CMO/CME
in the Phaco era Myth or Reality ?

6TH December 2015

Nicholas Lee, FRCS, FRCophth
Consultant Ophthalmologist
The Western Eye Hospital
The Hillingdon Hospital
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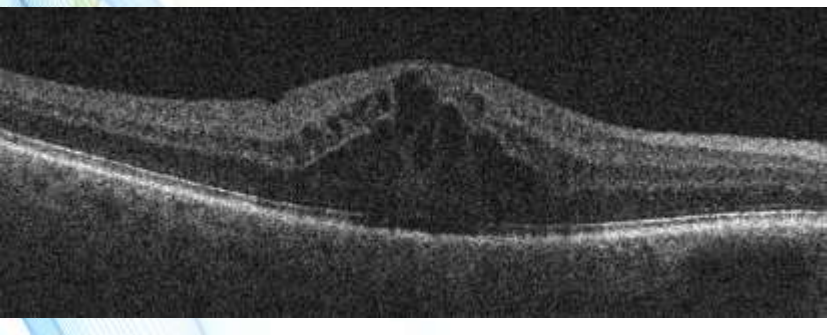

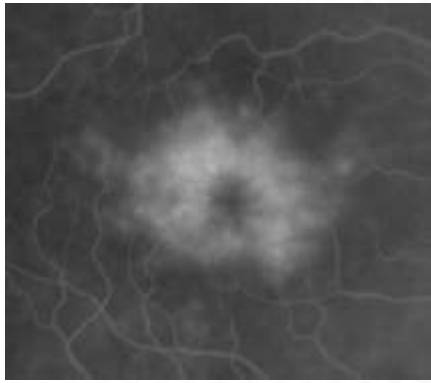

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Disclosures Sponsorships/Consultant

This is an Alcon sponsored promotional event.
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Post Cataract Macular Edema in Diabetic Patients

Objectives

- Understand the development and impact of macular oedema – Irvine-Gass Syndrome Post Cataract Surgery
- Explore the increase in cost of cataract care if patients develop CME
- Explore the increased risk for macular edema development in diabetic patients

  Look at New developments in Post op Cataract Care

Postoperative Complications Associated With Modern Cataract Surgery

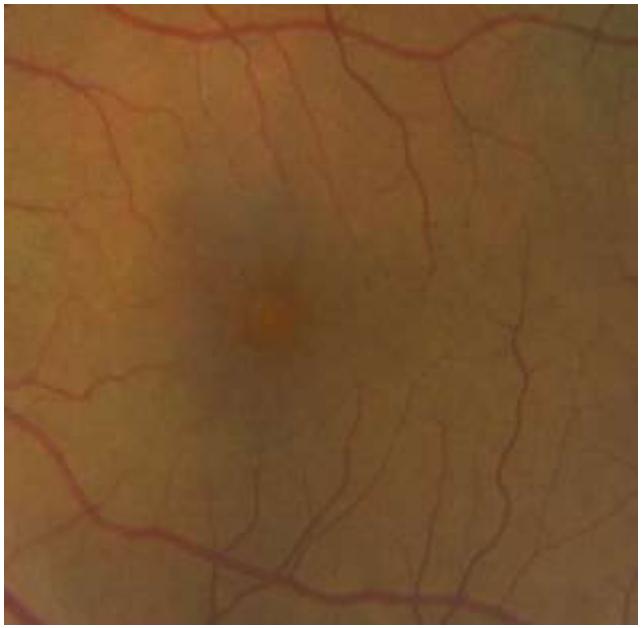
Complication	Range of Estimated Incidences (%)
Intraoperative	
Posterior capsular or zonular rupture	1.5 – 3.5
Vitreous loss/anterior vitrectomy or aspiration	0.8 – 1.39
Iris/ciliary body injury	0 – 1.2
Loss of nuclear material into vitreous	0.1 – 0.28
Suprachoroidal hemorrhage	0 – 0.14
Retrobulbar hemorrhage	0 – 0.1
Postoperative	
Cystoid macular edema	1.2 – 3.5
Corneal edema	0.03 – 5.18
IOL dislocation, removal, or exchange	0.19 – 1.1
Endophthalmitis	0.03
Retinal tear, break, or detachment	0.14 – 0.9
Persistent iritis	1.1

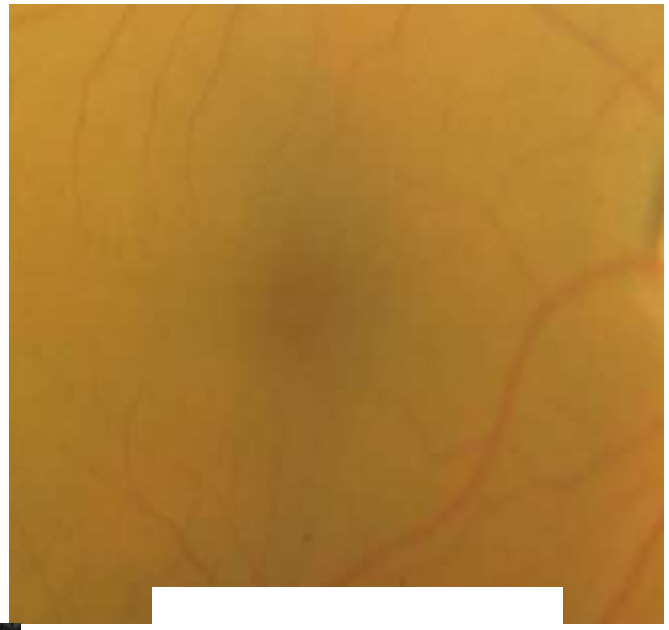
Related to inflammation

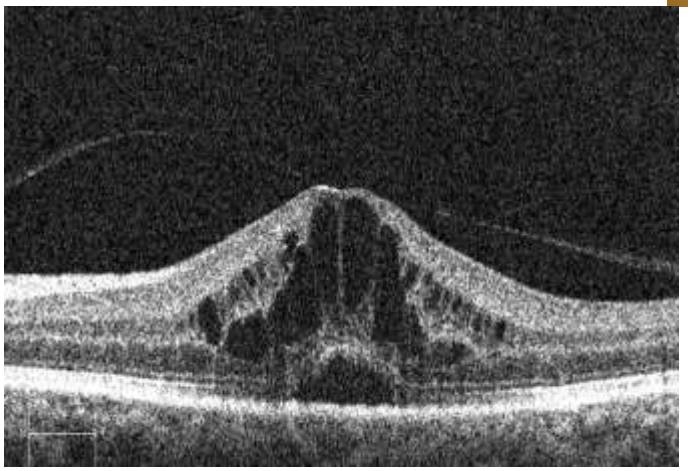
Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

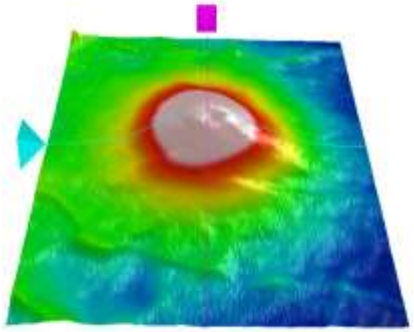
Abbreviation: IOL, Intraocular lens

Barry, et al. 2006.
American Academy of Ophthalmology Preferred Practice Patterns® Guidelines. Cataract in the Adult Eye. 2011.



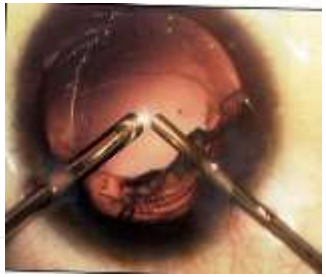






69 Year old GP Female 8 weeks post uncomplicated Phaco Surgery
Pre op Vision 6/24
Post op 3 weeks 6/6
8 Weeks post op 6/24

Surgery Causes Tissue Damage That Induces Inflammation



Normal Damage from Uncomplicated Surgery

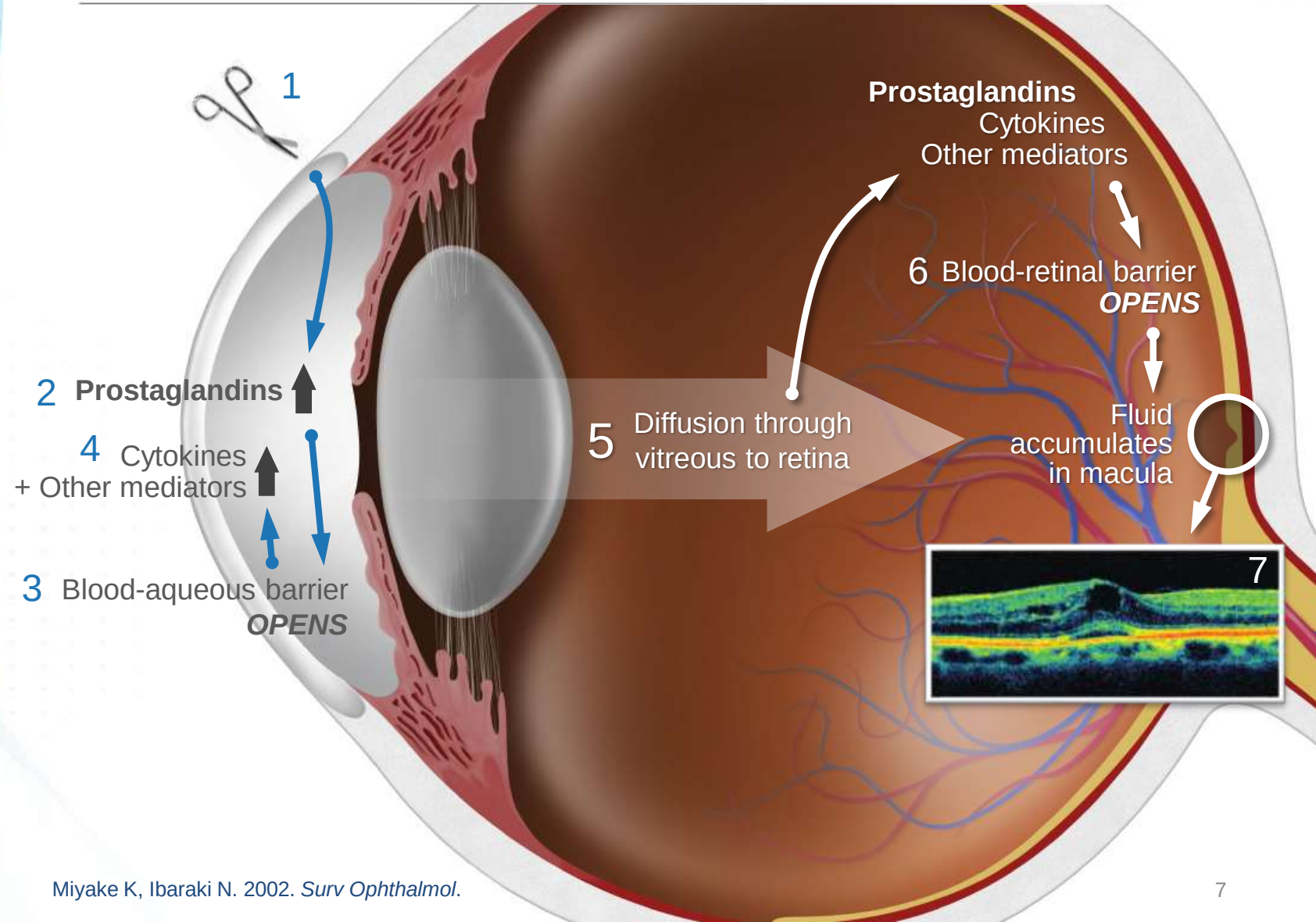
Surgical Complications
- Trauma to Iris
- Eg Iris Hooks
- Prolonged Surgery

Posterior Capsular Tears
Anterior Vitrectomy
Lens fragments

POSTOPERATIVE INFLAMMATION

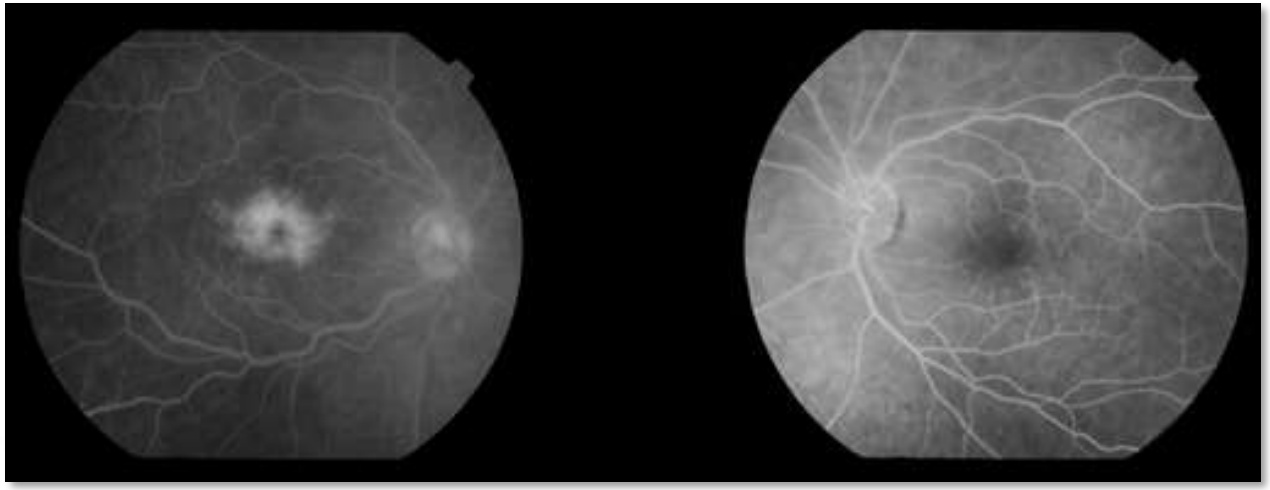
American Academy of Ophthalmology Preferred Practice Patterns® Guidelines. Cataract in the Adult Eye. 2011.
Lobo C. 2012. *Ophthalmologica*.

Inflammation May Lead to Macular Edema by Relaxing the Ocular-Blood Barriers



Miyake K, Ibaraki N. 2002. *Surv Ophthalmol*.

What Is Macular Edema?



Macular edema is a painless disorder that affects the central retina, or macula.

Macular edema is caused by the breakdown of the blood-retina barrier, which increases vascular leakage.

Increased vascular leakage causes fluid to accumulate in the macula, which leads to edema and increased macular thickness.

Difficult to differentiate vs DIABETIC MACULAR OEDEMA. Post op Hyperfluorescence of Optic disc on Fundus fluorescein angiography. Treat DME Prior to surgery On table Anti-VEGF/Steroids

Cavallerano A. 1997. Macular Disorders, an Illustrated Diagnostic Guide.
Kanski J. 1999. Clin Ophthalmol.

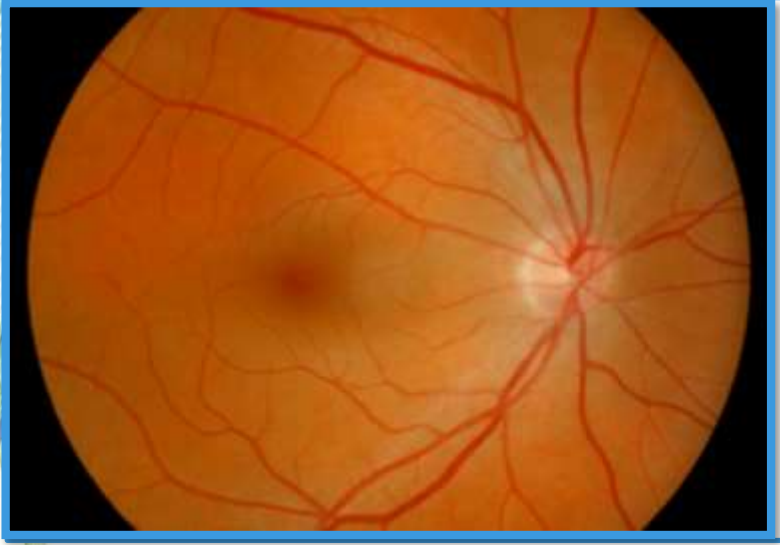
Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

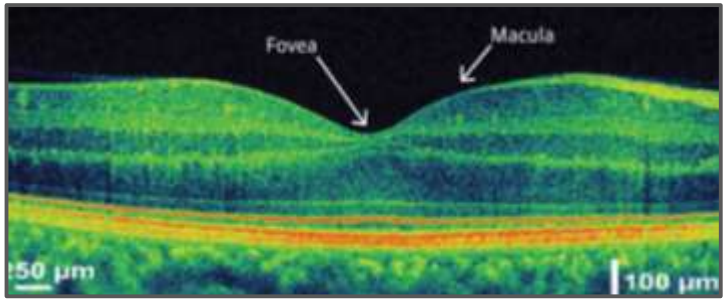
Irvine – Gass Syndrome

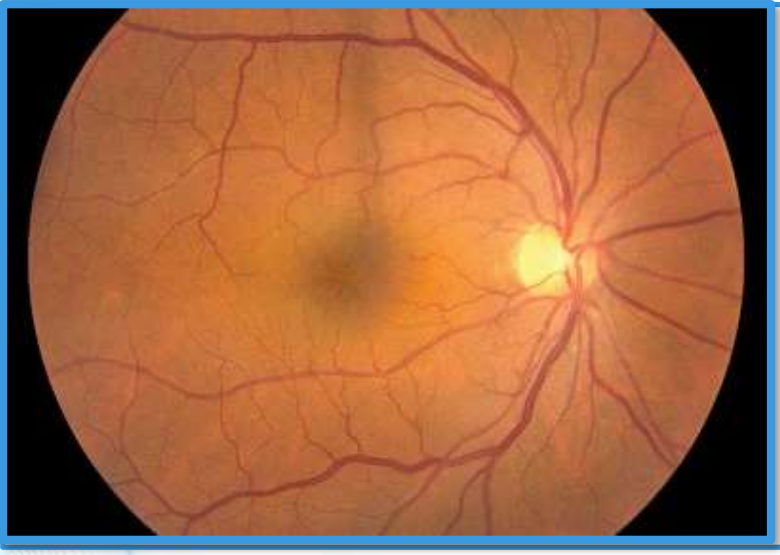
- Irvine described 1st 1953
- Gass Norton FFA 1966
- Irvine 1976 Survey of Ophthalmology review
- Over 100 Papers on the subject
- Medicare Estimate 47% increase in cost of cataract care if patients develops CME.

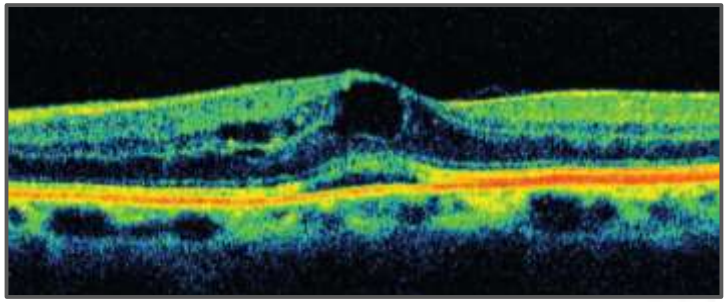
Irvine AR A newly defined vitreous syndrome following cataract surgery, interpreted according to recent concepts of the structure o the vitreous. AM J Ophthalol 1953 36: 599-619
Gass JD nortwon EW Cystoid macular edema and papilledema following cataract extraction: a flluorescein fundscopic and angiographic study. Arch ophthalmol 1966; 76:646-681
Irvine AR Cystoid Maculopathy . Surv Ophthalmol 1976:21:1-17

Healthy Vs Macular Oedema Retina Fundus Photograph and SD-OCT ?Baseline OCT



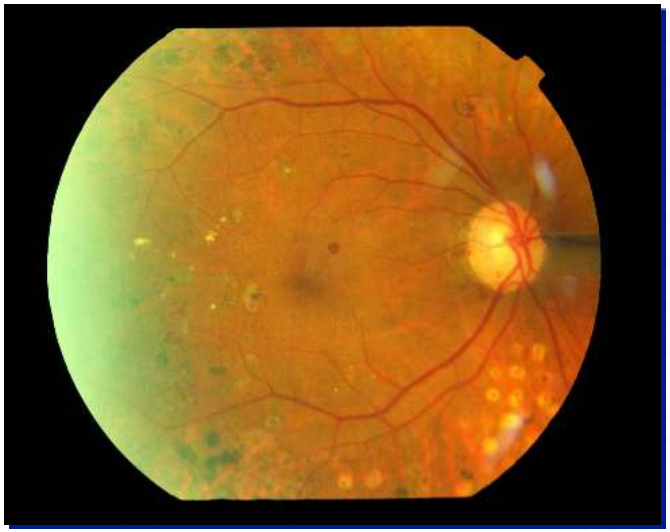






Irvine-Gass Syndrome

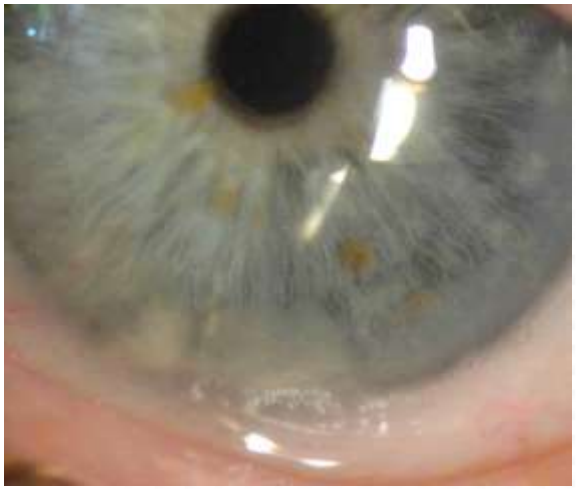
- Angiographic CME – Normal Vision
  - Normal OCT
- Clinically Significant CME
  - Reduced vision, CME on OCT
  - Within 4 months of surgery-Usually 4-6 Weeks



- Late CME > 4 months
- Chronic CME Lasts > 6 Months
- Diabetic macular oedema VS Irvine-Gass – Co-exist

Aetiology and Risk factors

- Type of Cataract surgery
- Light toxicity
- Vitreo macular traction
- Inflammatory mediators
- Use of Adrenaline in BSS
- Intracameral Drugs eg Cefuroxime
- Vitreous loss
- Integrity of capsule
- Hypertension
- Diabetes



Light Toxicity

- Microscope light Xenon/Halogen
  - Unfiltered (Very blue)
  - UV Filter (Natural Tungsten like)
  - Yellow Filter (very yellow)
- Light occluder made no difference in study. Kraff 1976
- UV Absorbing IOLS ?
- Yellow/Blue <500nm Blocking Lenses?
  - 10/11 Reviews No evidence.

◆**Kraff et all Effect of pupillary light occluder on CME J Cataract Refract Surgery 1996 22:770-774**

◆**Nagpal post op CME Ophthalmol clin North Am 2001 :14 651-659**

◆Henderson BA, Grimes KJ **Blue-blocking IOLs: a complete review of the literature.** Surv Ophthalmol. 2010 May-Jun;55(3):284-9.

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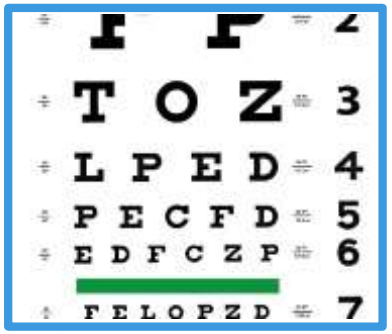
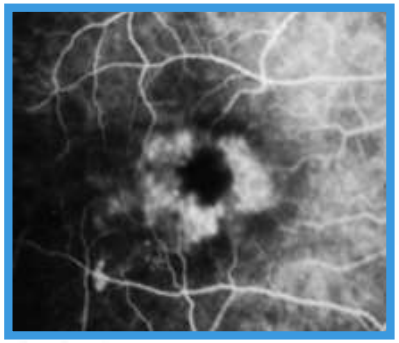
Frequency of Macular Edema Development After Cataract Surgery



Estimated Incidence

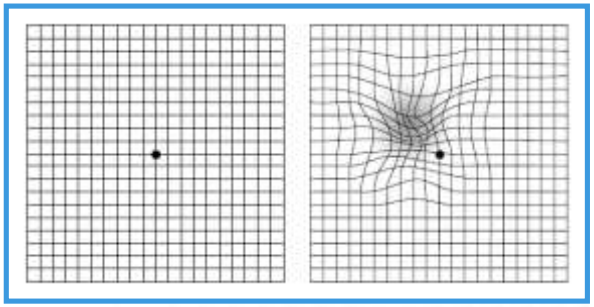
Clinically Significant Macular Edema
Associated with decreased visual acuity

≤5.8%



Cystoid Macular Edema
Detected by ocular imaging

4%-20%

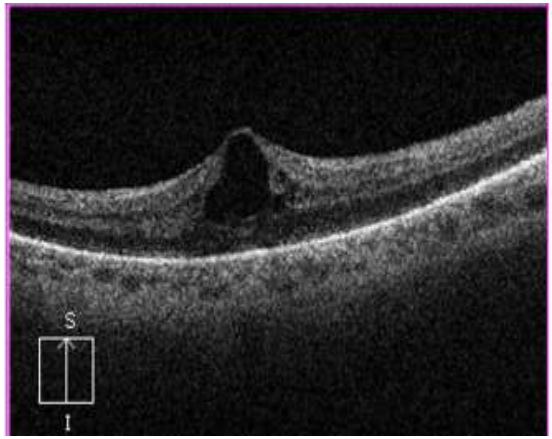


Wielders LHP, et al. 2013. *Cataract Refract Surg Today Europe.*

Macular Edema Is Associated With Reduced Quality of Vision

Quality of Vision

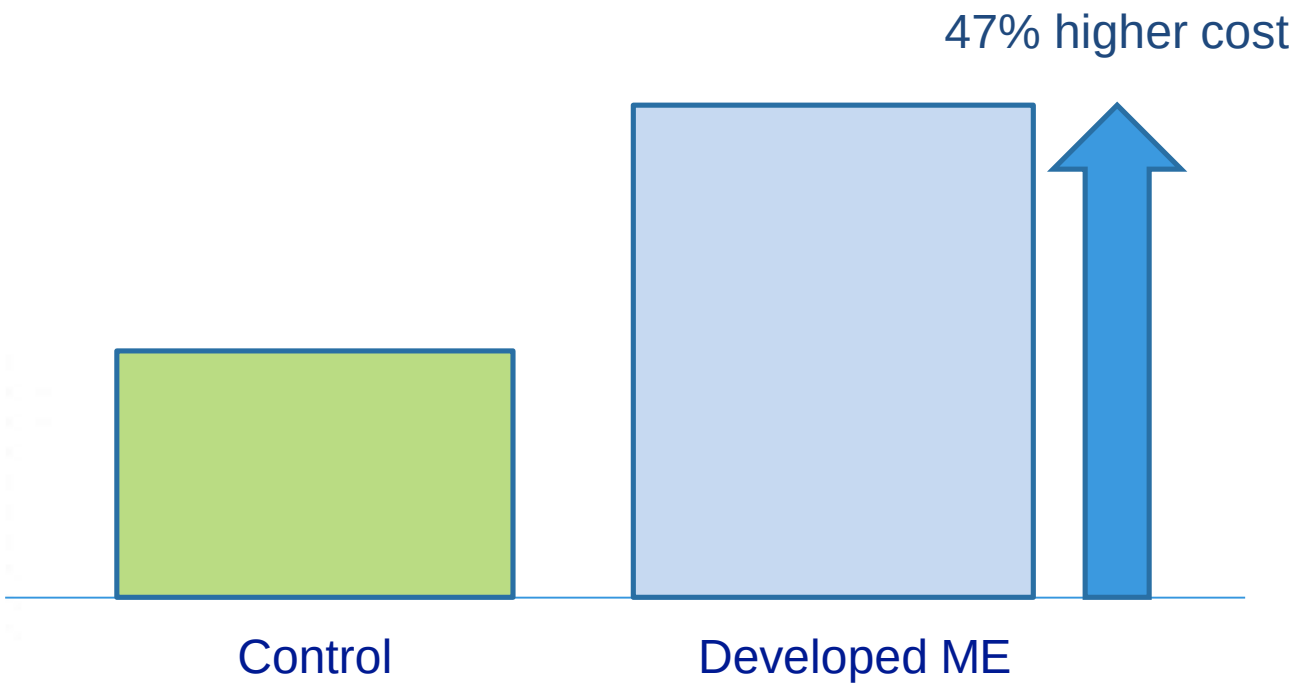
- Cystoid macular edema is **a common cause of decreased vision** after cataract surgery.
- Cystoid macular edema can develop even if cataract surgery was successful and uncomplicated.
- Patients may experience vision that is **reduced in quality without being reduced in acuity.**



Lobo C. 2012. *Ophthalmologica*.
Henderson BA, et al. 2007. *J Cataract Refract Surg.*
Wittpenn JR, et al. 2008. *Am J Ophth.*

Cost of Managing Macular Edema Post Cataract Surgery

Preventing macular edema is likely to result in cost savings in both normal and diabetic patients.

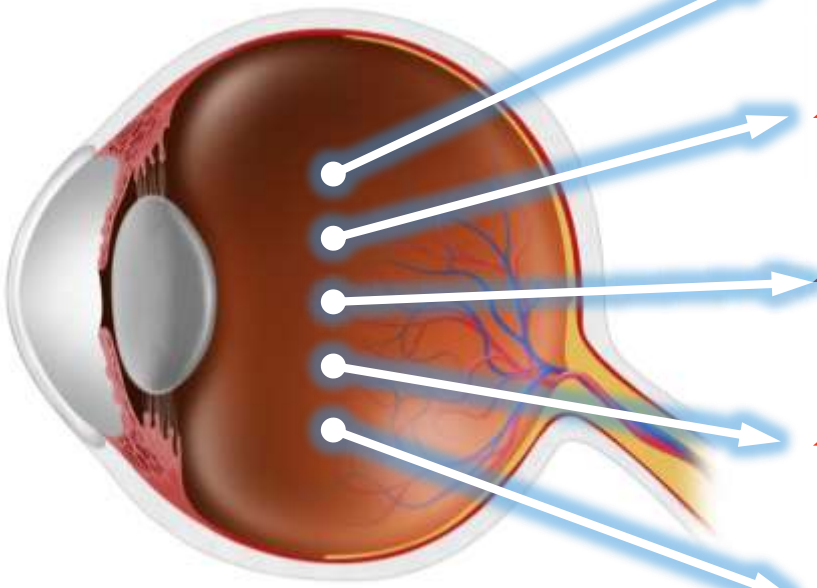


Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Schmier JK, et al. *Retina* 2007.

Vitreous Prostaglandin Levels Are Higher in Eyes With Proliferative Diabetic Retinopathy

Compared to patients without any diabetic retinopathy, patients with proliferative diabetic retinopathy have:

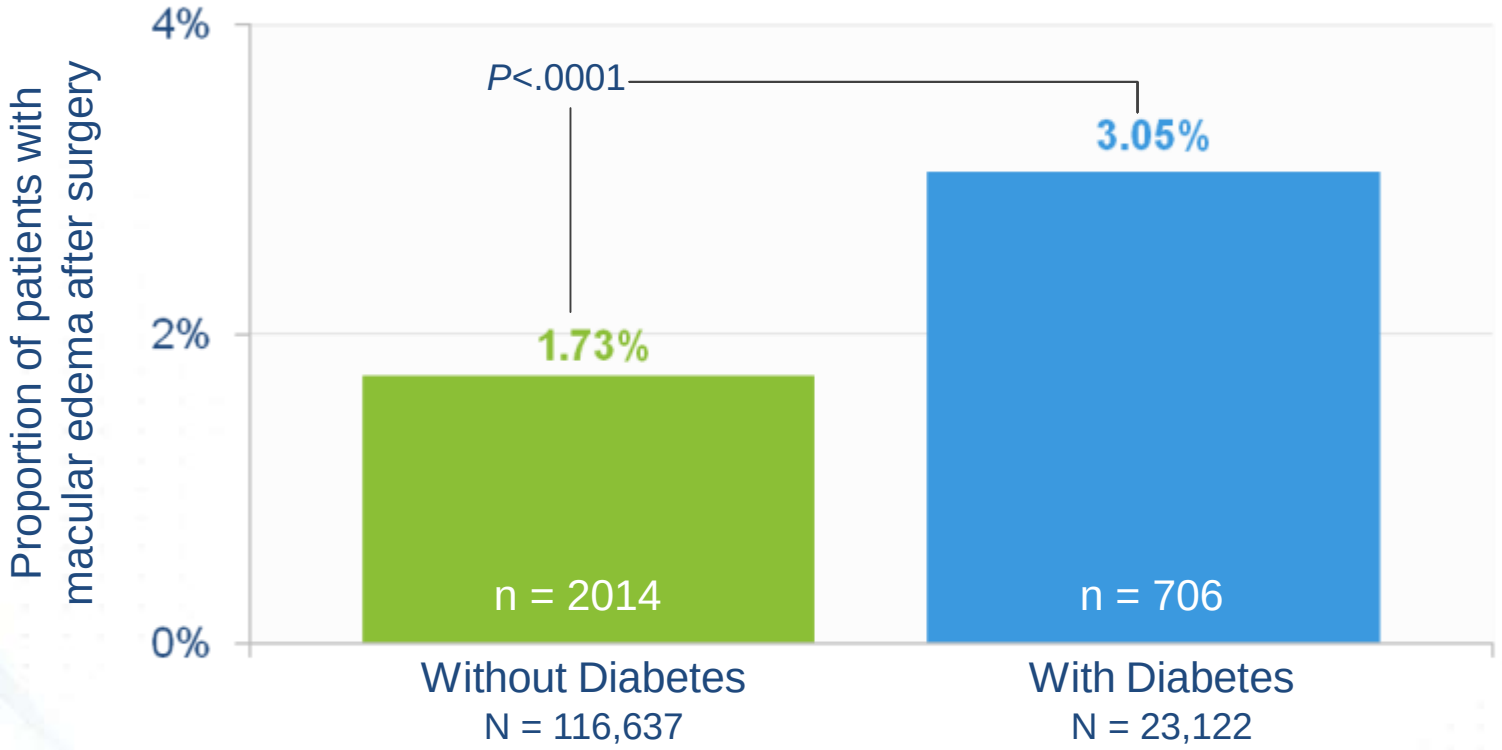


- 5.4x — Higher vitreous levels of interleukin-6
- 14.2x — Higher vitreous levels of interleukin-8
- 1.5x — **Higher vitreous levels of PGE_2**
- 2.2x — Higher vitreous levels of TNFα
- 33.7x — Higher vitreous levels of VEGF

Abbreviations, PGE2, prostaglandin E2; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor
Schoenberger SD, et al. 2012. *Invest Ophthalmol Vis Sci.*

Higher Incidence of Postopera Macular Edema With Diabete

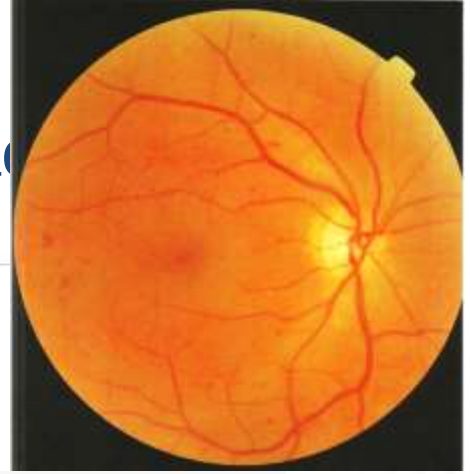
- Among patients filing Medicare claims for cataract surgery.
- Includes mix of cases with and without diabetic retinopathy.



NOTE: Based on patients with 1 or more cataract claims from the 1997–2001 Medicare 5% Beneficiary Encrypted Files; patients were analyzed by diagnosis of cystoid macular edema in the same quarter as or within the following 3 quarters after surgery.
Schmier JK, et al. 2007. *Retina*.

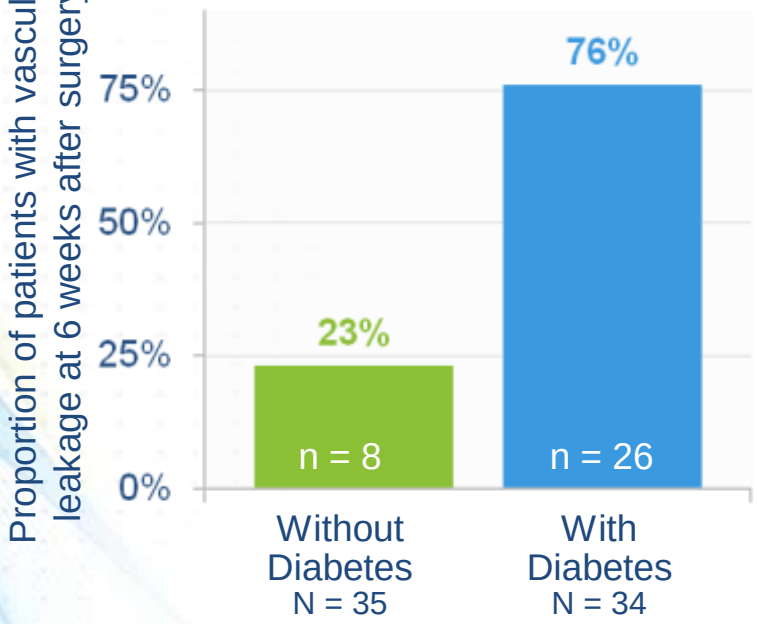
Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Higher Incidence of Postoperative Ma Edema With Diabetic Retinopathy

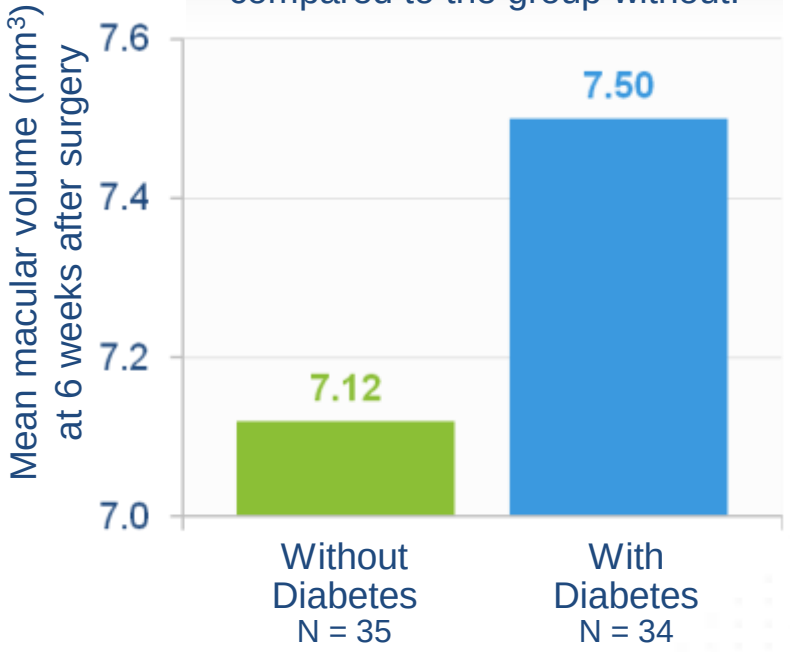


- All diabetic patients in the study had mild or moderate diabetic retinopathy.

Vascular leakage was detected in 3 times as many patients with diabetes compared to those without.



Mean macular volume was larger (P<0.05) in the diabetic nonproliferative patient group compared to the group without.

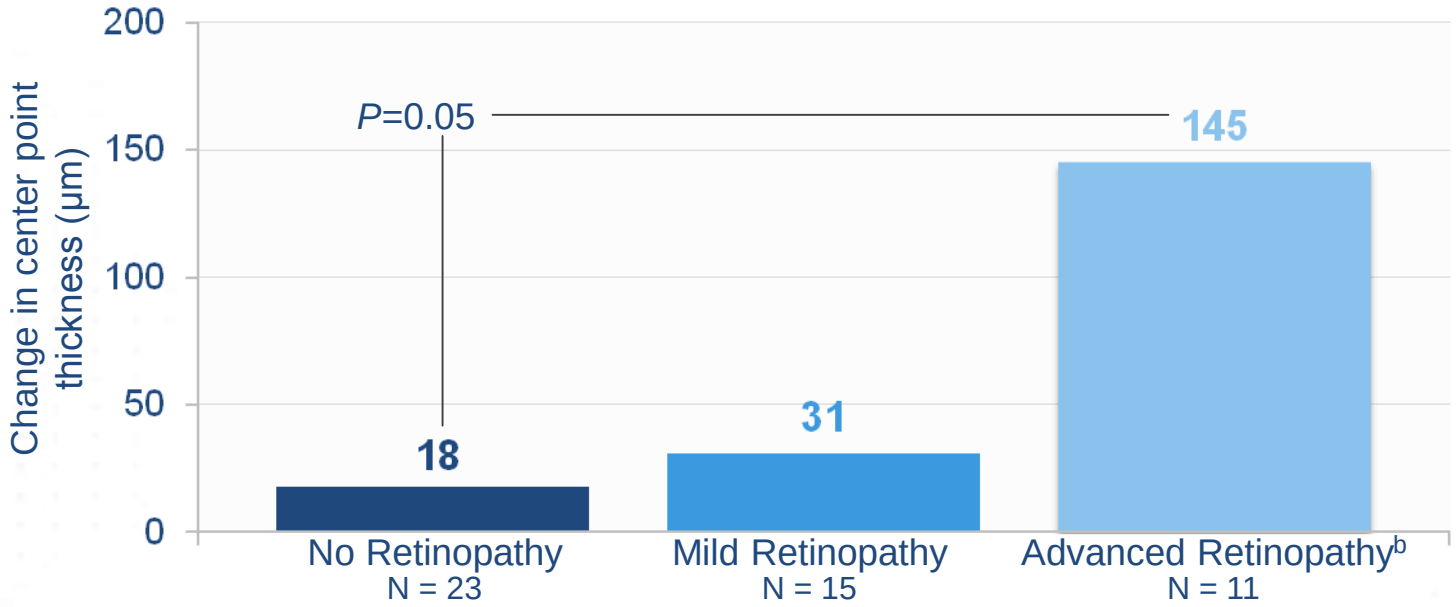


Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Eriksson U, et al. 2011. *Graefes Arch Clin Exp Ophthalmol.* *BASELINE* *6.65 mm³* *6.79 mm³*

Thicker Macular Edema in Patients With Advanced Diabetic Retinopathy

- Diabetic patients with varying severity of diabetic retinopathy.
- All patients had normal center point thicknessa ≤4 weeks.
- All phacoemulsification procedures were performed without complication.



a Center point thickness was measured on OCT as retinal thickness at the center point of the fovea.
b Advanced diabetic retinopathy included moderate and severe nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy.

Kim SJ, et al. 2007. *Ophthalmology*.

Reasons for Increased Incidence of Macular Edema After Cataract Surgery in Patients With Diabetes

Higher levels of prostaglandins and other proinflammatory cytokines in the vitreous
Proliferative diabetic retinopathy vs without diabetic retinopathy

Higher incidence of vascular leakage after cataract surgery
Mild or moderate diabetic retinopathy vs without diabetes

Larger mean macular volume after cataract surgery
Mild or moderate diabetic retinopathy vs without diabetes

Higher incidence of macular edema diagnosis after cataract surgery
Diabetes vs without diabetes

Schoenberger SD, et al. 2012. *Invest Ophthalmol Vis Sci.*
Eriksson U, et al. 2011. *Graefes Arch Clin Exp Ophthalmol.*
Schmier JK, et al. 2007. *Retina*.

Cystoid Macular Oedema after Cataract Surgery

Robert Johnston

Cheltenham General Hospital

Publishing in Ophthalmology
On Line Link will be sent

AMERICAN ACADEMY® OF OPHTHALMOLOGY
The Eye M.D. Association

Risk Factors and Incidence of Macular Edema after Cataract Surgery

A Database Study of 81 984 Eyes

Colin J Chu, Robert L Johnston, Charlotte Buscombe, Ahmed B Sallam, Quresh Mohamed, Yit C Yang for the UK pseudophakic macular edema study group

Ophthalmology – in press

Financial disclosures

- Director of Medisoft Limited.
- The data extraction and open access fees were sponsored by Alcon, but they have had no involvement in the study design, analysis or interpretation.

Importance & Incidence of CMO

- Cataract surgery common operations performed worldwide.
- Pseudophakic macular edema (PME) is the commonest early postoperative complication to limit vision.

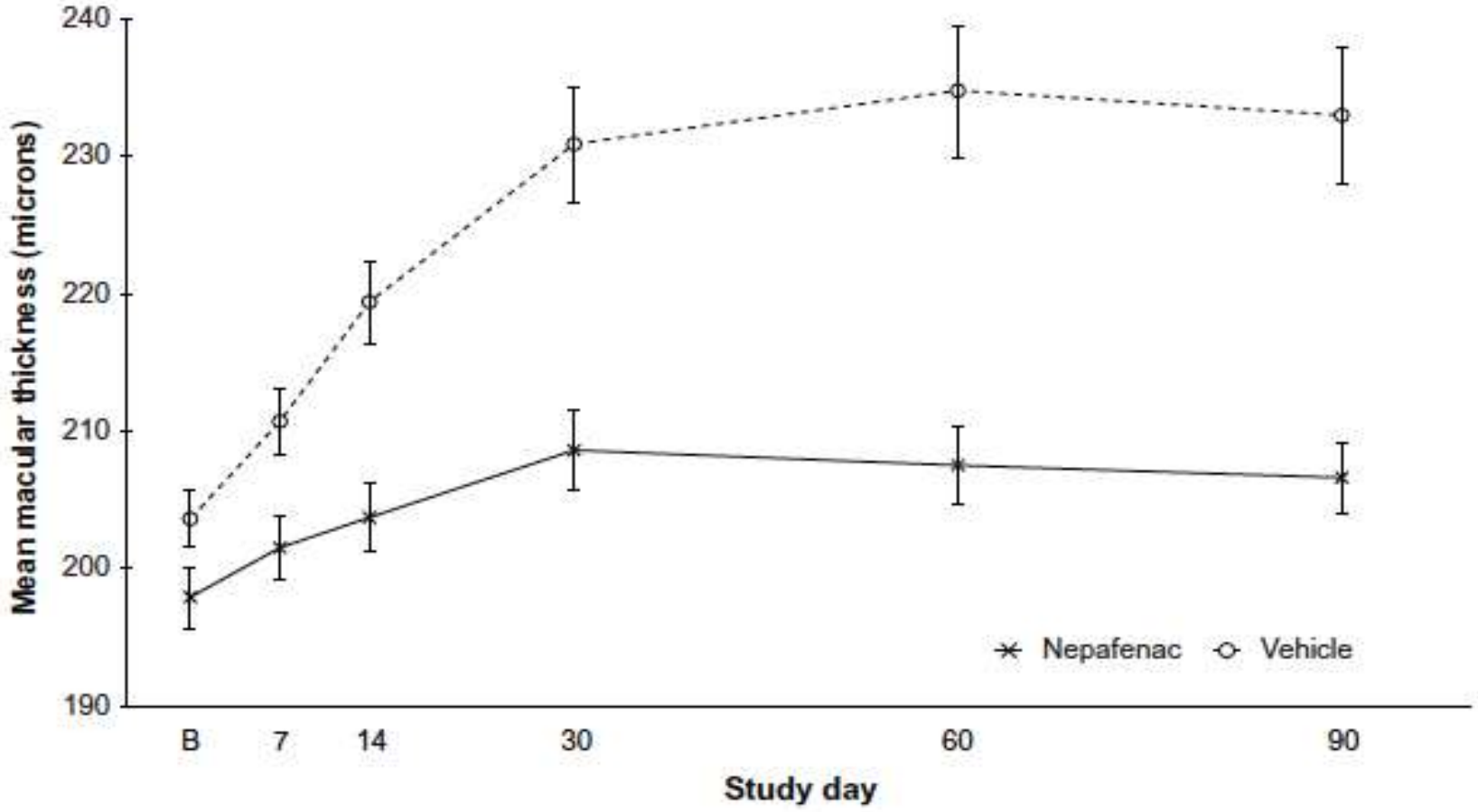
What is the incidence of PME and what are the risk factors?

•Largest **previous** clinical study was 1,659 eyes in the US. *(Henderson et al, 2007)*

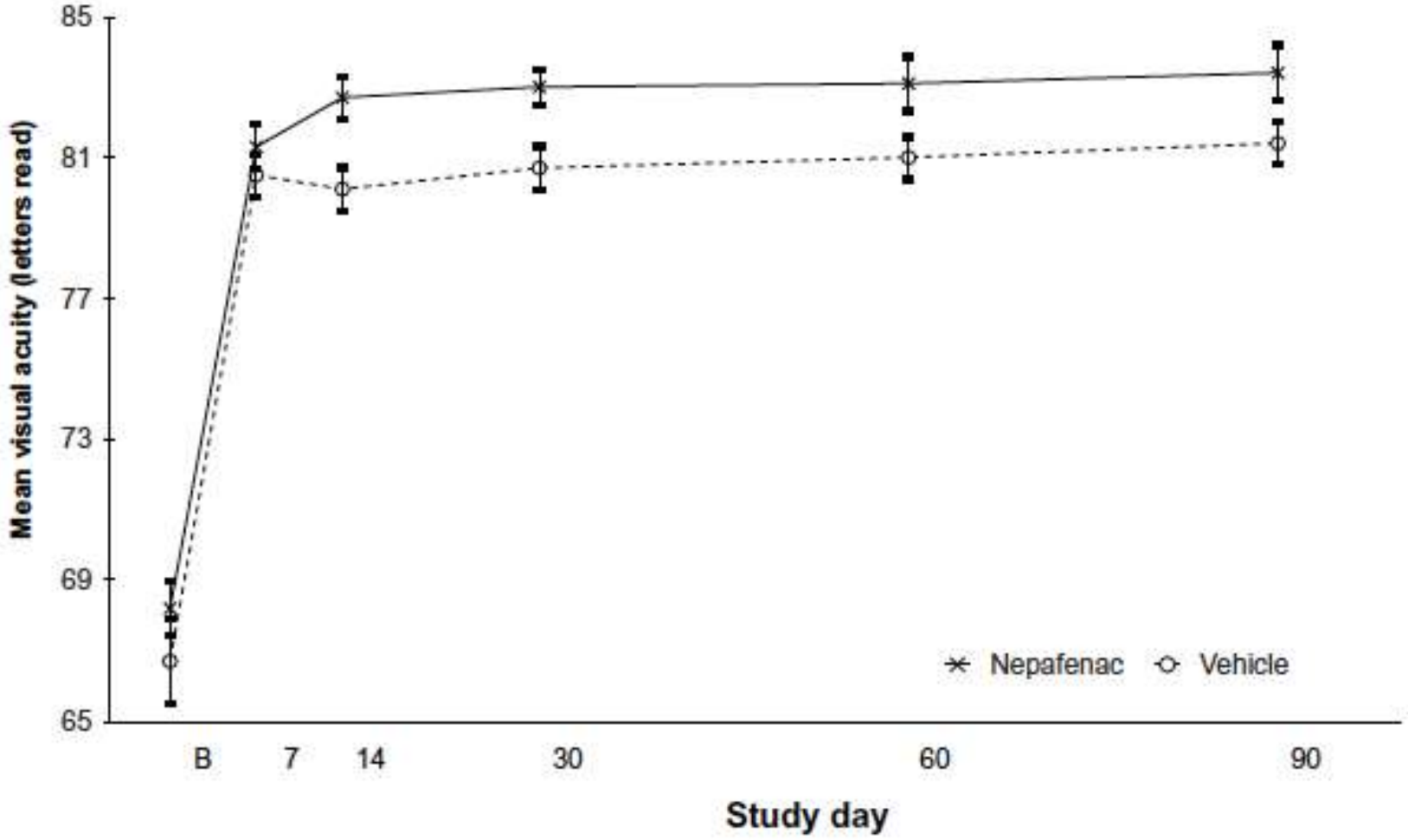
- It did not analyse patients with Diabetes.

•This study **81,984** eyes, including those in patients with diabetes, using Medisoft EMR

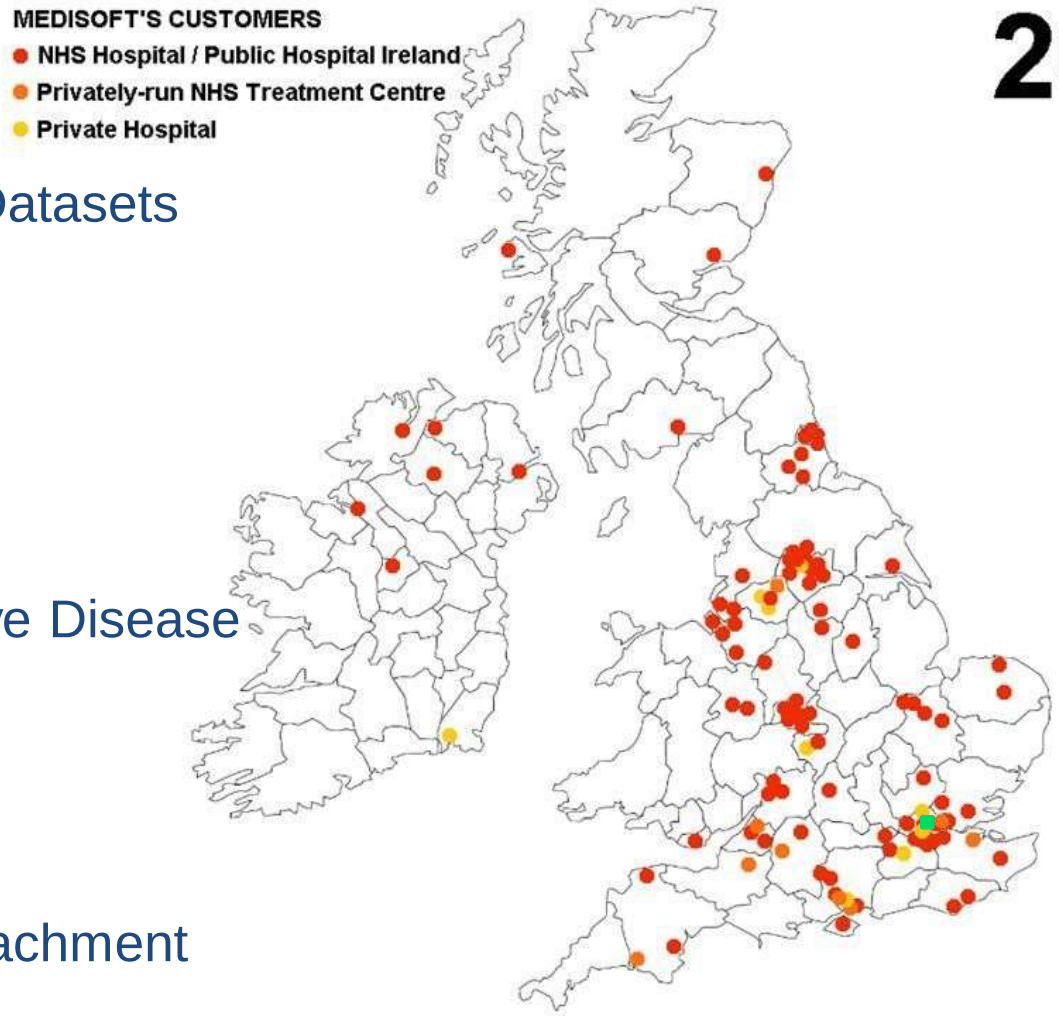
Role of Non-steroidal's Singh et al Macular Thickness



Visual Acuity



Medisoft Electronic Medical Record



- Nationally Agreed Datasets

Cataract

Glaucoma

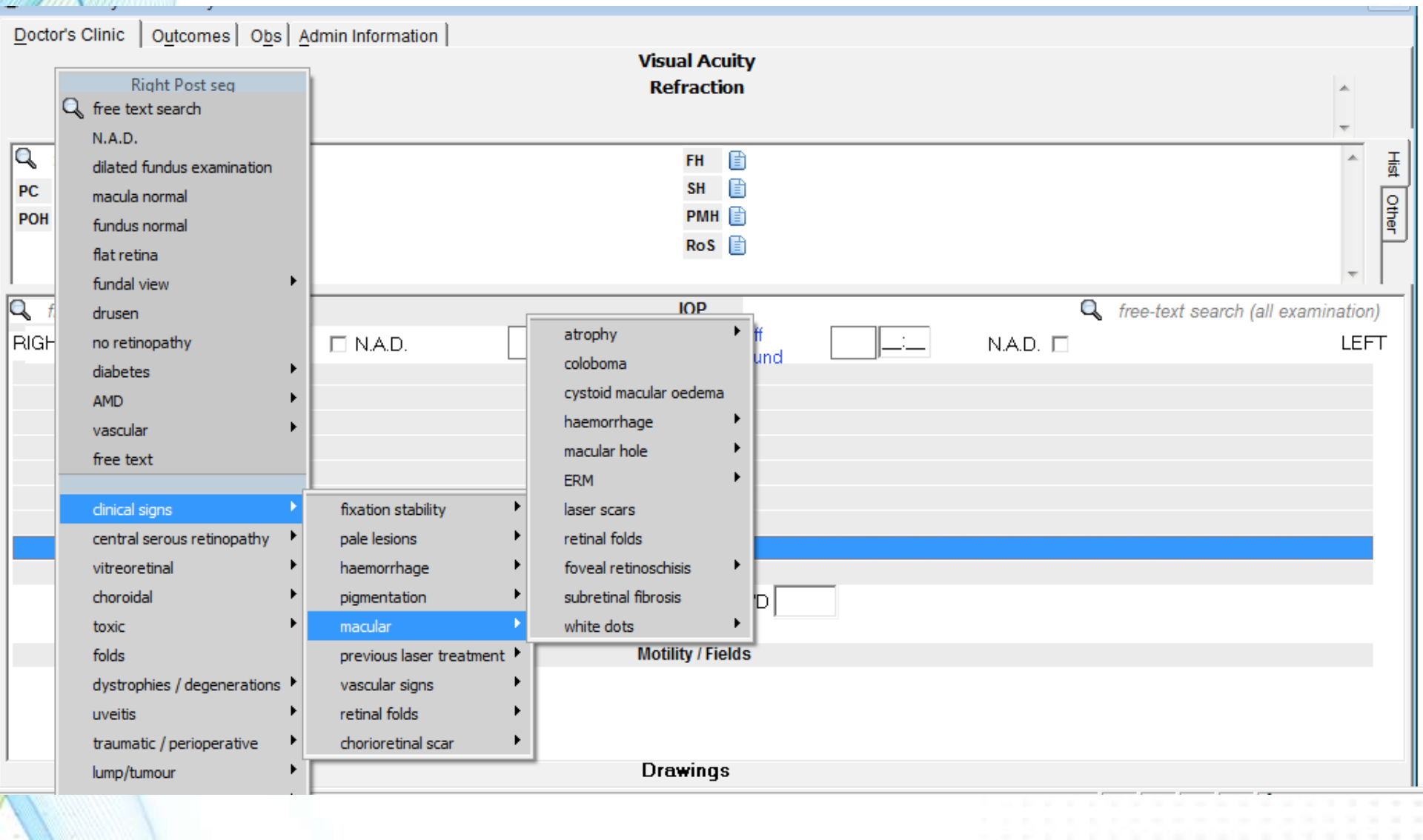
Diabetic Eye Disease

AMD

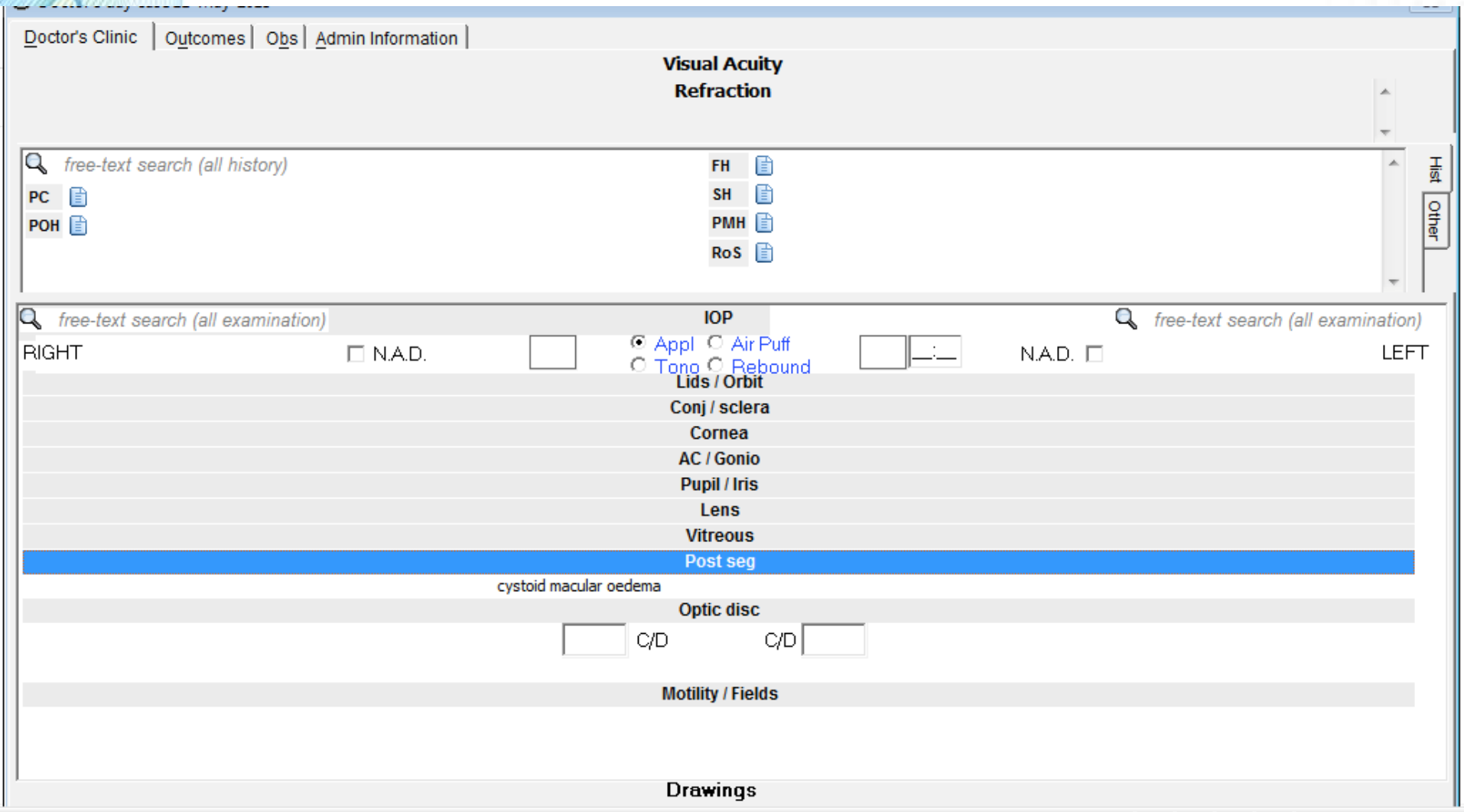
Retinal Detachment

Royal College of Ophthalmologists' National Cataract Audit

Structured data

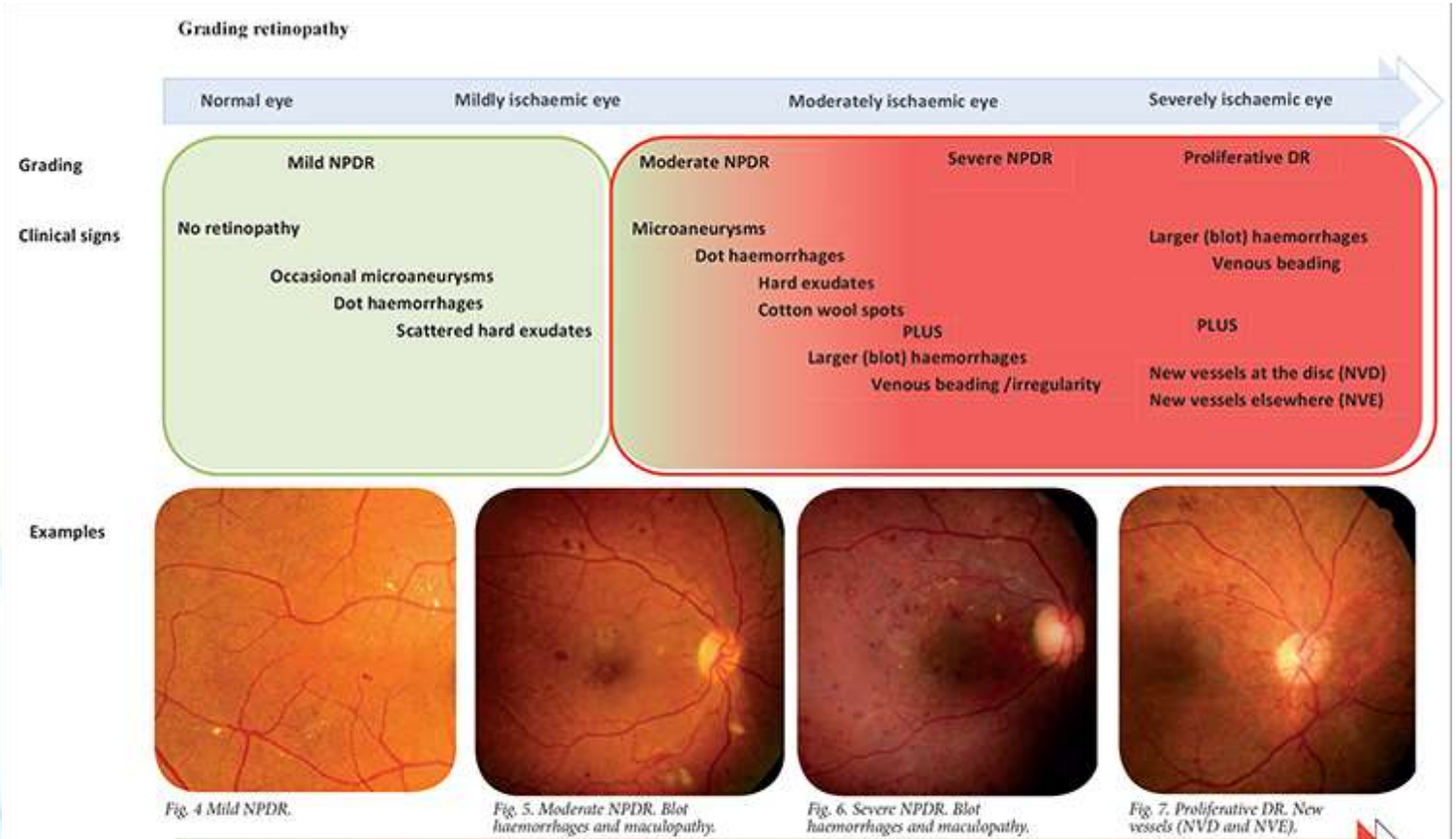


Right click to add as diagnosis

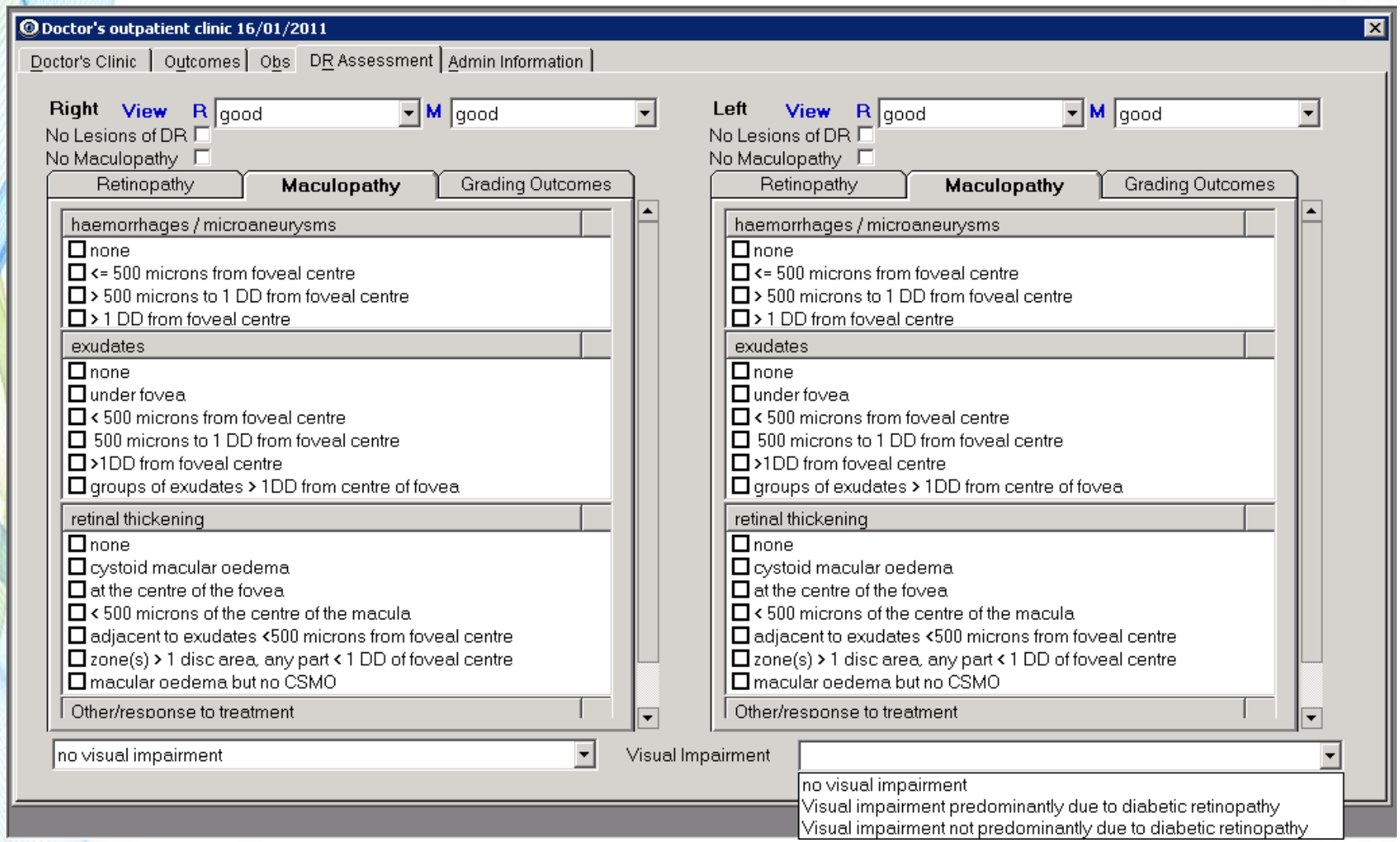


UK & Medisoft unique

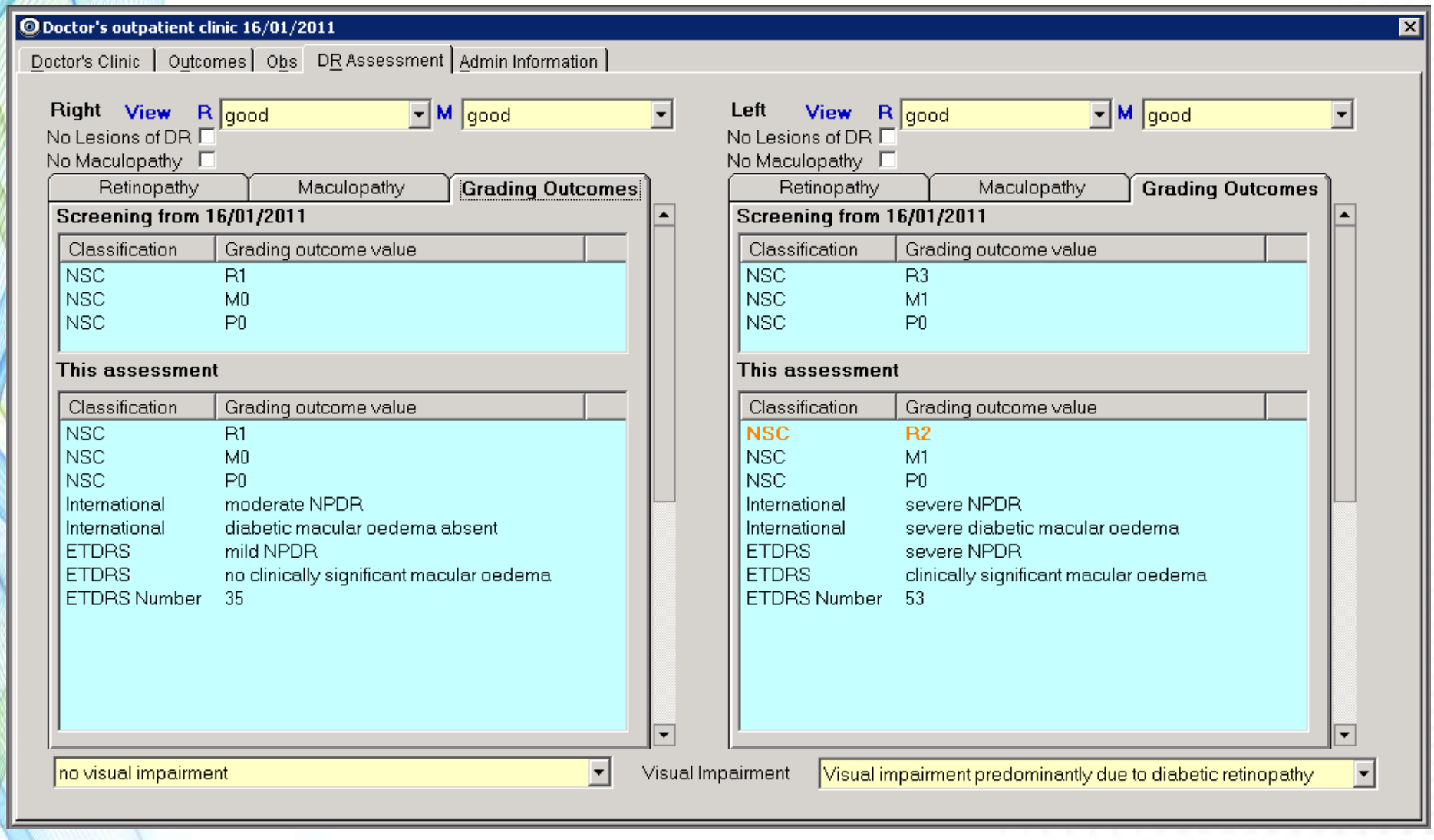
- Structured diabetic retinopathy assessment
- Pre & post-operatively
- Use Routinely at Hillingdon Now - National DRSS Grading set



Macular thickening
THH – Quick to enter data –
Cannot Save/Print/email till Completed all fields



Precise ETDRS grading



Data In
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Home - Report Manager - Windows Internet Explorer

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Type	Name	Description	Last Run	Modified Date	Modified By
	AMD			28/11/2013 16:37	GLOS\medisoft
	Cataract			28/11/2014 15:55	GLOS\medisoft
	Data Sources			07/07/2014 12:05	GLOS\medisoft
	Medical Retina			16/10/2014 12:43	GLOS\medisoft

Items in Home

- SQL Server Back Office
- Cloud Based
- Hospital Based
- Instant Live Audits

Incidence of Post-Cataract Surgery Cystoid Macular Oedema - Report Manager - Windows Internet Explorer

http://glnt426/Reports/Pages/Report.aspx?ItemPath=%2fCataract%2fIncidence+of+

Home > Cataract > Incidence of Post-Cataract Surgery Cystoid Macular Oedema

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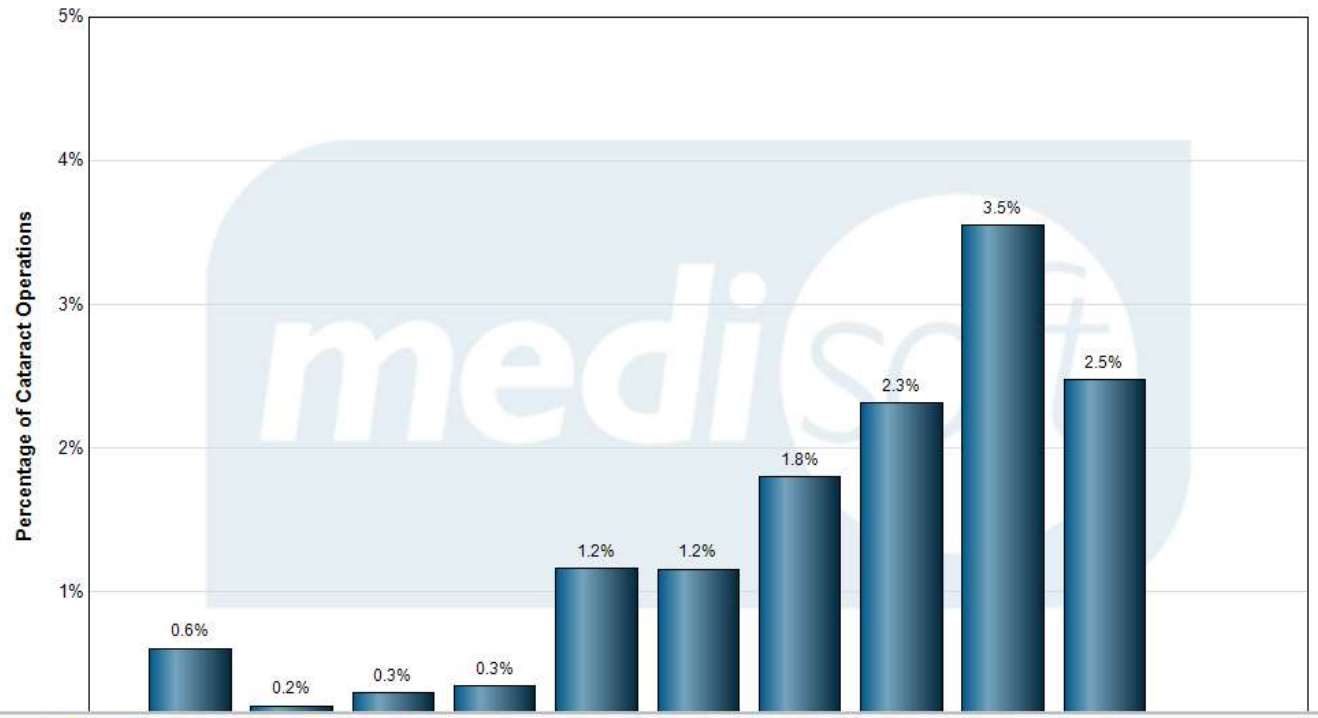
Cataract Date From	21/11/2005	Cataract Date To	09/01/2015
Age Range Start	0 NULL	Age Range End	113 NULL
Pre-Operative CMO Prophylaxis	NSAID within 2 weeks Pre-Op, N	Post-Operative CMO Prophylaxis	NSAID Prescribed Post-Op, No N
Diabetic Status	Not Diabetic, Diabetic - Type No	Pre-OP ETDRS Grade	ETDRS Grade Not Applicable / N
Pre-Op DMO	CSMO, Macular Oedema but no	Operative Complications	none, conjunctival buttonhole, c
Other Pre-Op Risk Factors	None, Epiretinal Membrane, Pros		

View Report

1 of 2 ? 100% Find | Next

Incidence of Post-Cataract Surgery Cystoid Macular Oedema

(Click on a column to drill-down)



Start

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12/01/2015

Incidence of Post-Cataract Surgery Cystoid Macular Oedema

⊟ Report Description

This report shows the incidence of post-cataract surgery cystoid macular oedema, recorded within 3 months, by year of surgery. Filters can be applied to lim
particular patient/eye groups. An excel data export allows even more detailed analysis.

⊞ Report Criteria

Click to View Selected Criteria

⊟ Report Summary Data

Report Year	Total Cataract Operations	Total Cataract Operations Filtered	Eyes with Post Op CMO	Percentage Eyes with Post Op CMO
2009	4223	4215	49	1.2%
2010	4231	4227	49	1.2%
2011	3217	3216	58	1.8%
2012	3546	3541	82	2.3%
2013	4031	4026	143	3.6%
2014	4399	4393	109	2.5%
2015	89	89	0	0.0%
Total	**23736**	**23707**	**490**	**2.1%**

⊞ Export Report Source Data

Click to View Report Source Data

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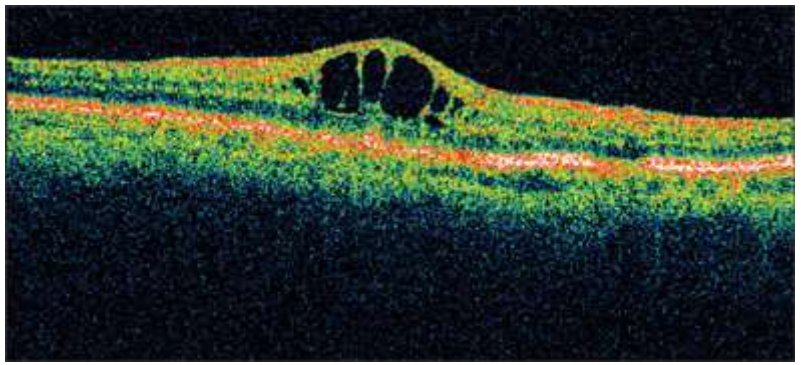
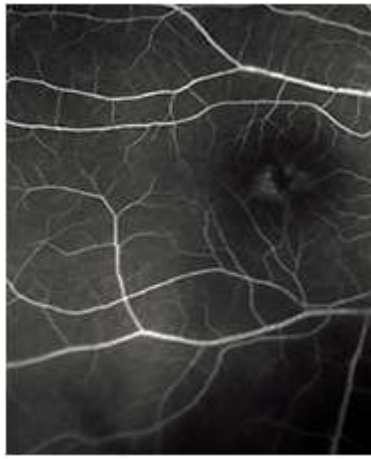
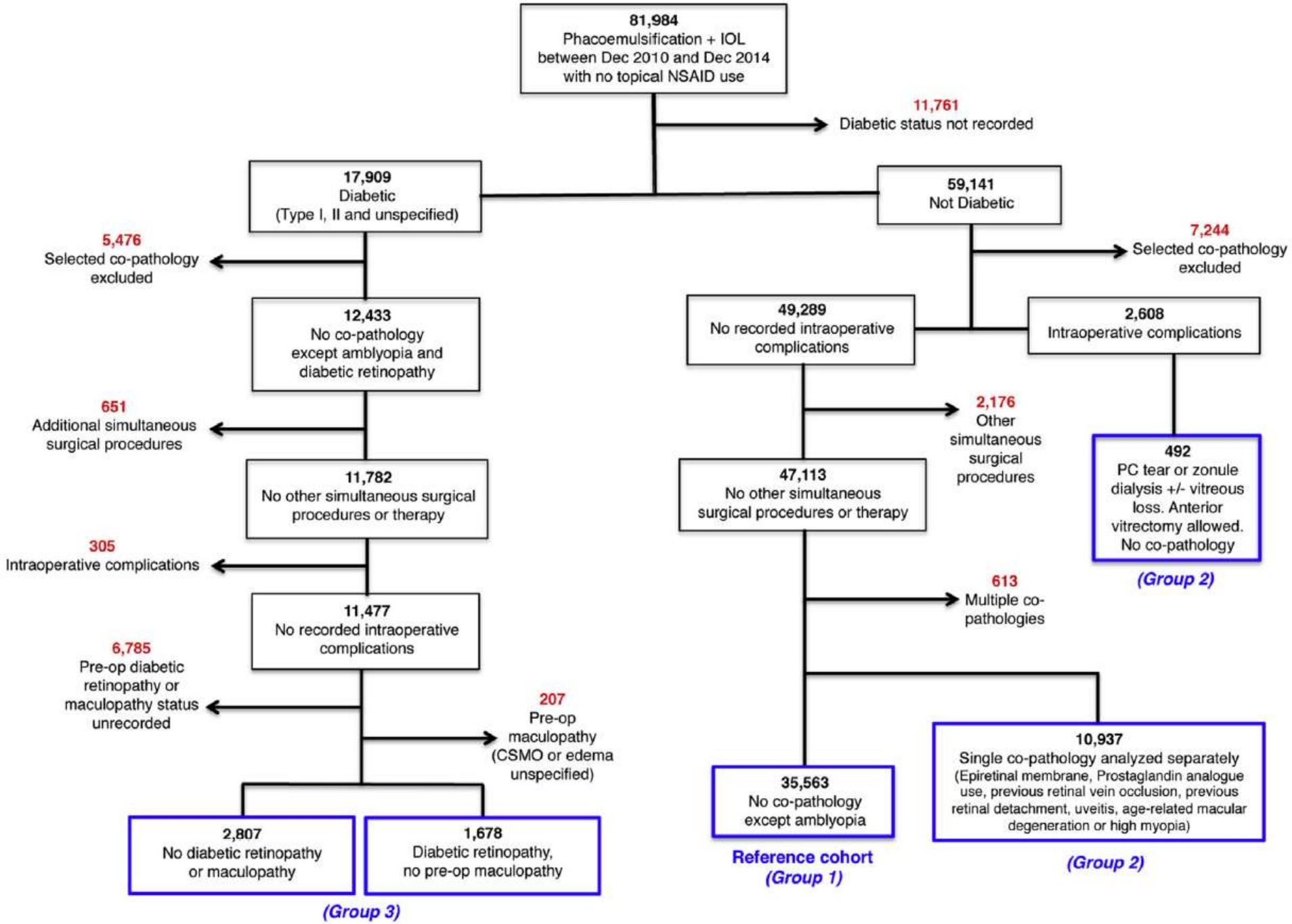




Methods

- 8 centres, IG permission, anonymised data extracted & collated
- No prophylactic NSAIDs
- Diabetic retinopathy status
- Specific filtered single risk factors
  - Epiretinal membrane
  - Previous retinal vein occlusion
  - Previous RD surgery
  - Uveitis
  - PC tear / vitreous loss
  - Prostaglandin analogue use
  - Dry AMD


81,984
Phacoemulsification + IOL between Dec 2010 and Dec 2014 with no topical NSAID use
11,761
Diabetic status not recorded
17,909
Diabetic (Type I, II and unspecified)
59,141
Not Diabetic
5,476
Selected co-pathology excluded
7,244
Selected co-pathology excluded
12,433
No co-pathology except amblyopia and diabetic retinopathy
49,289
No recorded intraoperative complications
2,608
Intraoperative complications
651
Additional simultaneous surgical procedures
2,176
Other simultaneous surgical procedures
11,782
No other simultaneous surgical procedures or therapy
47,113
No other simultaneous surgical procedures or therapy
492
PC tear or zonule dialysis +/- vitreous loss. Anterior vitrectomy allowed. No co-pathology
(Group 2)
305
Intraoperative complications
11,477
No recorded intraoperative complications
613
Multiple co-pathologies
6,785
Pre-op diabetic retinopathy or maculopathy status unrecorded
207
Pre-op maculopathy (CSMO or edema unspecified)
35,563
No co-pathology except amblyopia
10,937
Single co-pathology analyzed separately (Epiretinal membrane, Prostaglandin analogue use, previous retinal vein occlusion, previous retinal detachment, uveitis, age-related macular degeneration or high myopia)
2,807
No diabetic retinopathy or maculopathy
1,678
Diabetic retinopathy, no pre-op maculopathy
Reference cohort
(Group 1)
(Group 2)
(Group 3)

Group 1

No Diabetes

No risk factors

The incidence of post-operative clinically significant PME

of 1.17%

(415 eyes had CMO of 35,563 eyes at risk)

Table 1. Nominal Data Characteristics of the Baseline Reference Cohort (Group 1) Comparing Eyes with Pseudophakic Macular Edema after Surgery with Those without Pseudophakic Macular Edema

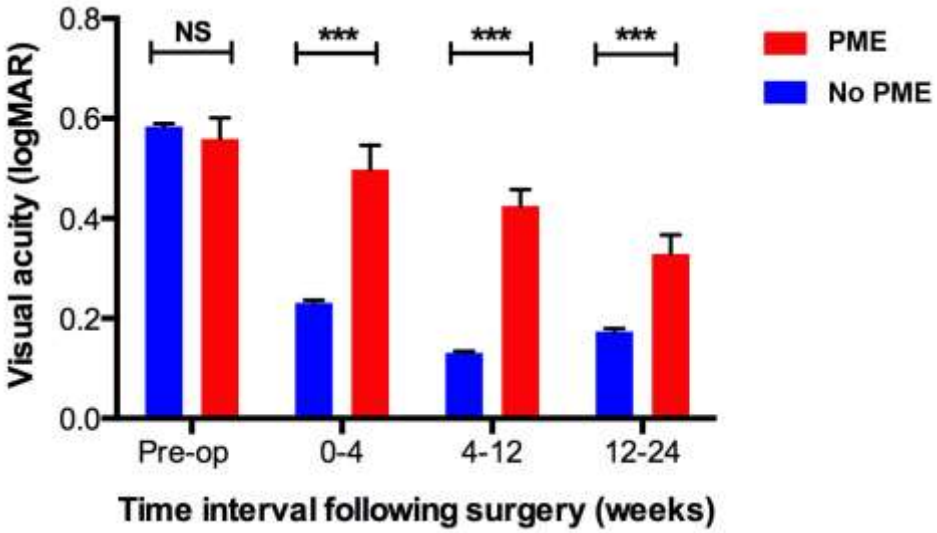
	No Pseudophakic Macular Edema (No. of Eyes)	Pseudophakic Macular Edema (No. of Eyes)	Incidence (%)	*P* Value
Gender				
Male	13,679	193	1.391	0.0019
Female	21,469	222	1.023	
Eye				
Left	17,377	210	1.194	0.637
Right	17,770	205	1.140	
Pupil size				
Small	737	11	1.471	0.538
Large	29,408	344	1.156	
Surgeon experience				
Junior surgeon (resident)	2459	33	1.265	0.514
Senior surgeon (consultant)	17,792	197	1.107	

Male gender was associated with an increased incidence of postoperative pseudophakic macular edema. Small pupils or surgeons in the early years of training did not show a higher risk of postoperative pseudophakic macular edema. *P* values are shown for chi-square tests with Yates' correction.

Table 2. Continuous Data Characteristics of the Baseline Reference Cohort (Group 1) Comparing Eyes with Pseudophakic Macular Edema after Surgery with Those without Pseudophakic Macular Edema

	No Pseudophakic Macular Edema			Pseudophakic Macular Edema			
	Mean	*Standard Deviation*	*No. of Eyes*	*Mean*	*Standard Deviation*	*No. of Eyes*	**P Value**
Age (yrs)	74.42	10.42	35,146	76.33	9.53	414	0.0002
Preoperative VA (logMAR)	0.590	0.495	35,109	0.567	0.567	415	0.3476
Postoperative VA (logMAR)							
Within 4 wks	0.224	0.285	15,251	0.496	0.362	241	<0.0001
4–12 wks	0.140	0.243	18,738	0.422	0.308	371	<0.0001
12–24 wks	0.178	0.252	9259	0.328	0.281	236	<0.0001
Axial length (mm)	23.40	1.183	35,137	23.35	1.164	415	0.3919
IOP (mmHg)							
Before surgery	16.15	3.175	26,780	16.43	3.285	343	0.1048
First within 3 months after surgery	14.90	3.374	21,479	15.31	3.264	371	0.0202

IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.
Statistically significant findings included older age in the cystoid macular edema group, with a relatively lower VA at all time points studied. Intraocular pressure decreased after surgery as expected, but was higher in the pseudophakic macular edema group. *P* values were generated by multiple *t* tests using the Holm-Sidak method for multiple comparisons using an α of 5.00.



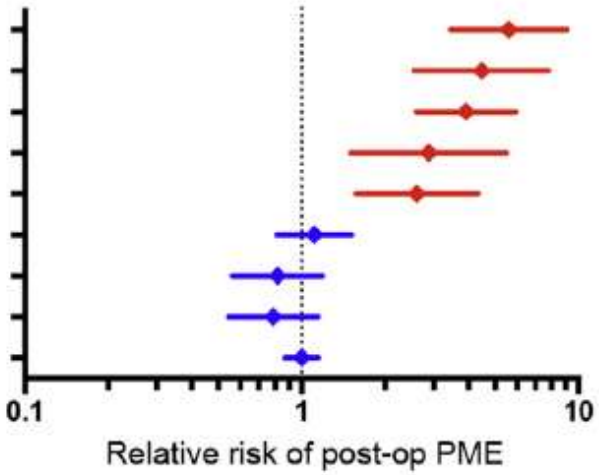
Group 2

No Diabetes

Eyes with a single ‘risk factor’

Group 2 – Eyes with a single 'risk factor'

	No PME (eyes)	PME (eyes)	Incidence (%)	Relative risk (and 95% CI)
Epiretinal membrane	229	16	6.53	5.596 (3.452 to 9.074)
Retinal vein occlusion	218	12	5.22	4.471 (2.556 to 7.820)
Previous RD repair	479	23	4.58	3.926 (2.604 to 5.919)
Uveitis	259	9	3.36	2.878 (1.503 to 5.509)
PC-tear/vitreous loss	477	15	3.05	2.610 (1.573 to 4.339)
Prostaglandin analogues	3,350	44	1.30	1.111 (0.816 to 1.513)
High Myopia	3,009	29	0.95	0.818 (0.562 to 1.190)
Dry ARMD	3,230	30	0.92	0.789 (0.545 to 1.140)
Reference cohort	35,148	415	1.17	1.000 (0.874 to 1.145)



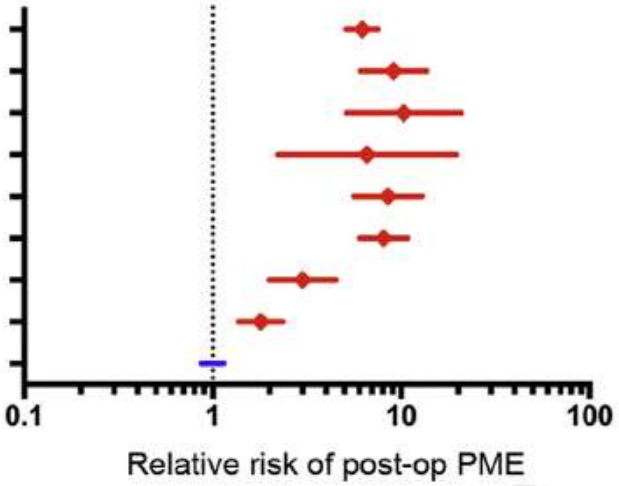
Group 3

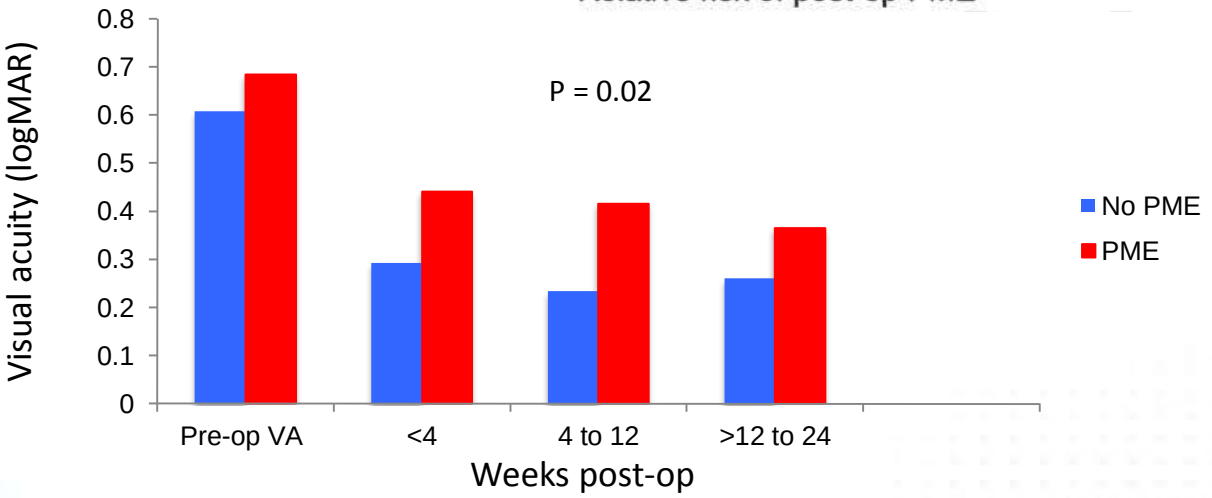
Diabetes & Diabetic Retinopathy

No other risk factors

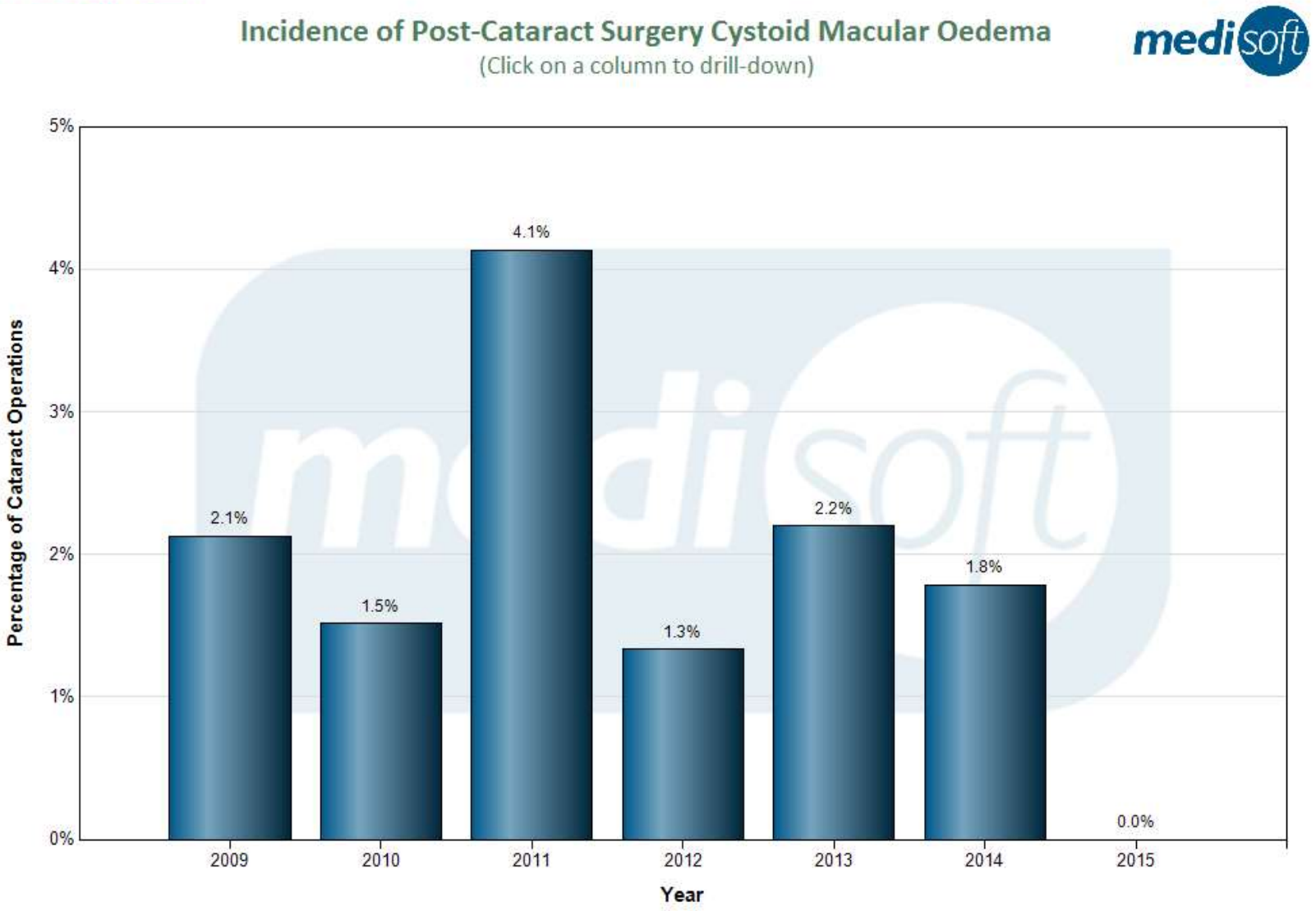
Group 3 – Eyes from patients with Diabetes

	No PME (eyes)	PME (eyes)	Incidence (%)	Relative risk (and 95% CI)
Any DR	1,556	122	7.27	6.230 (5.122 to 7.578)
PRP and stable PDR	185	22	10.63	9.108 (6.066 to 13.675)
All PDR	51	7	12.07	10.342 (5.130 to 20.853)
Severe NPDR	36	3	7.69	6.592 (2.213 to 19.634)
Moderate NPDR	190	21	9.95	8.529 (5.621 to 12.941)
Mild NPDR	432	45	9.43	8.084 (6.025 to 10.848)
Very mild NPDR	662	24	3.50	2.998 (2.001 to 4.493)
DM no DR	2,748	59	2.15	1.801 (1.375 to 2.360)
Reference cohort	35,148	415	1.17	1.000 (0.874 to 1.145)

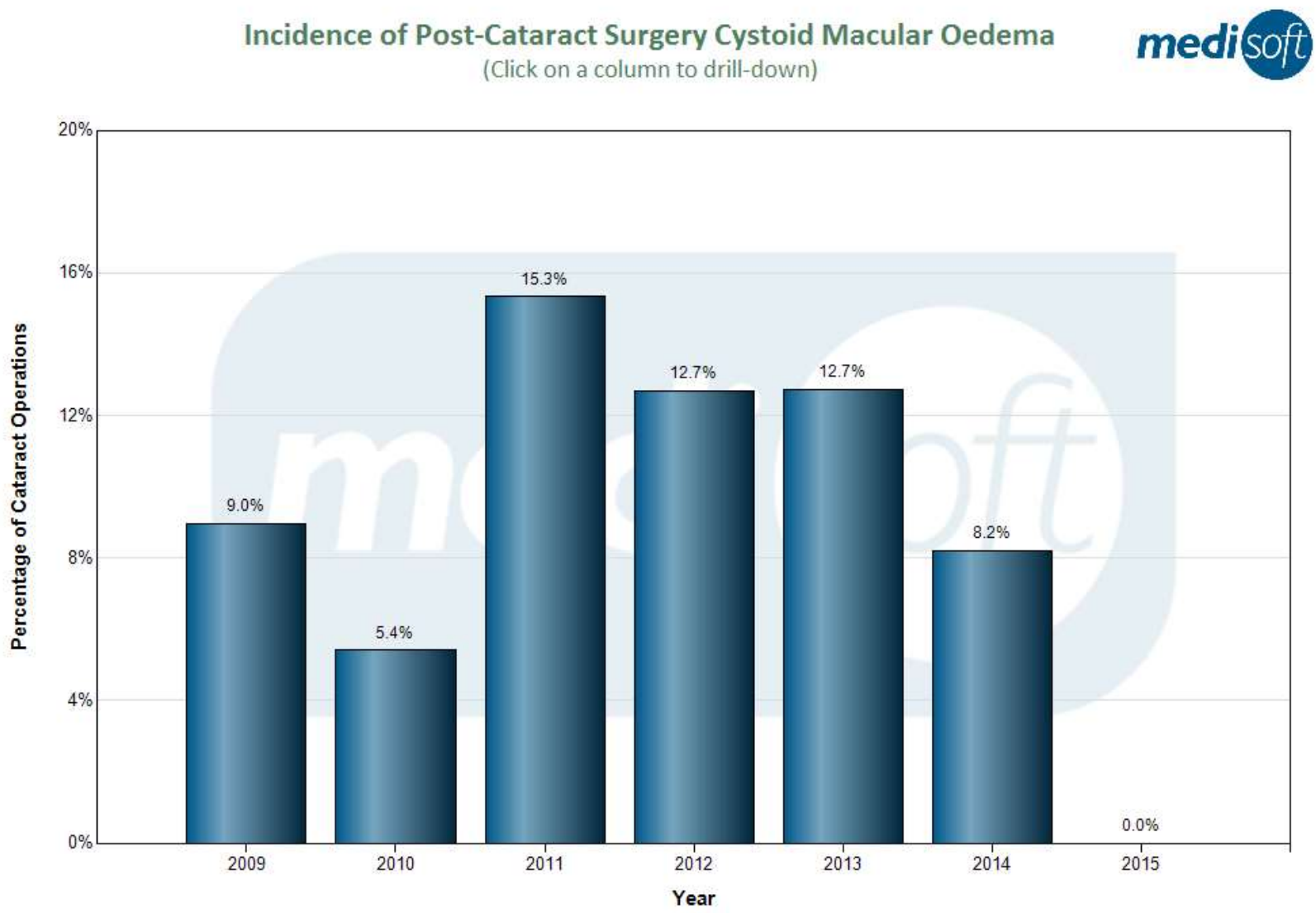




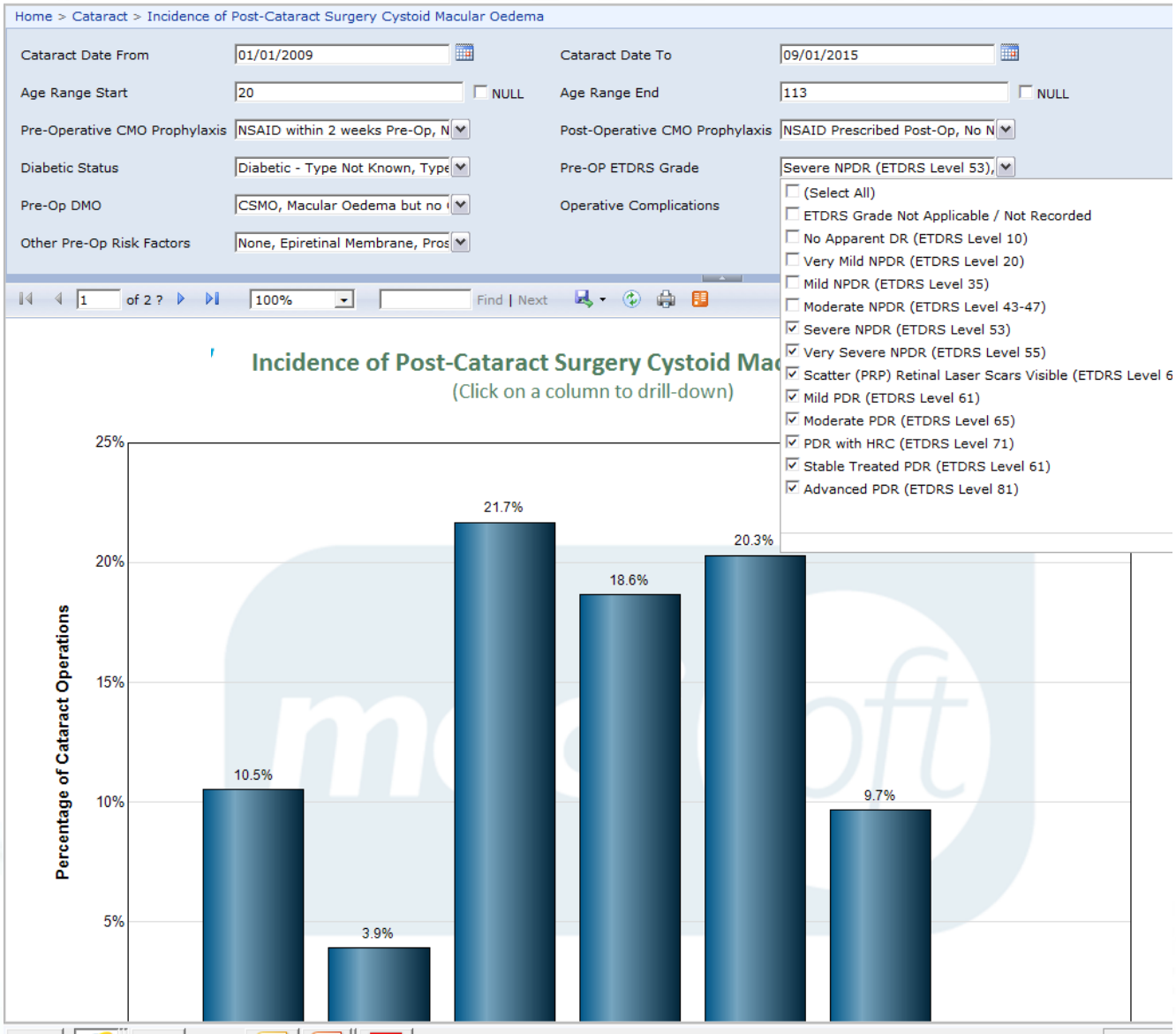
Diabetes – no retinopathy (n = range 94 – 224)
)



Diabetes + any retinopathy (n = range 145 – 220)



Diabetic – ≥ severe retinopathy (n =

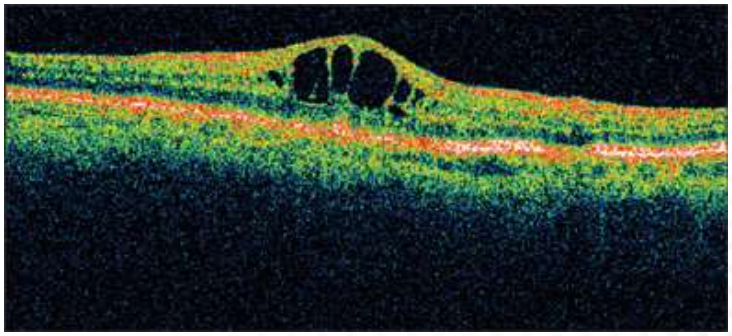


Conclusions of this study

- Uncomplicated cases real-world incidence is at least **1.17%**.
- Visual acuity in eyes developing PME did not recover to comparable levels, even with treatment within 12-24 weeks.
- Therefore prophylaxis in high risk groups may be advisable.
- <u>High risk groups include:</u>
  - Eyes from patients with Diabetes with or without retinopathy.
  - Surgical complications including PC rupture.
  - Co-pathology including ERM, Uveitis, previous RVO and RD.
- Pre-operative topical prostaglandin analogue use is not associated with increased incidence of PME.
- Prevention better than Cure

Additional analyses needed

- Health economics analysis
  - Number of visits
  - Additional treatments
  - Visual acuity impact long-term
- Phase 2
  - Impact of NSAIDs
  - Nevanac License for Prevention of DMO in Diabetics
  - Approval by Hospital Pharmacy Boards
  - Increased use of NSAID post operatively world wide
  - Routine use of OCT



Thanks

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When to give NSAIDs
Aim of Physicians is to prevent not Treat CMO

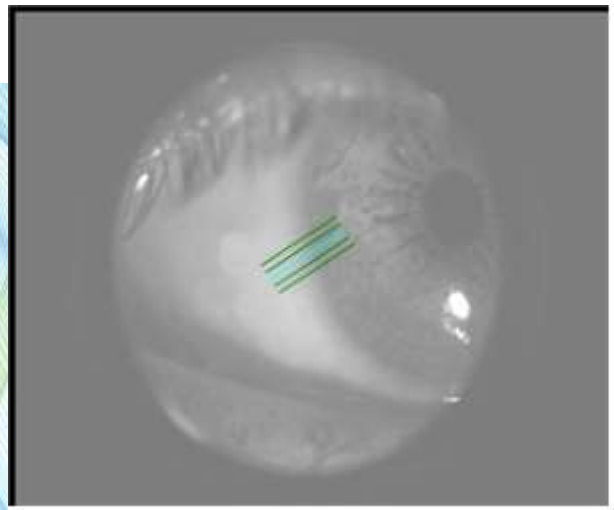
- Consensus
  - Pre-operative 1-2 days
  - But 1-2 hours may be enough
  - Post-op 3-4 weeks if no risk factors qds
  - 60 days in license
  - Once a day formulation due soon
- Geographical variation
  - USA Combined with steroids & antibiotics
  - Denmark used alone

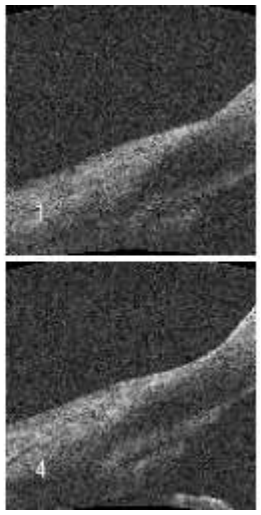
Risks of NSAIDs

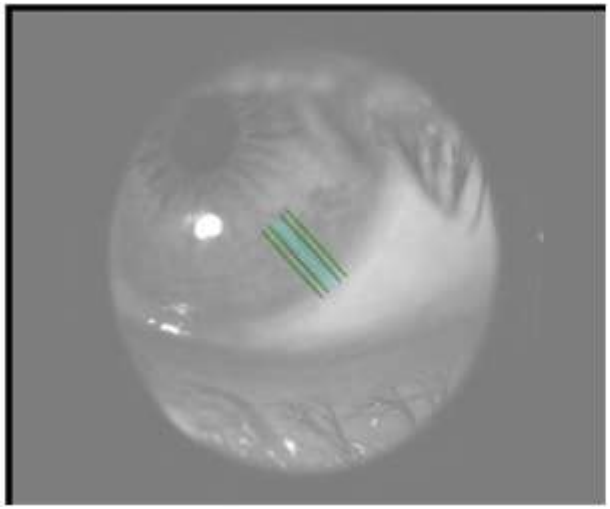
- Corneal complications
  - Punctate keratitis
  - Epithelial defects
  - Delayed wound healing
  - Stinging & irritation
  - Corneal infiltrates / melts

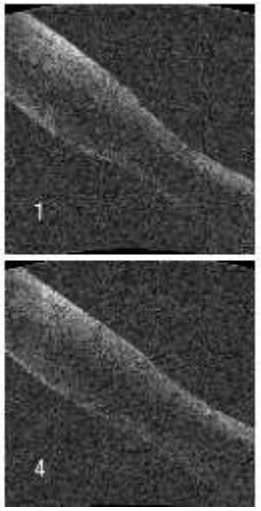
- Diclofenac, ketorolac & bromfenac – poor corneal penetration

- J Cataract Refract Surg. 2007 Nov;33(11):1974-5.
- **Nepafenac-associated corneal melt.**
- Wolf EJ1, Kleiman LZ, Schrier A.
- **Author information**
- **Abstract**
- We describe a patient with systemic graft-versus-host disease who developed a nonhealing epithelial defect after cataract surgery that healed on cessation of a topical nonsteroidal antiinflammatory drug (NSAID) (ketorolac). The patient developed a central corneal perforation in the fellow eye while on a new NSAID formulation (nepafenac) after routine cataract surgery. Our case suggests that new topical NSAIDs may be similar to older NSAID formulations in promoting corneal melting in patients predisposed to poor epithelialization and corneal wound healing.





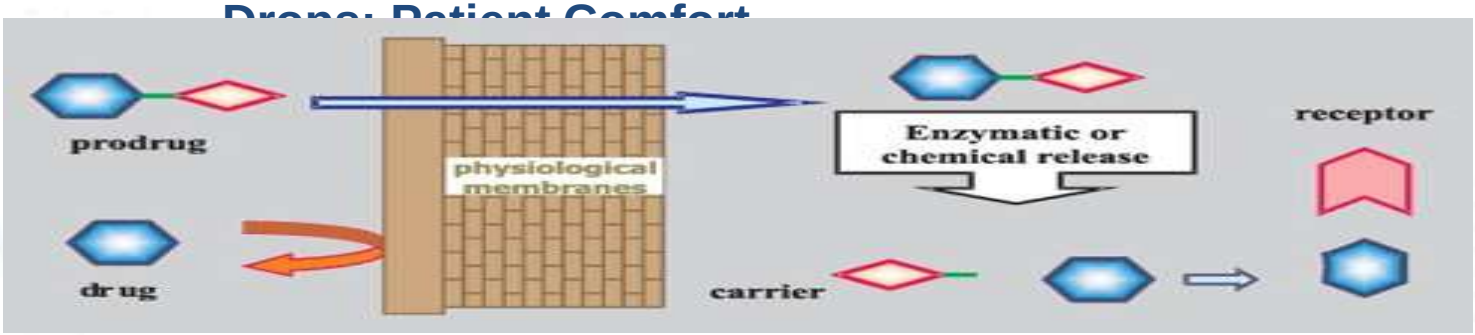




Claimed advantages of Nepafenac

- Nepafenac – pro-drug, rapidly penetrates cornea, ‘deaminated’ to amfenac by intraocular hydrolases
- No stinging, or burning
- RCT, double-masked, vehicle controlled study
- Patients with diabetes having cataract surgery
- CMO 3.2% vs 16.7%
- OCT (≥ 30% increase in subfield thickness)

- Clinical Trials Gov
  - **Comparison of Diclofenac vs. Nepafenac Ophthalmic Drops: Patient Comfort**



Singh et al. Clinical Ophthalmology June 2012, RCT, double-masked 263 diabetic patients

Clinical available NSAID's

Generic	Brand	Manufacturer	Chemical class	Formulation
Ketorolac	Acular	Allergan	Phenylalkanoic acid	0.5% solution
Diclofenac	Voltaren	Novartis	Phenylacetic acid	0.1% solution
Nepafenac	Nevanac	Alcon	Arylacetic acid	0.1% suspension
Bromfenac	Xibrom	Bausch and Lomb	Phenylacetic acid	0.09% solution

Relative Potency of NSAID
Lower is more effective NSAID

	IC50 COX-2 (nM)
Bromfenac	6.6
Ketorolac	120

	IC_{50}COX-2 (nM)
Bromfenac	23
Diclofenac	85
Amfenac	150

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2709021/table/t3-opth-3-199/

Bromfenac Side effects

Ocular adverse events	Bromfenac 0.09%	Vehicle
Number	356 (100%)	171 (100%)
Iritis	7.0%	18.1%
Abnormal sensation in eye	6.5%	8.2%
Eye pain	4.2%	11.7%
Eye pruritis	3.9%	2.9%
Posterior capsule opacification	3.9%	4.1%
Partial vision loss	3.1%	9.4%
Eye irritation (burning/stinging)	2.5%	4.7%
Eye redness	2.2%	7.6%
Conjunctival hyperemia	2.2%	11.1%
Photophobia	2.0%	11.1%

Clin Ophthalmol. 2009; 3: 199–210.

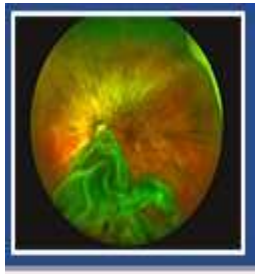
Bromfenac vs ketorolac vs diclofenac for the treatment of acute pseudophakic CME

- Rho et al80 presented results of a study comparing bromfenac ophthalmic solution with diclofenac and ketorolac for the treatment of acute pseudophaakic CME. Sixty-four eyes with documented CME after uncomplicated cataract surgery were randomized to receive bromfenac bid, diclofenac qid, or ketorolac qid for 3 months.
- All 3 treatment groups achieved statistically significant visual improvement,
- The differences between the groups were not significant, there was a trend toward significance for the bromfenac group.
- Rho concluded that twice-daily bromfenac was statistically as effective as diclofenac or ketorolac dosed 4 times daily

Rho DS, Soll SM, Markovitz BJ. Bromfenac 0.09% versus diclofenac sodium 0.1% verseus ketorolac tromethamine 0.5% in the treatment of acute pseudophakic cystoids macular edema: diclofenac versus ketorolac. Proceedings of the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting; Ft. Lauderdale, FL. April 30–May 4, 2006; p. AF211

Conclusions

- Patient need – there is a problem with CMO
- Under-recognised
- Nepafenac
  - Licensed for diabetics having cataract surgery
  - Prevention & treatment post-op pain & inflammation
  - To treat cystoid macular oedema
  - Anecdotally great in uveitics



Ophthalmology

Post-cataract Prevention of Inflammation and Macular Edema by Steroid and Nonsteroidal Anti-inflammatory Eye Drops

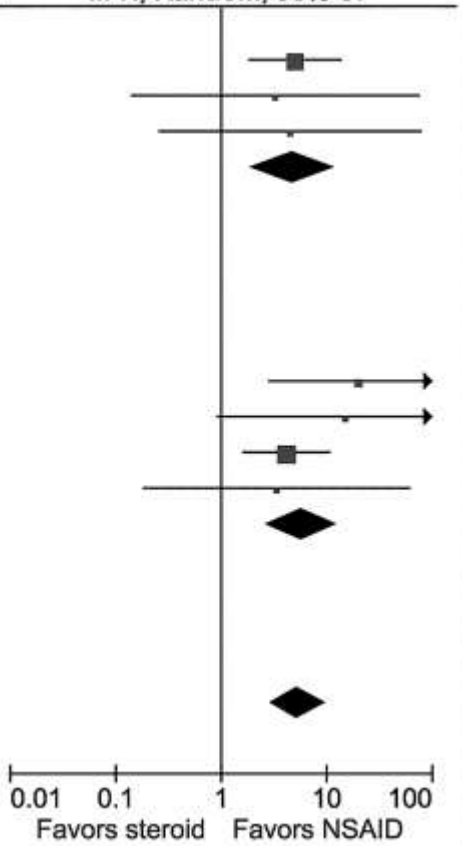
A Systematic Review

Line Kessel, MD, PhD, Britta Tendal, PhD, Karsten Juhl Jørgensen, MD, DrMedSci, Ditte Erngaard, MD, Per Flesner, MD, PhD, Jens Lundgaard Andresen, MD, PhD, Jesper Hjortdal, MD, DrMedSci

Manuscript no. 2013-1766.

CME at 1 month post surgery
Steroids Vs NSAID

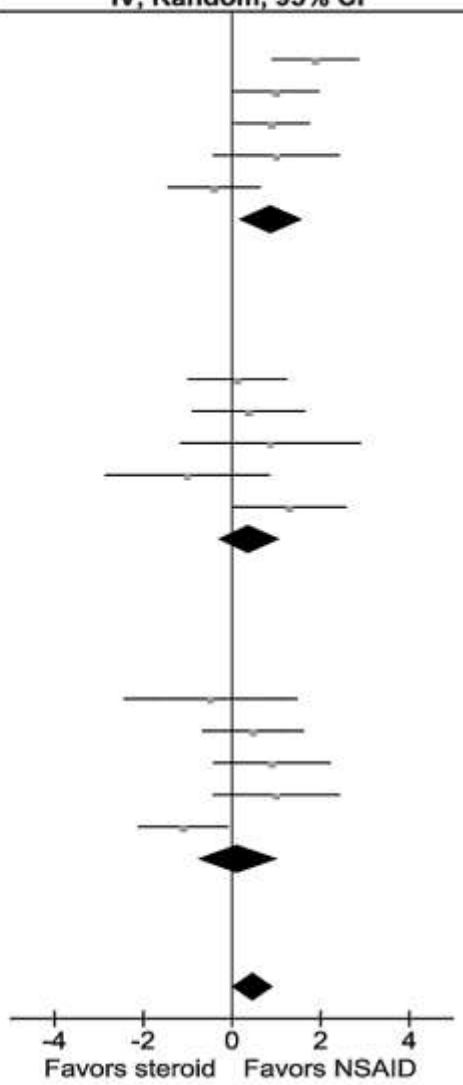
Study or Subgroup	Steroid Events	Steroid Total	NSAID Events	NSAID Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Beta- and dexamethasone						
Asano 2008	20	69	4	69	34.7%	5.00 [1.80, 13.87]
Miyanaga 2009	1	23	0	25	3.6%	3.25 [0.14, 76.01]
Wang 2013 B	4	41	0	20	4.4%	4.50 [0.25, 79.72]
Subtotal (95% CI)		**133**		**114**	**42.7%**	**4.77 [1.90, 11.96]**
Total events	25		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 3.33 (P = 0.0009)						
3.1.2 Fluorometholone						
Miyake 2000	20	53	1	53	9.3%	20.00 [2.78, 143.69]
Miyake 2007	7	25	0	25	4.6%	15.00 [0.90, 249.30]
Miyake 2011	16	27	4	28	39.2%	4.15 [1.59, 10.83]
Wang 2013	3	43	0	20	4.2%	3.34 [0.18, 61.77]
Subtotal (95% CI)		**148**		**126**	**57.3%**	**5.84 [2.64, 12.91]**
Total events	46		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 4.36 (P < 0.0001)						
Total (95% CI)		**281**		**240**	**100.0%**	**5.35 [2.94, 9.76]**
Total events	71		9			
Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 6 (P = 0.81); I² = 0%						
Test for overall effect: Z = 5.47 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						



Ophthalmology 2014 121, 1915-1924DOI: (10.1016/j.ophtha.2014.04.035)
1, 1915-1924DOI: (10.1016/j.ophtha.2014.04.035)
almology 2014 121, 1915-1924DOI: (10.1016/j.ophtha.2014.04.035

INTRA-OCULAR PRESSURE

Study or Subgroup	Steroid Mean	Steroid SD	Steroid Total	NSAID Mean	NSAID SD	NSAID Total	Weight	Mean Difference IV, Random, 95% CI
6.1.1 Beta- and dexamethasone								
Asano 2008	13.27	3.18	63	11.39	2.47	65	8.4%	1.88 [0.89, 2.87]
Laurell 2002	15	2.6	59	14	2.7	55	8.5%	1.00 [0.03, 1.97]
Missotten 2001	14	2.6	74	13.1	2.7	71	9.2%	0.90 [0.04, 1.76]
Miyanaga 2009	10	2.5	22	9	2.5	25	5.8%	1.00 [-0.43, 2.43]
Wang 2013 B	12	2	38	12.4	2.2	27	8.0%	-0.40 [-1.45, 0.65]
Subtotal (95% CI)			**256**			**243**	**39.8%**	**0.88 [0.16, 1.61]**
Heterogeneity: Tau² = 0.40; Chi² = 9.77, df = 4 (P = 0.04); I² = 59%								
Test for overall effect: Z = 2.38 (P = 0.02)								
6.1.2 Loteprednol and prednisolone								
El-Harazi 1998	16.7	1.59	10	16.58	1.17	19	7.5%	0.12 [-1.00, 1.24]
El-Harazi 1998 B	16.7	1.59	10	16.32	1.8	19	6.6%	0.38 [-0.90, 1.66]
Hirneiss 2005	14.6	2.702	12	13.73	1.8293	7	3.7%	0.87 [-1.17, 2.91]
Holzer 2002	12.7	4.1	29	13.7	3.1	30	4.2%	-1.00 [-2.86, 0.86]
Roberts 1995	16.56	2.702	27	15.26	1.8293	22	6.6%	1.30 [0.03, 2.57]
Subtotal (95% CI)			**88**			**97**	**28.6%**	**0.40 [-0.27, 1.08]**
Heterogeneity: Tau² = 0.07; Chi² = 4.54, df = 4 (P = 0.34); I² = 12%								
Test for overall effect: Z = 1.18 (P = 0.24)								
6.1.3 Fluorometholone and rimexolone								
Hirneiss 2005 B	13.25	2.702	14	13.73	1.8293	7	3.9%	-0.48 [-2.44, 1.48]
Miyake 2000	11.85	3.12	48	11.37	2.64	49	7.3%	0.48 [-0.67, 1.63]
Miyake 2007	14.2	2.8	25	13.3	1.9	25	6.4%	0.90 [-0.43, 2.23]
Miyake 2011	10	2.5	22	9	2.5	25	5.8%	1.00 [-0.43, 2.43]
Wang 2013	11.3	2	43	12.4	2.2	27	8.1%	-1.10 [-2.12, -0.08]
Subtotal (95% CI)			**152**			**133**	**31.5%**	**0.14 [-0.74, 1.03]**
Heterogeneity: Tau² = 0.55; Chi² = 8.94, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 0.32 (P = 0.75)								
Total (95% CI)			**496**			**473**	**100.0%**	**0.50 [0.05, 0.96]**
Heterogeneity: Tau² = 0.39; Chi² = 28.40, df = 14 (P = 0.01); I² = 51%								
Test for overall effect: Z = 2.17 (P = 0.03)								
Test for subgroup differences: Chi² = 1.75, df = 2 (P = 0.42), I² = 0%								



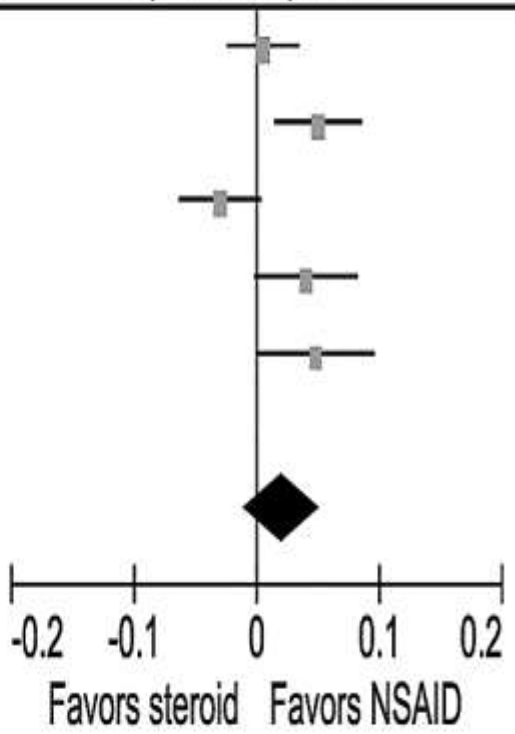
Ophthalmology 2014 121, 1915-1924DOI: (10.1016/j.ophtha.2014.04.035

Visual Acuity between two groups

Study or Subgroup	Steroid Mean	Steroid SD	Steroid Total	NSAID Mean	NSAID SD	NSAID Total	Weight	Mean Difference IV, Random, 95% CI
Asano 2008	-0.066	0.078	52	-0.071	0.08	58	22.6%	0.00 [-0.02, 0.03]
Endo 2010	-0.04	0.085	31	-0.09	0.056	31	20.6%	0.05 [0.01, 0.09]
Miyanaga 2009	0.07	0.08	22	0.1	0.01	25	21.3%	-0.03 [-0.06, 0.00]
Wang 2013	0.084	0.1	43	0.044	0.07	21	18.6%	0.04 [-0.00, 0.08]
Wang 2013 B	0.092	0.12	41	0.044	0.07	20	17.0%	0.05 [0.00, 0.10]
Total (95% CI)			**189**			**155**	**100.0%**	**0.02 [-0.01, 0.05]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.12$, df = 4 (P = 0.007); $I^2 = 72\%$

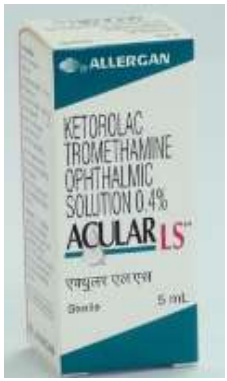
Test for overall effect: Z = 1.30 (P = 0.19)



Ophthalmology 2014 121, 1915-1924DOI: (10.1016/j.ophtha.2014.04.035

Topical Steroids VS NSAID

- 15 Trials were identified
- High quality evidence that Post operation inflammation less in NSAID group
- 3.8% VS 25.3% !
- No adverse events in either group
- Slightly higher iop rise in Steroid group.
- Different steroids used, but no difference in effectiveness found
- 5 different NSAID but study not designed to distinguish which is the best non-steroidal anti-inflammatories

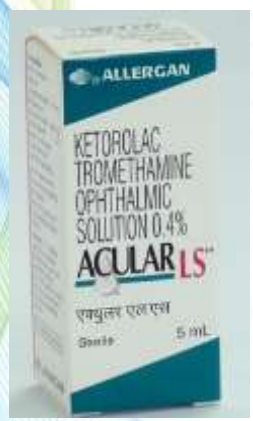


What have We done in London

- **Non – Diabetics** ALL get Bromfenac twice per day for one month post surgery since 2011

- TobraDex
  Four times a day for a week then
  Twice per day for a week and stop.

- **Diabetics** get Nevanac Pre and Post surgery for 2 months.
- Plus TobraDex



Patient Eye Drop Chart

TobraDex WEEK 1 & 2

EYEDROP CHART AFTER OPERATION

	TobraDex Week one Four times per day (Steroid and antibiotic)				**TobraDex Week 2 Twice per day (Steroid and antibiotic)**			
	Breakfast	**Lunch**	**Tea**	**Before Bed**	**Breakfast**		**Tea**	
Monday								
Tuesday								
Wednesday								
Thursday								
Friday								
Saturday								
Sunday								

Audit of Post operation CME at The Hillingdon Hospital – London Fundus fluorescein angiography & OCT Proven

- Audit 2011 14 cases of CME out of 906 cataract operations were identified in the 6-month period prior to the use of Bromfenac

  compared to

- 4 cases out of 838 in following 6 months. The association between CMO and bromfenac was statistically significant according to Fisher's exact test (*P*=0.03).

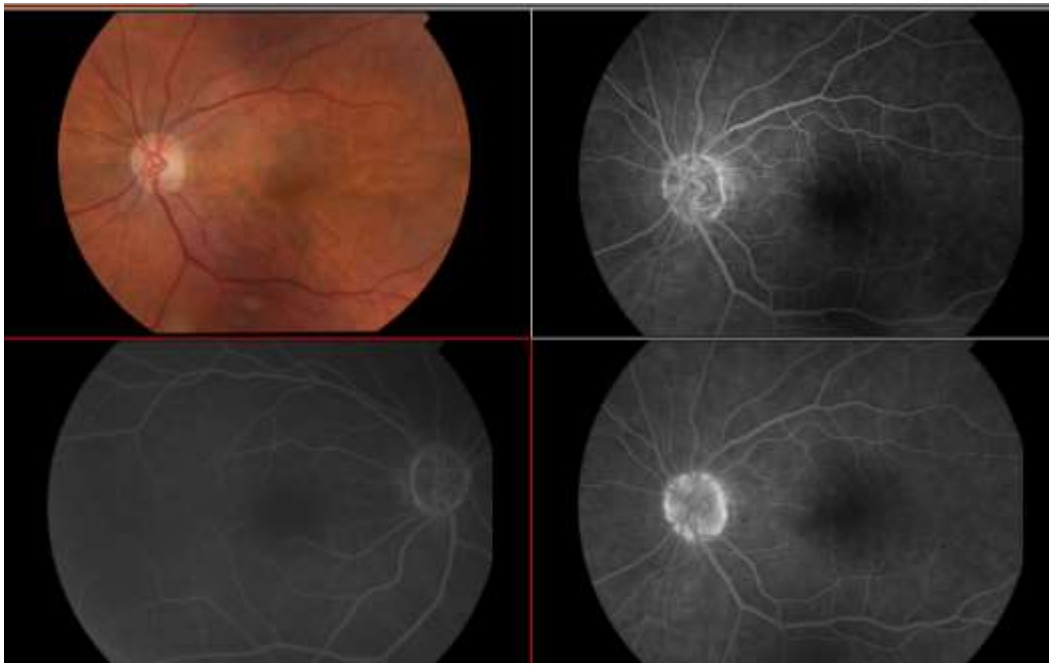
- Audit 2014 No confirmed Irvine-Gass in past year in diabetics!
- WEH – 5 Cases Diabetics
  - 1 prescribed in clinic – forgot to take
  - 4 arrived at theatre None prescribed/preop

CMO case despite Nevanc

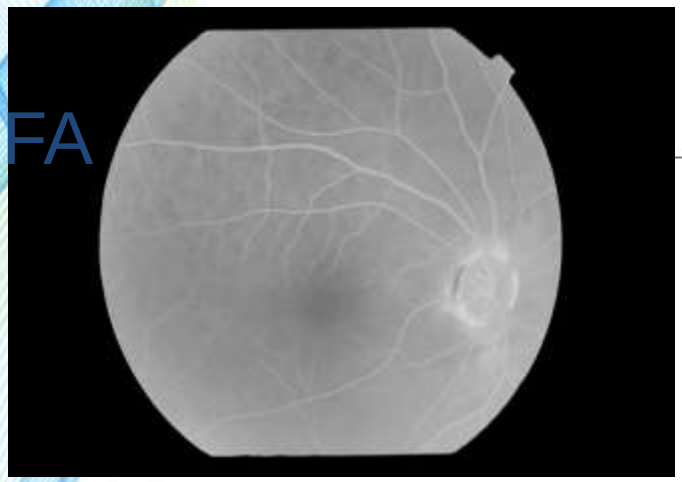
- 75 Year NIDDM,
- Previous RD Surgery
  - Intravitreal Gas
- Senior Surgeon Phaco
- Floppy Iris and Small pupil
- Anterior Capsule tear
- Prolonged surgery.

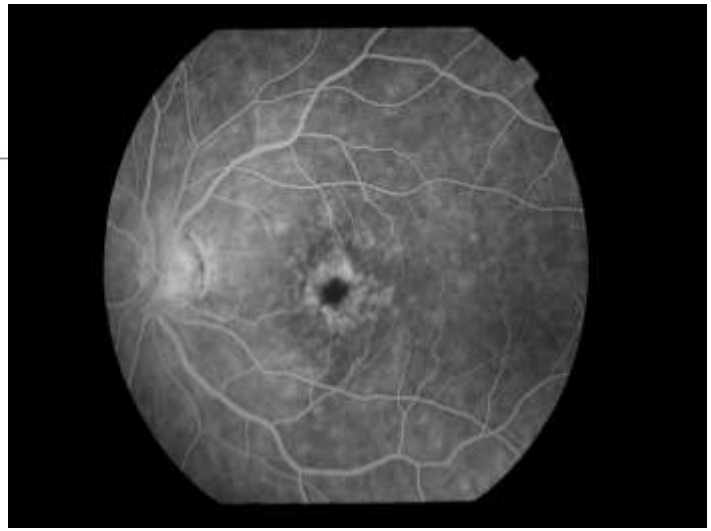
- Post operation Drops
- TobraDex and Nevanac

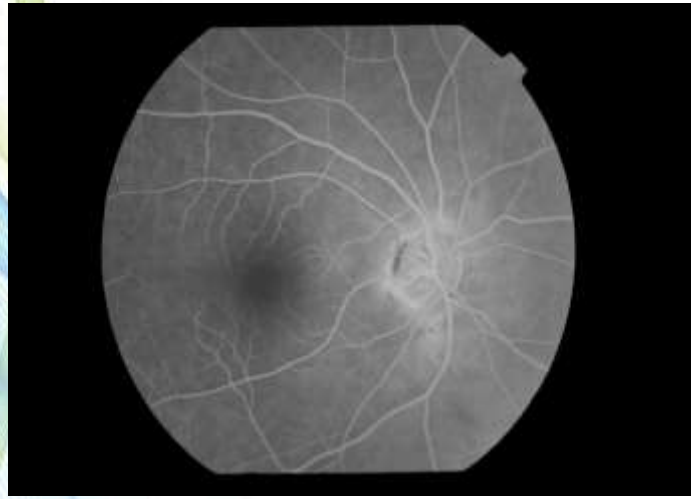
- Slight Distortion 4 weeks after operation
- OCT small changes and Leakage on Disc FFA.
- Vision 2 Months 0.12 same as fellow eye & No CMO
- Continues on Nevanac

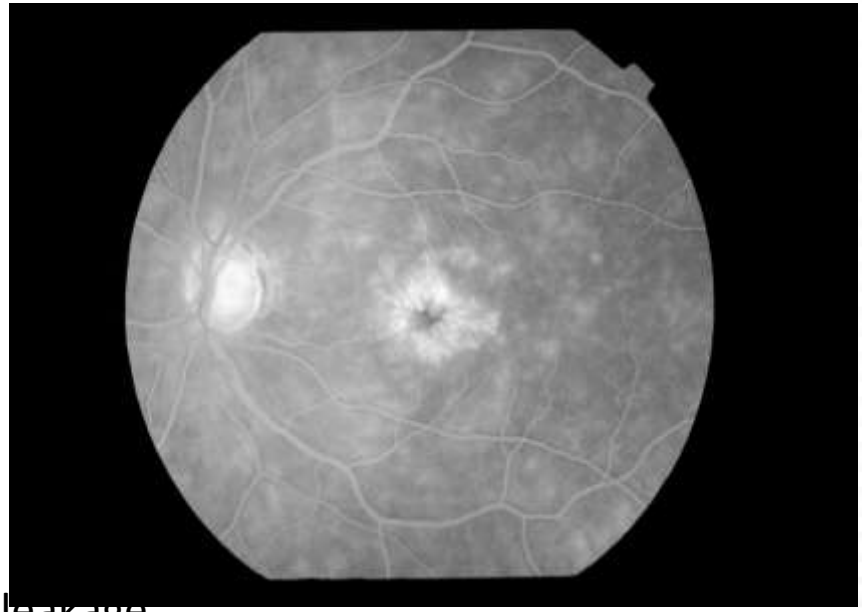


FFA









Petaloid Leakage with Optic Disc leakage

PRevention of Macular EDema After Cataract Surgery (PREMED)

- 1350 Participants
- Bromfenac
- Dexamethasone QID
- Bromfenc & Dexamethasone
- Bromfenac &peroperative subconjunctival injection of 40 mg triamcinolone acetonide
- Bromfenac & Peroperative intravitreal bevacizumab
- Bromfenac & Dexamethasone & Triamcinolone & Bevacizumab

- *Multi centre European Study*
- *sponsor* Maastricht University Medical Centre
- *Collaborator ESCRS*
- *Non diabetics over 21*
- *Change in Vision over time*
- *Change in OCT thickness*
- *Change in IOP*

- *The study is expected to complete in July 2015. [22]*

More information on Clinical Trials Web site https://clinicaltrials.gov/ct2/show/NCT01774474

Dropless Cataract surgery
AA0 2015 Hot topic
Unmet need

- **Compliance**
  - **Avoid non-compliance**
- **Quality of life**
- **Manual dexterity**
  - Physical limitations eg Strokes etc
- **Ocular surface toxicity**
- **Penetration into the eye**
  - Peaks and troughs
- **Elderly**
  - Alzheimer's – Forgetting drops
  - Simplifies Post op Regime

Dropless Cataract surgery
AA0 2015 Hot Topic
Benefits of Intraocualr Antibiotics and Steriods

- High Effective prophylaxis against infection
- Pre-Emptive control of inflammation
- Greater patient Convenience
- Better Compliance
- Less cost?

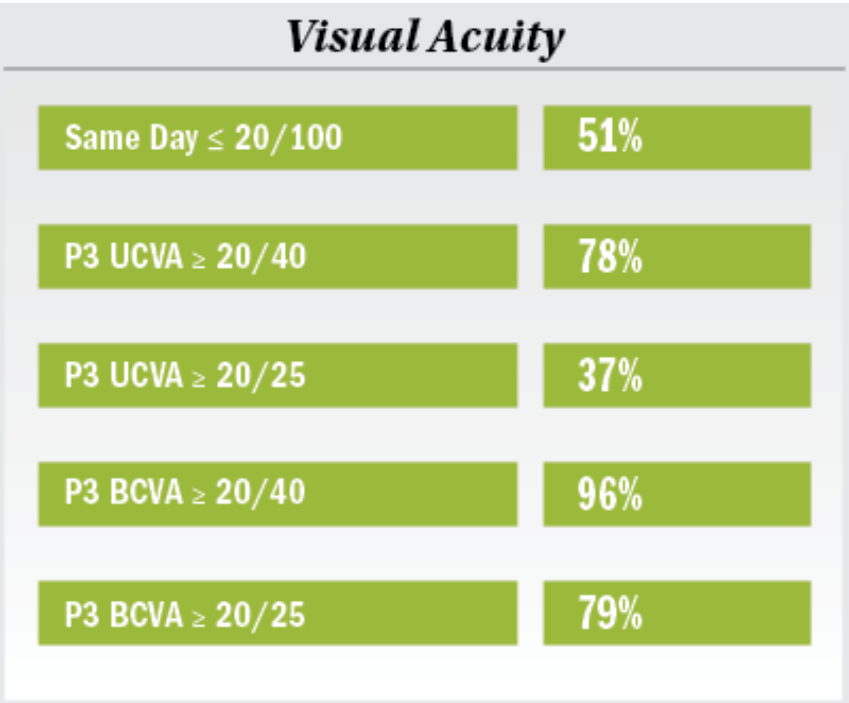
- Number of Options being trialed
  - Subtenons Kenalog – 10 – 40mg
    - IOP issues, but inexpensive
    - Available to all – rarely used
  - Triamcinolone & Moxifloxacin = TriMoxi or TriMoxVanc
    - Compounding pharmacy – USA
  - OTX-DP
    - Dexamethasone Punctal Pellet
  - IBI-10090 Dexmatheasone Suspesion
    - Anterior chamber bioabsorbable Dexmethasone

Transzonular medicine

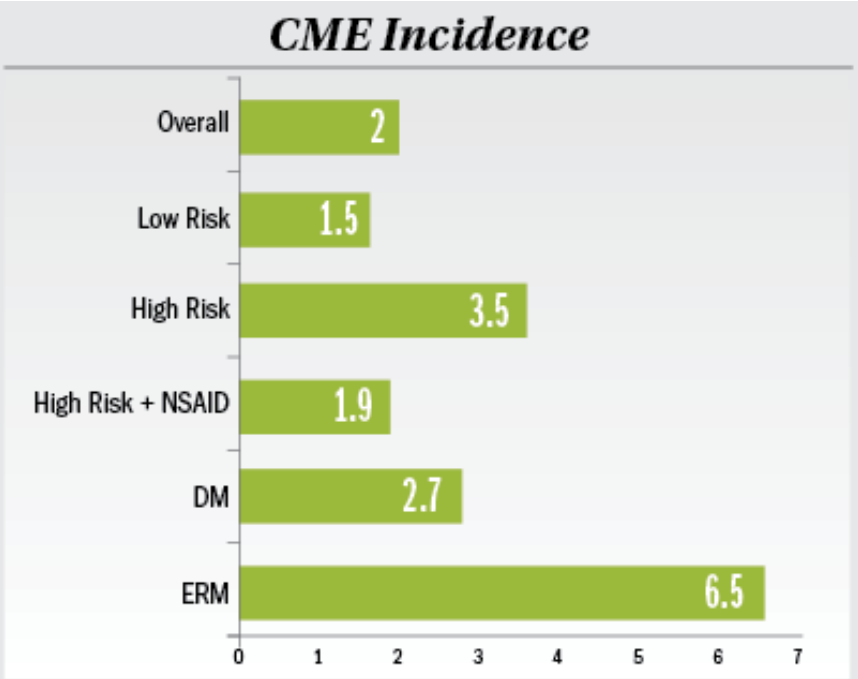
- This is the injection of drugs via the anterior approach through the zonules
- Idea is to avoid the need for post op drops entirely.
- Early trials encouraging
- TriMoxi (triamcinolone acetonide and moxifloxacin hydrochloride, Imprimis Pharmaceuticals) and TriMoxi+Vancomycin (Imprimis Pharmaceuticals) use patent-pending technologies that allow for the combination of drugs into a single, cost-effective intraocular injection.
- “A retrospective analysis including data from a consecutive series of 1575 eyes shows that intravitreal placement of triamcinolone/moxifloxacin during cataract surgery is a safe and effective method for preventing inflammation, endophthalmitis, and cystoid macular edema.”

Cheryl Guttman Krader; Reviewed by Stewart Galloway, MD **Intravitreal antibiotic + steroid makes dropless cataract surgery possible**

- Prepared by a compounding pharmacy, the preservative-free product contains 15 mg triamcinolone +1 mg moxifloxacin per mL. A dose of 0.2 mL is placed into the anterior vitreous after IOL implantation and prior to viscoelastic removal using a 27-gauge cannula passed through the zonules via the ciliary sulcus inferiorly.
- None needed more steroids but 22% needed a NSAID due to high risk of CMO.



By 3 weeks, best-corrected visual acuity was 20/40 or better in 96% of eyes and 20/25 or better in 79%.



Not all high-risk eyes were prescribed supplemental treatment with a topical nonsteroidal anti-inflammatory drug, but the incidence of cystoid macular edema was only 1.9% in those eyes that were. *(Figures courtesy of M. Stewart Galloway, MD)*

AA0 2015 Topical Steroids vs NSAID Transzonular medicine
Ahad Mahootchi

- Comparative case series 415 per group 1245 total number
- 90 Day follow up
-

	CMO
Group 1 – Standard care Steroids and NSAID	1.9%
Group 2 –Transzonular and Post op steroids	1.9%
Group 3 – Transzonular and NSAID	0% (0.5%)

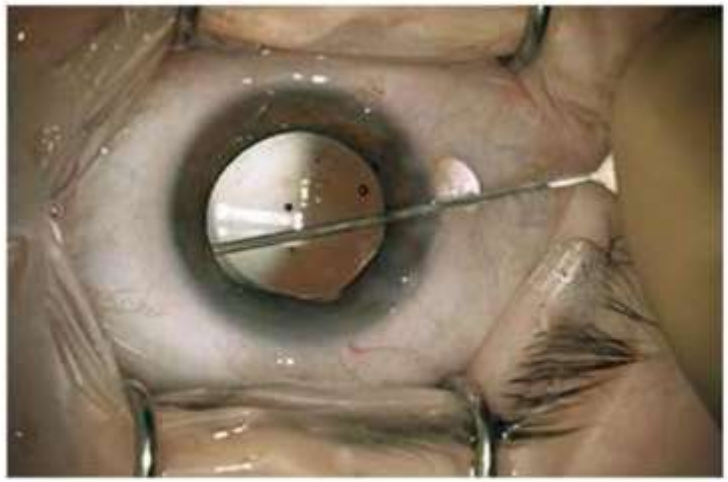


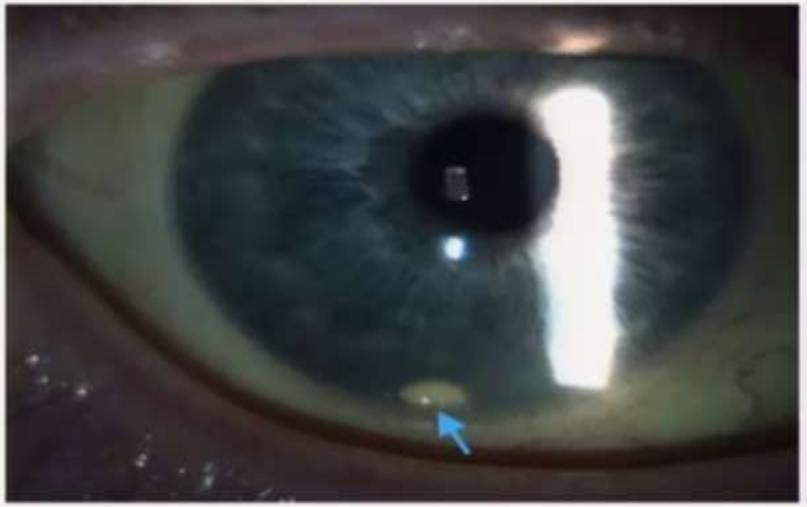
Figure 1: The surgeon performs the transzonular TriMoxi+Vancomycin injection using a 27-gauge hydrodissection cannula.
COURTESY: JAMES S. LEWIS, MD

A Phase 3 Trial of a Novel Intracameral Dexamethasone Drug Delivery Suspension for Treating Inflammation Following Cataract Surgery

Eric Donnenfeld, MD
Clinical Professor of Ophthalmology, New York University
Trustee Dartmouth Medical School
Edward Holland, MD
Wendy Murahashi, MD
for the C13-04 Study Investigators

IBI-10090 Dexamethasone Suspension for Intraocular Administration

- A novel, bioabsorbable drug delivery product for anterior chamber intracameral placement of dexamethasone
- Therapeutic levels are maintained for up to 21 days with a single administration[a]
- Evaluated in a Phase 3 trial for treatment of inflammation associated with cataract surgery

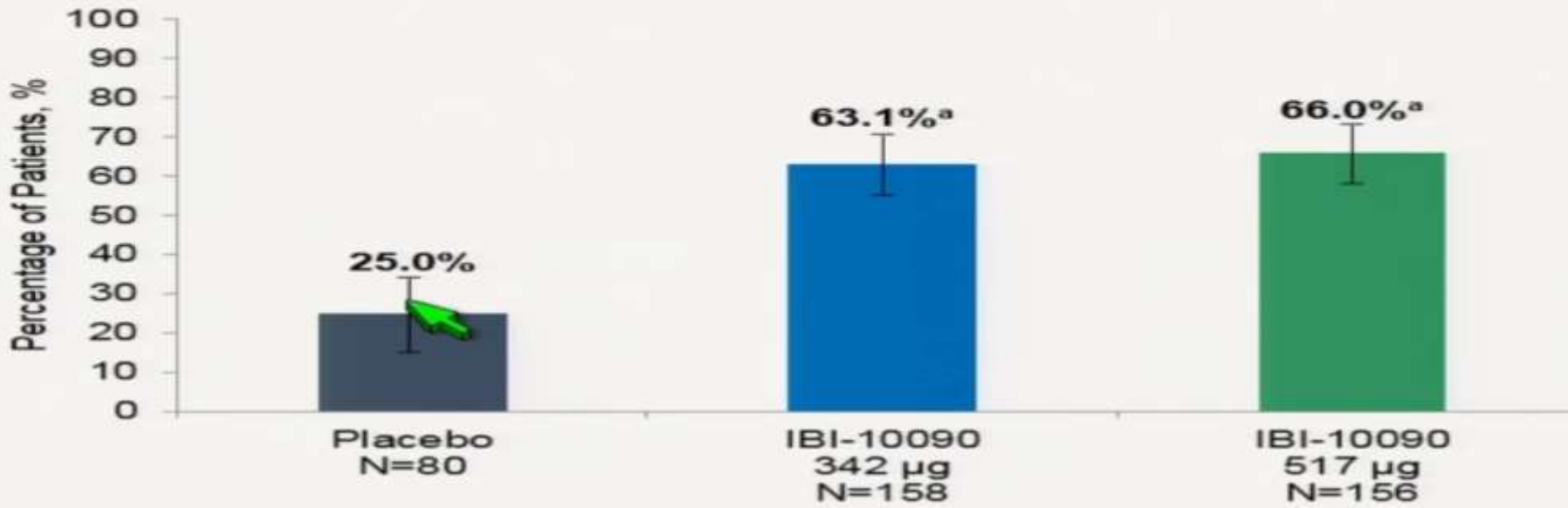


Patients Requiring Rescue Medication

Postoperative Day	Placebo N=80	IBI-10090 342 µg N=158	IBI-10090 517 µg N=156
1	6 (7.5%)	0	0
3	14 (17.5%)	0	4 (2.3%)
8	13 (16.3%)	3 (1.9%)	3 (1.9%)

Primary Endpoint

Percentage of Patients With ACC Grade=0 at Day 8



Phase 3 Clinical Trials Evaluating Sustained Release Dexamethasone (DEXTENZA™) for Treatment of Post-operative Inflammation and Pain

Thomas Walters, MD

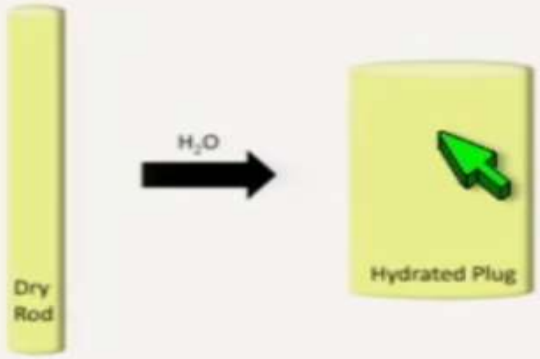
Texan Eye, Austin, TX

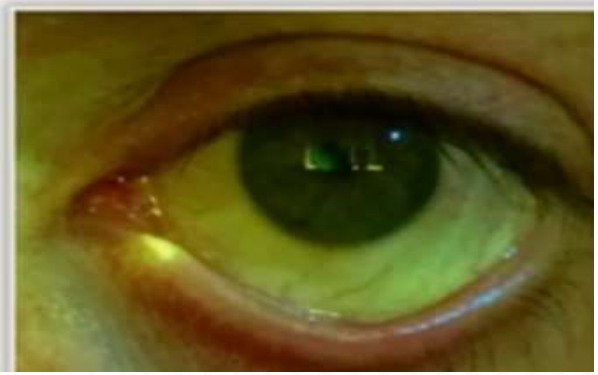
Phase 3 Studies Conducted under IND

Sponsored by Ocular Therapeutix, Inc.

OTX-DP Product Design

- Polyethylene glycol-based hydrogel drug product
- Provides a sustained and tapered release of dexamethasone to the ocular surface **for up to 30 days**
- One-time administration at the conclusion of surgery
- Fluoresces under blue light and yellow filter for placement and retention confirmation
- Resorbs and exits the nasolacrimal system; remov not required





Conclusions

- Strong safety profile shown for OTX-DP in both studies – No safety concerns
- OTX-DP was statistically superior over placebo for the absence of pain at Day 8 for both studies
- OTX-DP was statistically superior over placebo for the absence of Anterior Chamber cells:
  - In the first Phase 3 study
  - Not in the second Phase 3 study
- NDA for pain indication submitted to FDA
- Conducting third Phase 3 study to expand labeling to include inflammation

Dilating the pupil for surgery

- **Old Practice - Eye drops four times an hour, then every half hour by nurses**
- **Current Practice - Mydriasert Pellet**
- **- Slow and sustained**
- **-Maximal Dilatation**
- **Future practice - Intracameral on the table**
- **Tropicamide, Phenylephrine, & Lidocaine**
- **- Less dilation, but continues**
- **- Fast 20 Seconds**
- **Improved patient flow, Less waiting for patient Less discomfort**

- Mydriatic insert and intracameral injections compared with mydriatic eyedrops in cataract surgery: Controlled studies
- Journal of Cataract and Refractive Surgery.
- Behndig, Anders, MD, PhD; Korobelnik, Jean-François, MD. Published July 1, 2015. Volume 41, Issue 7. Pages 1503-1519.

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  - OTX-DP Dexamethasone Punctal Pellet
  - IBI-10090 Dexmatheasone Suspension Intracameral

The Future Pathway

- Walk in, Theatre, walk out – 1 hour
- On table Intracameral Dilatation
- On table Intercameral Antibiotic – Cefuroxime – Others?
- On Table Long acting Steroid
- NSAID Once a day Gel

GO DROP LESS™

Make Irvine-Gass a Complication of the past

Use a NSAID

More information

EyeNews

“A Paradigm shift in the way we approach Cataract Surgery”

www.nicholaslee.co.uk

NEVANAC Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 1 ml of Nevanac suspension contains 1 mg nepafenac, benzalkonium chloride 0.05 mg. Indication(s): Prevention and treatment of postoperative pain and inflammation associated with cataract surgery. Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients. Posology and method of administration: Adults, including the elderly: For the prevention and treatment of pain and inflammation, 1 drop in the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 21 days of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to120 minutes prior to surgery. For the reduction in the risk of macular oedema associated with cataract surgery in diabetic patients, 1 drop in the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 60 days of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery. Children and adolescents: Not recommended. Hepatic and renal impairment: No dose adjustment warranted. Contra-indications: Hypersensitivity to nepafenac, any of the excipients, or to other nonsteroidal anti-inflammatory drugs (NSAIDs); and in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs. Warnings and precautions: Do not inject, or swallow. Instruct patients to avoid sunlight during treatment. Use of topical NSAIDs may result in keratitis, in some susceptible patients, continued use may be sight threatening. Topical NSAIDs may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Topical NSAIDs should be used with caution in patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases, rheumatoid arthritis or repeat ocular surgeries within a short period of time. These patients may be at increased risk for corneal adverse reactions which may become sight threatening. Prolonged use of topical NSAIDs may increase patient risk for occurrence and severity of corneal adverse reactions. Ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. Use NEVANAC with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time. Concomitant use of prostaglandin analogues and NEVANAC is not recommended. Benzalkonium chloride may cause keratopathy and irritation and is known to discolour soft contact lenses. Contact lens wear is not recommended during the postoperative period following cataract surgery. Patients should be advised not to wear contact lenses during treatment with NEVANAC. Close monitoring is required with frequent or prolonged use. An acute ocular infection may be masked by the topical use of anti-inflammatory medicines. NSAIDs do not have any antimicrobial properties. In case of ocular infection, their use with anti-infectives should be undertaken with care. Cross-sensitivity: Potential exists for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Interactions: In vitro studies have demonstrated a very low potential for interaction with other medicinal products and protein binding interactions. Pregnancy and lactation: Pregnancy: not recommended during pregnancy and in women of childbearing potential not using contraception. Lactation: Can be used during lactation. Effects on ability to drive and use machines: If blurred vision occurs wait until the vision clears before driving or using machinery. Undesirable effects: Common: Punctate keratitis. Frequency not known: Dizziness, impaired corneal healing, corneal scar, reduced visual acuity, eye irritation, eye swelling, blood pressure increased. Serious: Keratitis, choroidal effusion, corneal epithelium defect, corneal opacity. Prescribers should consult the SmPC in relation to other side effects. Overdose: No experience of overdose with ocular use. Application of >1 drop/eye is unlikely to lead to unwanted sideeffects. Practically no risk of adverse effects due to accidental oral ingestion. Incompatibilities: Not applicable. Special Precautions for Storage: Do not store above 30˚C. Legal Category: POM. Package Quantities and Basic NHS Costs: 5ml £14.92. MA Number(s): EU/1/07/433/001. Further information available from the MA Holder: Alcon Laboratories (UK) Ltd, Frimley Business Park, Frimley Camberley, Surrey, GU16 7SR United Kingdom. Date of preparation: 20 May 2013 (V9). Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Alcon Medical Information. Tel: 0871 376 1402. Email: GB.ADR@alcon.com