOVS; May 2001, Vol .42 (6): 1134-1145*
3. *http://en.wikipedia.org/wiki/Prostaglandin_analogue last accessed on 22nd August 2012*

Different types of PGA used in glaucoma management

- The commercially available PGAs are as follows:-

PG analogues	Year of launch
Latanoprost 0.005%	1996
Unoprostone isopropyl 0.15%	2000 (not available in India)
Bimatoprost 0.03 & 0.01%	2001 & 2010
Travoprost 0.004% & travoprost 0.004% with Ionic buffer system	2001
Tafluprost 0.0015%	2008

- Most of these medications are considered as prodrug (with some controversy on bimatoprost) as they are dispensed in their inactive form & are hydrolysed by corneal enzymatic degradation into active molecules (biological free acid)[2].

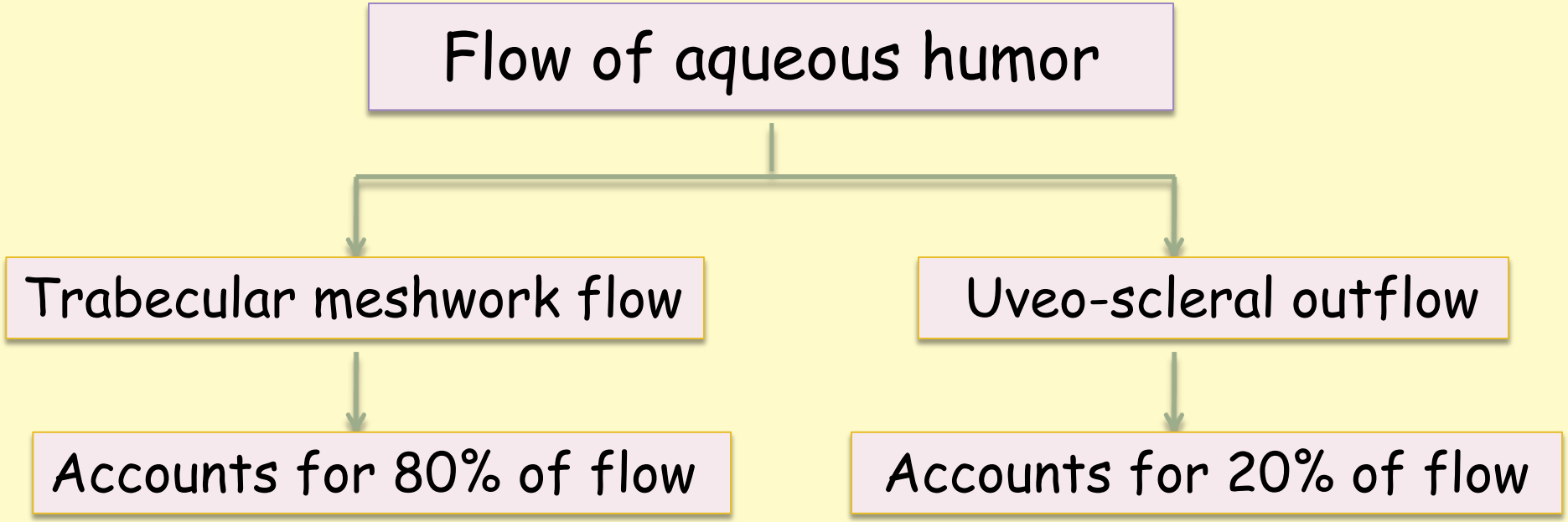
Ophthalmology Times, July 1, 2002

2. Highlights of ophthalmology Jounal. 1(2)

3. http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=3681

How do PG analogues work?

- PG analogues reduce IOP by increasing aqueous humor outflow through uveoscleral pathway.



Eye .1997;11:149-154

Produced by ciliary process

↓

Moves backwards

↓

Ciliary body

↓

supraciliary &

↓

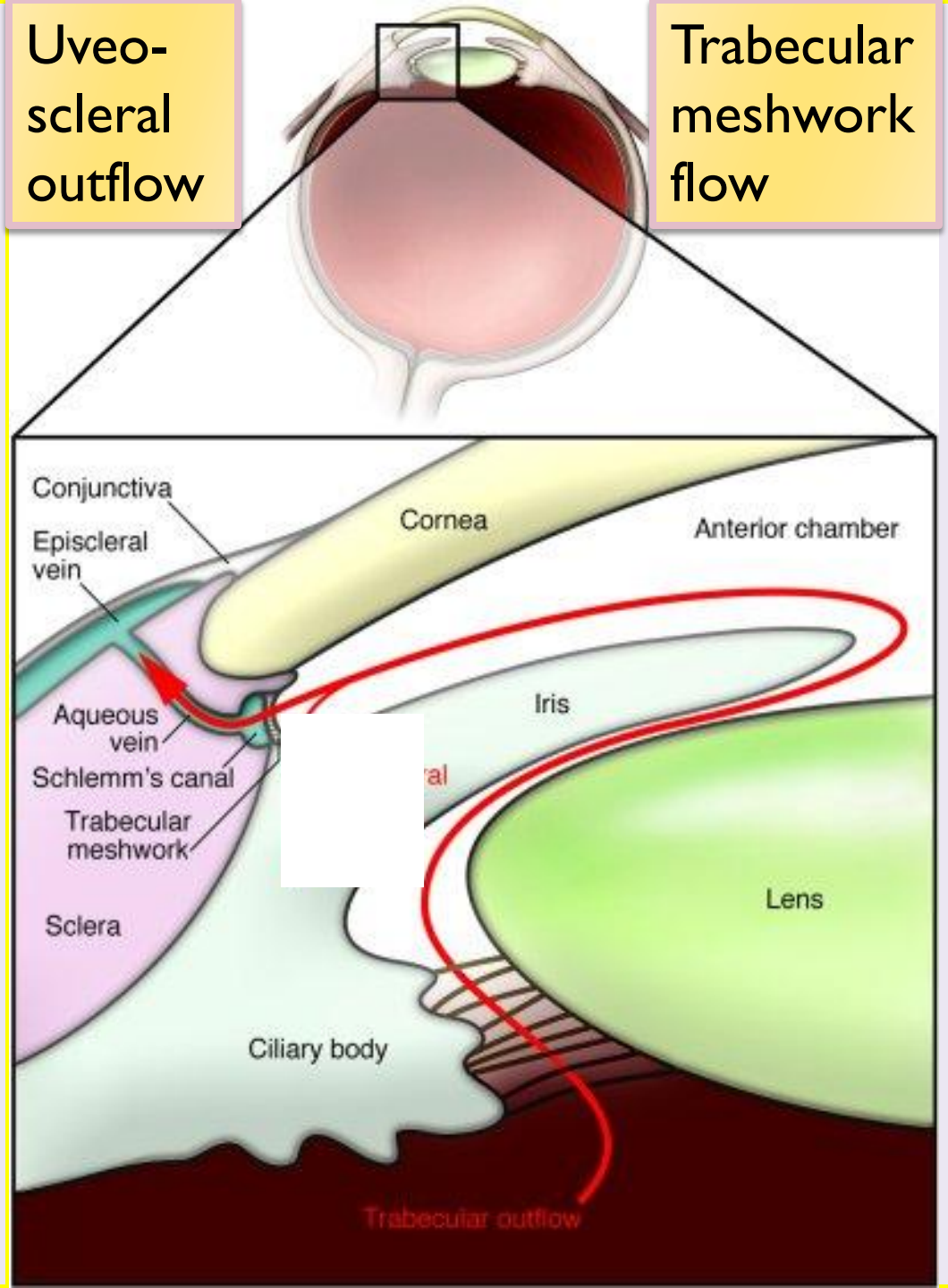
suprachoroidal spaces

↓

Sclera

Uveo-scleral outflow

Trabecular meshwork flow



Produced by ciliary process

↓

Enters posterior chamber

↓

Moves out through pupil

↓

Irido-corneal angle.

↓

Drained through trabecular meshwork

↓

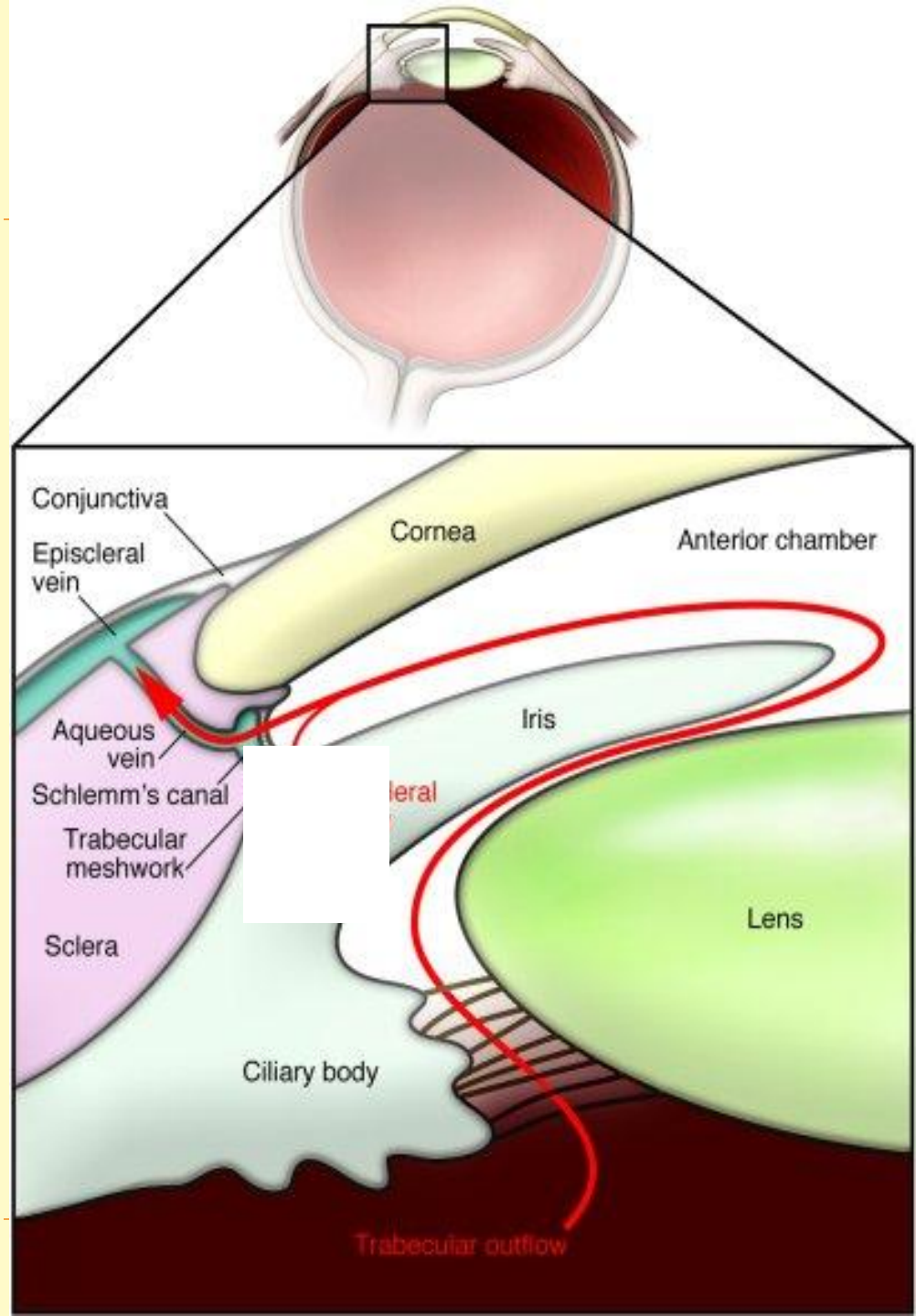
Enters schlemm's canal

↓

Drained in aq. vein

How do PG analogues work?

- They increase uveoscleral outflow by 2 mechanisms:
- ✓ Relaxation of ciliary muscle
- ✓ Decreased resistance in the uveoscleral pathways due to changes in extracellular matrix



Eye .1997;11:149-154

Mode of action- post instillation in eye.

Prostaglandin + ester — PRODRUG

Cornea — Corneal esterases

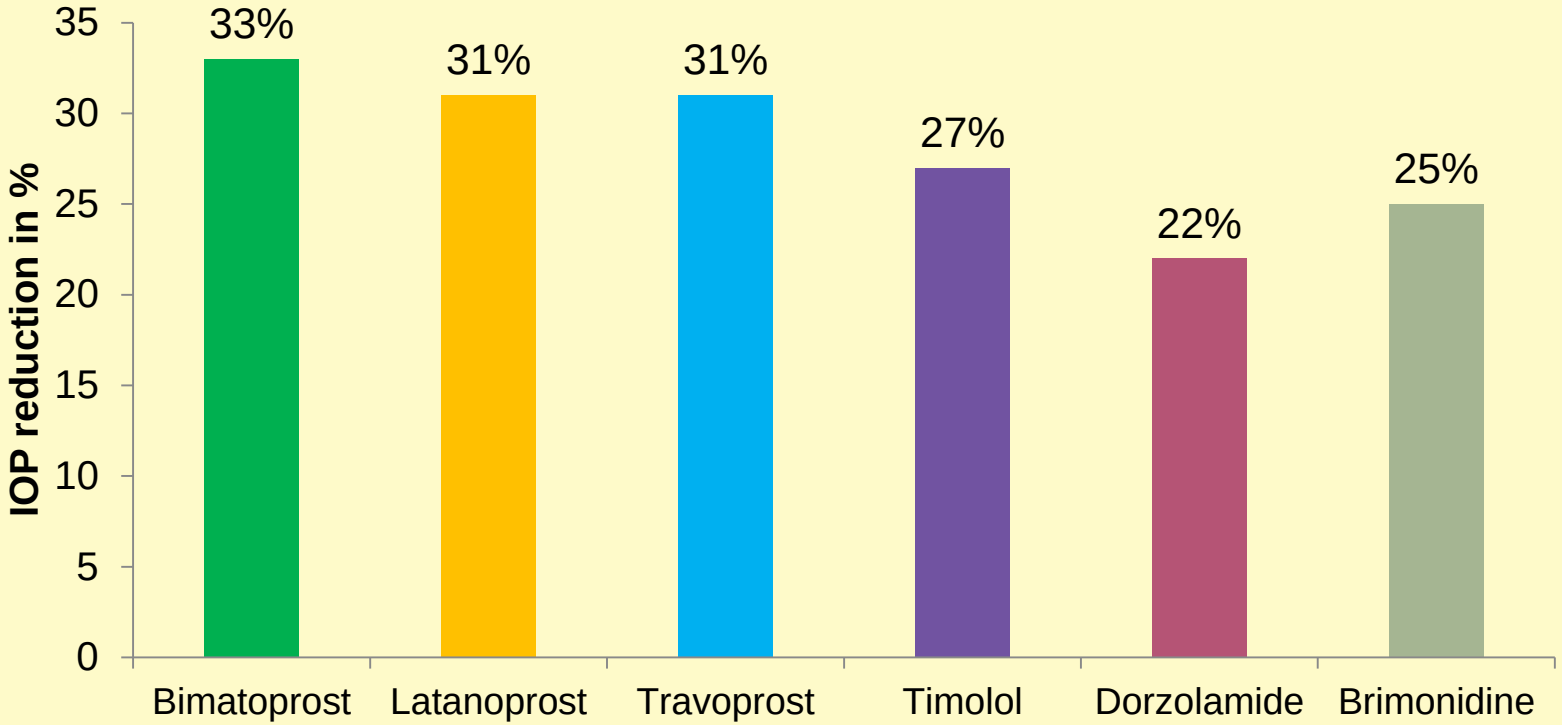
C-
ns

MMPs

ECM

Amongst all PGA Travoprost has strong affinity to Fp receptors

IOP reduction by various anti-glaucoma medications

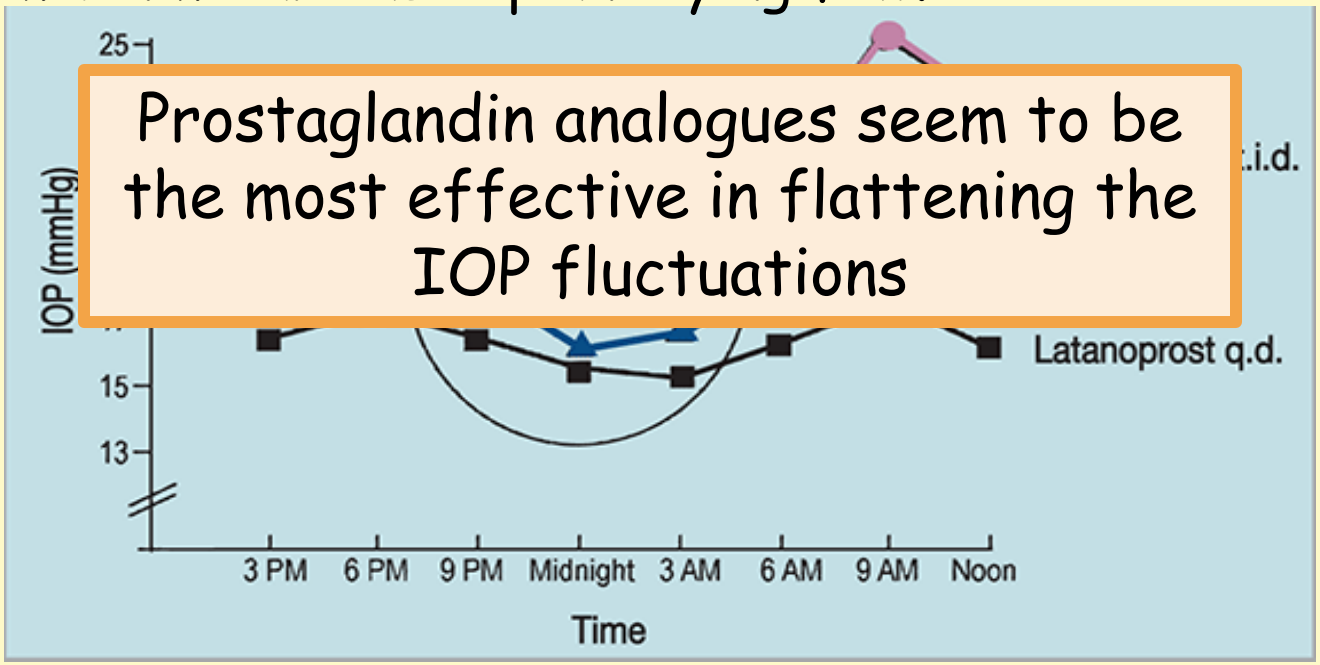


- PGAs as a class appear to provide excellent control of both short- and long-term IOP fluctuation in comparison to all other classes of anti-glaucoma drugs.
- Reduction in IOP from baseline was 31-33% for peak & 28-29% for trough.

Surv Ophthalmol.2009; 54 (6): 643-662
http://www.glaucomaassociates.com/medications.html last accessed 22nd August 2012.
J. Of Clinical Epidemiology; 2009: 1-5

Prostaglandin analogues: Proven for 24 hour IOP Control

- IOP fluctuations are considered as independent & stronger risk factor of visual field progression.
- Recent studies have shown a blunting of the nocturnal spikes in IOP, when we are asleep and lying flat.

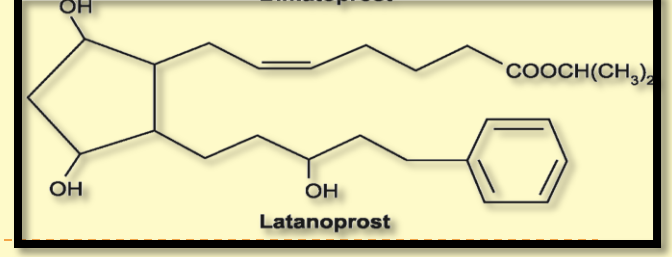


- Comparison of IOP over 24hr period in patients treated with dorzolamide (CAI), timolol (β-blocker) & Latanoprost (PGA)

Ref: Invest Ophthalmol Vis Sci 2000; 41: 2566-2573

http://www.revophth.com/content/d/cover_focus/i/1227/c/23095/ last accessed 22nd August 2012.

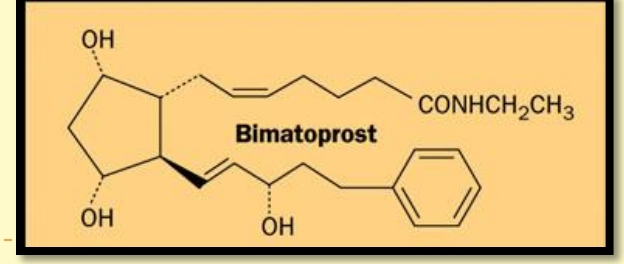
Latanoprost 0.005%



- The first agent to receive a first line indication in the EU for patients with POAG or ocular hypertension since the introduction of cholinergics and betablockers.
- Latanoprost has Undergone extensive clinical trials for efficacy, drug interactions, and side effects.
- Sustained long term IOP control
  - 2 years as monotherapy
  - 5 years as adjunctive therapy
- 25% more effective vs. beta blocker
- 37% more effective vs. alpha-agonist
- 52% more effective vs. CAI's
- Monotherapy with Latanoprost can be an alternative with timolol & dorzolamide

Surv. Ophthalmol 47 (suppl): 2002
Surv of Ophthalmol; 47 (suppl 1): S65-S72 2002
J of Glaucoma 2002; 11: 90-96
Survey of Ophthalmology; 47 (suppl 1): 2002; S148-S154
Br. J. Ophthalmol 2000; 84: 579-582
Ref: http://www.docguide.com

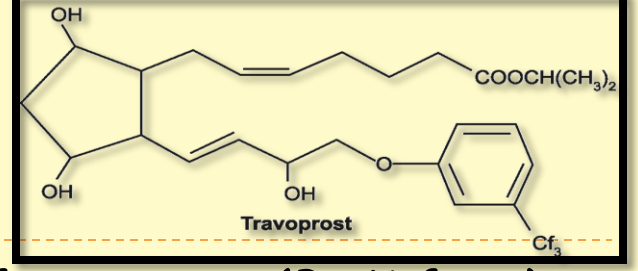
Bimatoprost 0.03% & 0.01%



- Equal efficacy when compared with other PGAs.
- Bimatoprost 0.03% was associated with significant hyperaemia which lead to patient non-compliance hence lower strength formulation of bimatoprost (0.01%) was introduced in 2010 which had 4 times higher concentration of BAK than the initial formulation to increase penetration of thr drug in ocular tissues.
- Bimatoprost 0.03% provides:-
- Significantly greater reductions in IOP of about 2–4 mmHg than timolol 0.5% given twice daily.

Clinical Ophthalmology 2007;1(3):225-232
Am J ophthalmol .2010;149 (4):661-671

Travoprost 0.004%



- Also available as Travoprost with ionic buffer system (BAK free) with equivalent IOP lowering efficacy as travoprost 0.004% with BAK.
- The development this BAK free formulation might prove to be beneficial for patients having concomitant OSD & for those with a sensitivity to the preservative BAK.
- Provide a treatment option for practitioners who prefer to prescribe a BAK free product for chronic therapy.
- IOP reduction was maintained for 84 hrs.
- Equal efficacy when compared with other PGAs.
- Sustained long term IOP control upto 48 months
- Travoprost 0.004% lowered IOP more than timolol, The decrease from baseline was 30% to 33% for travoprost compared with a 22% to 29% decrease for timolol.
- Substantially additive to timolol as adjunctive therapy.

1. Travoprost EMEA monograph 2004
2. Clinical Therapeutics. 2004, 26(1): 84-90
3. American J of Ophthalmology 2001; 132 : 472 - 484

Comparison of all the 3 prostaglandin analogues

	Latanoprost 0.005%	Bimatoprost 0.03%	Travoprost 0.004%
Molecular form	Isopropyl ester analog of $PGF_{2\alpha}$	Prostamide	Isopropyl ester analog of $PGF_{2\alpha}$

Travoprost EMEA monograph 2004

Results of Randomized Trials Comparing the Efficacy of the Prostaglandin Analogues

Author/ Reference	Drugs/ Condition	n	Design	Duration	Sponsor	Mean Diurnal IOP at Last Visit, mm Hg
Yildirim	Lat/Bim/Trav POAG	48	Parallel	8 weeks	Indep	Lat 17.9 Bim 17.7 Trav 17.3
Hepsen						m 15.4 Trav
Orzales						m 15.3 Trav
Parrish	Lat/Bim/Trav POAG/OH	410	Parallel	12 weeks	Pharmacia	Lat 16.7 Bim 16.4 Trav 16.8

No clinically significant differences exist among these agents regarding their ability to lower intraocular pressure.

Surv Ophthalmol.2008; 53:S69–S84

Tafluprost

- Received approval in 2012. Available as preservative free unit dose vials.
- Shows similar to slightly lower IOP lowering capabilities (29%) when compared to latanoprost.
- New molecule effective & well tolerated for upto 24 months.
- Data on tafluprost is limited.
- Available in India

Acta Ophthalmologica.2010;88(1):12-19

Unoprostone

- Unlike the 20-carbon molecular skeleton of arachidonic acid, unoprostone a, 22-carbon molecule.
- Unoprostone administered two times daily lowered IOP by 17%.
- Less effective than the other 3 analogs in clinical trials.

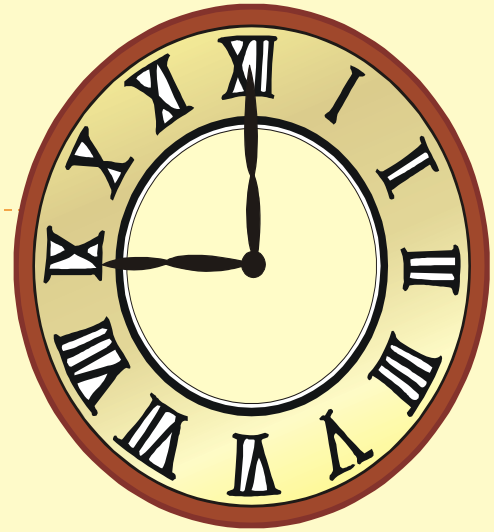
http://www.agec.org/2010/10/switching-prostaglandin-analogs-in-the-treatment-of-glaucoma/ Last accessed 21st August 2012

Inidcations

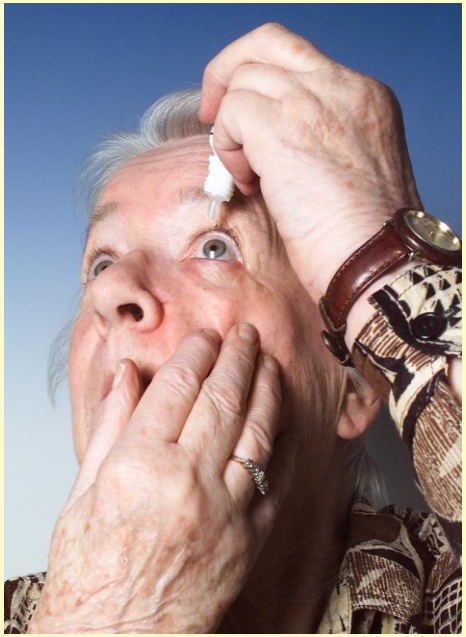
- PGAs are indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.
- Allied indications:-
- Control of Post-operative IOP spikes
- Reducing Intraocular Pressure in
  - Primary angle closure glaucoma
  - Steroid induced glaucoma
  - Pigmentary glaucoma
  - Paediatric glaucoma (latanoprost 0.005% studied)

Ref: Surv Ophthalmol 2002 47 (suppl1.) S125 – S128
J. Cataract Refract Surgery 1998; 24: 964 – 967
Surv. Ophthalmol. 2002; 7 (Suppl 1): S129 – S132
J of Glaucoma 2000; 9: 179 – 182
Ophthalmology 1999: 106: 550 - 555

Dosage regimen



- The recommended treatment regimen is one drop in the affected eye once daily (usually recommended in the evening).
- More frequent dosing of these agents resulted in decreased efficacy of the drug (related to development of receptor subsensitivity)



Ref: 1. Drugs and Aging 1999; 14(5): 387-398
2. Drugs and Aging 2003; 20(8): 597-630.
http://www.vaeye.com/Specialties/glaucoma-treatment/prostaglandin-analogues.aspx. Last accessed 20th August 2012.

PGA safety

- Relatively safe local & systemic side effect profiles when compared to other classes of drugs like β-blocker,α-agonists.
- Safe to use in glaucoma patients with concomitant cardiovascular or cardiopulmonary contraindications .
- Side effects associated- itching, burning, stinging, conjunctival hyperaemia, increased iris pigmentation (which can be permanent), hypertrichosis, increased eyelash growth, peri-orbital tissue changes.
- Cystoid macular edema & recurrences of herpetic eye disease have been reported. These drugs are contraindicated in patients with active intraocular inflammation (uveitis). Prostaglandins should be used with caution in patients who have had cataract surgery or other problems with the lens of the eye, or who are at risk for swelling in the macula at the back of the eye.

http://www.webmd.com/eye-health/prostaglandin-analogs-for-glaucoma last accessed 20th August 2012.
http://www.glaucomaassociates.com/medications.html last accessed 22nd August 2012.
Eur J Ophthalmol. 2007 Jul-Aug;17(4):521-7

Prostaglandins in special population

- **Pregnancy**- Category C. Prostaglandins are biologically active and may be absorbed through the skin; caution should be exercised to avoid direct exposure to the drug in women who are pregnant or attempting to become pregnant.
- **Nursing** – Not recommended
- **Paediatric Use**-Safety and efficacy in paediatric population is not established.
- **Renal and Hepatic Impairment**- Efficacy not established; use with caution.

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a5e67c75-db88-4372-bb07-c8dd15c97631#section-8.3
http://www.medicines.org.uk/EMC/medicine/8031/SPC/TRAVATAN/

Take home message

- PGAs are currently considered our "**first line**" medications by virtue of several aspects.
- **Once daily** dosing (usually recommended to be instilled in the evening),
- An **impressive pressure decrease** (typically at least 20-30% from baseline),
- Very **favourable side effect profile**.
- All of the medications in this group have the ability **to increase eyelash length and thickness, darken eye (iris) color**, increase pigmentation of the skin surrounding the eye **(raccoon eyes)**, and cause **"red" eyes**. However, **there are usually no systemic side effects.**
- Between 1997 and 2003, new glaucoma drugs, primarily prostaglandins, improved intraocular pressure control and delayed surgery, **reducing glaucoma surgery by 22%.**

http://www.vaeye.com/Specialties/glaucoma-treatment/prostaglandin-analogues.aspx. Last accessed 20th August 2012.
Eur J Ophthalmol. 2007 Jul-Aug;17(4):521-7