



LONDON EYE
C O U R S E

Clinical Trials

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- This document contains a summary of landmark clinical trials which are likely to come up in Ophthalmology exit exams.
- The authors and londoneyecourse.com have simply summarised important clinical trials, and made no original contributions.
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Anti-VEGF for AMD, RVO, DMO

Simple way to remember average gain in VA in landmark anti-VEGF clinical trials (in case of brain-freeze..):

- ***~30% in AMD¹***
- ***~40% in DMO²***
- ***50-60% in BRVO/CRVO^{3,4,5,6}***

1) Heier JS et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012 Dec;119(12):2537-48.

2) Brown DM et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE.

Ophthalmology. 2013 Oct;120(10):2013-22. 3) Brown DM et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology. 2011 Aug;118(8):1594-602. 4) Clark WL et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-Week Results of the VIBRANT

Study. Ophthalmology. 2016 Feb;123(2):330-6. 5) Campochiaro PA et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month

outcomes of a phase III study. Ophthalmology. 2011 Oct;118(10):2041-9. 6) Korobelnik JF et al; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central

Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202-8.

AMD

AREDS 1

- Multicentre double masked RCT: 3640 participants, 6.3 years f/u, 2.4% lost to f/u
- Groups: Antioxidants VS Zinc VS Antioxidants & Zinc VS Placebo
- Results: **Antioxidants + zinc** most protective formula.
- Significantly reduced the risk of progression to advanced AMD by 25%.
 - Extensive intermediate drusen
 - At least 1 large drusen
 - Non-central geographic atrophy in 1 or both eyes
 - Advanced AMD or vision loss due to AMD in 1 eye
- Easy way to remember AREDS 1 formula: **ACE + ZINC**
 - Beta-carotene (precursor to vitamin **A**)
 - Vit **C**
 - Vit **E**
 - **Zinc**

AREDS 2

- β -carotene is contraindicated in smokers due to increased risk of lung cancer
- AREDS 2 (1,940 eyes, 5 years median follow up) included:
 - adding lutein and zeaxanthin (L+X), omega 3 fatty acids or both to AREDS 1 formula
 - replacing β -carotene with L+X
 - Reducing zinc dose
- Relevant findings:
 - Adding L+X or omega 3 fatty acids did not further reduce risk of progression to advanced AMD
 - no apparent effect of beta carotene elimination or lower-dose zinc on progression to advanced AMD
 - More lung cancers were noted in the beta carotene vs no beta carotene group (23 [2.0%] vs 11 [0.9%], nominal P = .04), mostly in former smokers.

MONTHLY Ranibizumab for Wet AMD

- MARINA
- Minimally classic and occult
- Sham injection control

- ANCHOR
- Predominantly Classic
- PDT control

- Ranibizumab superior to control groups
- ~90% of ranibizumab-treated patients lost <15 letters
- ~35% gained ≥ 15 letters

Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006 Oct 5;355(14):1419-31.

Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T; ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology. 2009 Jan;116(1):57-65.e5.

QUARTERLY Ranibizumab for Wet AMD

- PIER
- Monthly for 3 months then quarterly
- 12 months: Lost -0.2 to -1.6 letters → switched from quarterly to monthly → Gain in VA

- EXCITE
- Monthly vs Quarterly Lucentis
- Monthly better (12 months letter gain 8.3 vs 4.9)

Abraham P, Yue H, Wilson L. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. *Am J Ophthalmol.* 2010 Sep;150(3):315-324.e1.

Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnik JF, Schlingemann RO, Axer-Siegel R, Wiedemann P, Simader C, Gekkieva M, Weichselberger A; EXCITE Study Group. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology.* 2011 May;118(5):831-9.

PRN Ranibizumab for Wet AMD

- PRONTO
- Small single centre 2 year study (n=37)
- PRN (OCT guided) Lucentis treatment
- VA results similar to ANCHOR & MARINA
- Fewer intravitreal injections required

Lucentis vs Avastin

- **IVAN**¹ (UK) + **CATT**² (US) trials
- Non-inferiority multicentre RCTs
- Avastin and Lucentis (continuous or PRN)

- 2 years: Avastin NOT inferior to Lucentis when given fixed or PRN
- PRN treatment not as efficacious as continuous treatment
- Similar safety profile, no major red flags

1) Chakravarthy U, Harding SP, Rogers CA, Downes S, Lotery AJ, Dakin HA, Culliford L, Scott LJ, Nash RL, Taylor J, Muldrew A, Sahni J, Wordsworth S, Raftery J, Peto T, Reeves BC. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). *Health Technol Assess.* 2015 Oct;19(78):1-298. 2) Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology.* 2012 Jul;119(7):1388-98.

RBZ vs AFB for Wet AMD

VIEW 1 & 2 Trials

- Similar double-masked multicentre RCTs of 2,419 patients
- Monthly aflibercept (AFB) vs 2-monthly AFB (after 3 monthly doses) vs monthly ranibizumab (RBZ)

Results:

- All groups: >94% lost <15 letters, ~30% gained >15 letters
- ALL AFB groups produced similar efficacy (VA + anatomic measures) and safety (ocular + systemic) outcomes as monthly RBZ

PDT for Subfoveal Wet AMD

- Predominantly classic CNV
 - TAP study: multicentre double-masked RCT
 - Verteporfin PDT (n=351) vs Placebo (n=178)
 - 59% vs 31% lost <15 letters (p<0.001) at 2 years
- Minimally classic or Occult CNV
 - No evidence of benefit of PDT in TAP or VIO studies

Bressler NM; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. Arch Ophthalmol. 2001 Feb;119(2):198-207.

Kaiser PK; Visudyne In Occult CNV (VIO) study group. Verteporfin PDT for subfoveal occult CNV in AMD: two-year results of a randomized trial. Curr Med Res Opin. 2009 Aug;25(8):1853-60.

IPCV

EVEREST Trial (IPCV)

- Multicentre double-masked ICG guided RCT
- Verteporfin PDT Vs Lucentis Vs Combination (PDT + Lucentis)
- 61 Asian patients with symptomatic macular polypoidal choroidal vasculopathy (PCV)

RESULTS at 6 months:

Treatment	Complete polyp regression	Mean BCVA change (letters)
PDT	71.4%	10.9
PDT + RBZ	77.8%	7.5
RBZ	28.6%	9.2

- PDT (\pm RBZ) superior to RBZ monotherapy ($p < 0.01$) in achieving complete regression of polyps at 6 months
- No significant safety issues
- Limitations: Small sample size (~17 patients per arm!), study not powered for statistically significant BCVA differences, 6 months only, single ethnicity

LAPTOP study

- 12 months multicentre RCT (not blinded) for IPCV
- PDT monotherapy (single session) vs RBZ monotherapy (3 monthly)
- PRN treatment as needed in each group

- PDT arm (n = 47)
 - 17.0% had VA gain
 - 27.7% had VA loss.

- RBZ arm (n=46)
 - 30.4% had VA gain
 - 8.7% had VA loss

- VA results significantly better in RBZ arm, even at 24 months (P= .025).

Oishi A, Kojima H, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Fujihara M, Bessho N, Uenishi M, Kurimoto Y, Negi A. Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOP study results. *Am J Ophthalmol.* 2013 Oct;156(4):644-51.

Oishi A, Miyamoto N, Mandai M, Honda S, Matsuoka T, Oh H, Kita M, Nagai T, Bessho N, Uenishi M, Kurimoto Y, Negi A. LAPTOP study: a 24-month trial of verteporfin versus ranibizumab for polypoidal choroidal vasculopathy. *Ophthalmology.* 2014 May;121(5):1151-2.

CRVO/BRVO

CVOS

- The Central Retinal Vein Occlusion study (CVOS) defined ischaemic CRVO as fluorescein angiographic evidence of more than 10 disc areas of capillary non-perfusion on 7-field FFA.
- 44% of eyes with vision of $<6/60$ at presentation develop rubeosis
- No benefit from grid treatment for macular oedema
- Prophylactic PRP did not totally prevent NVA/NVI. Prompt NV regression more likely if eye did not undergo prophylactic laser.

BVOS

- Prognosis: BRVO > CRVO
- After one year: 50 – 60% of untreated BRVO retain VA \geq 6/12
- 63% of eyes with >5 DD of non-perfusion developed neovascularization (NV)
- Scatter photocoagulation before the NV development was NOT shown to be beneficial.
- Peripheral scatter argon laser photocoagulation reduced likelihood of VH compared to no treatment.
- At 3 years:
 - 65% vs 37% of laser treated v non-treated eyes, respectively, improved \geq 2 lines of vision (after 36 months).
 - 40% of treated eyes had < 6/12 VA at three years
 - 12% of treated eyes had 6/60 or worse VA
 - Average VA improvement in laser arm +1.3 lines, observation arm +0.23 lines

RVO LANDMARK TRIALS

- When the **CRUISE** arrived, the crowd cheered **BRAVO!**

COPERNICUS & GALILEO finally arrived to **VIRBRANT GENEVA..**

(yes I know they did not travel to Geneva, and were they cheered by everyone in their time, and that Geneva is not the most 'vibrant' city in Europe, but cannot think of another way of remembering the trial names!

For scientific accuracy, picture fictional characters rather than the real scientists if you want to use this mnemonic..)

RVO Trials

- Randomised double-blinded multicentre RCTs
- CRUISE: RZB for CRVO MO
- BRAVO: RZB for BRVO MO
- COPERNICUS + GALILEO: AFB for CRVO MO
- VIBRANT: AFB for BRVO MO
- **~50-60% gained >15 letters** ⁽¹⁻⁵⁾

1) Brown DM et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology*. 2011 Aug;118(8):1594-602.

2) Clark WL et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-Week Results of the VIBRANT Study. *Ophthalmology*. 2016 Feb; 123(2):330-6.

3) Campochiaro PA et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology*. 2011 Oct;118(10):2041-9.

4) Campochiaro PA et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology*. 2011 Oct;118(10):2041-9.

5) Korobelnik JF et al; GALILEO Study Group. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. *Ophthalmology*. 2014 Jan;121(1):202-8.

GENEVA

- Dexamethasone (Ozurdex) vs Sham implant for CRVO
- DEX implant 0.7mg (n = 421), DEX implant 0.35mg (n = 412), or sham (n = 423)
- Eyes that received x2 DEX implant 0.7mg:
 - 32% of eyes had \geq 15-letter BCVA improvement 60 days post 2nd implant, vs 5.3% in sham group:
 - 15% had raised IOP & 10% required IOP lowering therapy
 - Cataract progression: 30% Dex implant, 6% Sham

Diabetic Retinopathy

Diabetic Retinopathy Study (DRS) 1981

- Multicentre randomised RCT
- Patients: PDR in at least one eye OR severe NPDR in both eyes
- 1° outcome: Scatter PRP reduced severe visual loss by $\geq 50\%$ compared to no Rx (>5 years f/u)
- 2° outcomes: Reduced risks of retinopathy progression & elevated IOP
- PRP risks:
 - Mild VA loss soon after PRP, mainly due to DMO (Before advent of anti-VEGF)
 - Constriction of peripheral VFs

DRS (1981)

Two-year risk of severe VA loss without PRP > risk of harmful PRP effects in two groups of eyes:

- (1) eyes with new vessels and preretinal or vitreous hemorrhage
- (2) eyes with new vessels on or within one disc diameter of the optic disc (NVD) equaling or exceeding 1/4 to 1/3 disc area in extent

ETDRS Study (1989)

- Multicentre RCT (3,711 patients)
- **Aspirin 75mg**
 - did not affect retinopathy progression
- **Focal macular laser**
 - Reduced risk of moderate visual loss in ~50% of patients with CSMO
 - Focal treatment should be considered for eyes with CSMO (*see next slide*)
- **Scatter PRP**
 - Not recommended for mild-moderate NPDR
 - Should be considered for severe NPDR or early PDR
 - Should not be delayed if the eye has reached the high-risk proliferative stage.

CSMO

ETDRS study defined Clinical Significant Macular Oedema (CSMO), i.e. who would benefit from macular laser:

- Retinal thickening within 500 μm of the center of the fovea
- Hard, yellow exudates within 500 μm of the center of the fovea with adjacent retinal thickening
- At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea

Diabetic Retinopathy Vitrectomy Study (DRVS) 1985

- 616 eyes
- Severe VH resulting in $\leq 5/200$ vision for ≥ 1 month
- Groups:
 - 1) Early Vitrectomy Group - within 6 months
 - 2) Delayed Vitrectomy Group - after 12 months

- RESULTS

After 2 years of follow-up, % of eyes recovering VA of 10/20 or better:

- Significantly higher in the early vitrectomy group than in the deferral group (25% vs 15%)
- Significantly higher in early vitrectomy group in T1DM compared to delayed vitrectomy (36% vs 12%)
- Not significantly different for early vs deferred vitrectomy in T2DM (16% vs 18%)

United Kingdom prospective diabetes study (UKPDS)

- >5000 patients with T2DM
- Tight BP control:
 - 34% reduction in retinopathy progression & 47% reduction in VA loss of 3 lines compared with the 'less tight BP' control.
 - Reduced both diabetes-related morbidity and mortality
- Intensive Glycaemic control:
 - Diabetic retinopathy progression was reduced by 21% and the need for laser photocoagulation by 29% compared to the conventional treatment group.
 - Reduced microvascular complications but not mortality

Diabetes Control and Complications Trial (DCCT) 1993

- In Type 1 DM, when compared to conventional therapy, intensive glycaemic control resulted in:
 - 76% reduction in risk of developing retinopathy
 - Slowed retinopathy progression by 54%
 - 60% decrease in occurrence of clinical neuropathy
 - 54% reduction in occurrence of albuminuria (nephropathy)
- 2-3x increase in severe hypoglycaemia

RBZ DMO Trials

RISE

RIDE

RESOLVE

READ-2

RESTORE

REVEAL

RBZ in DMO

RISE + RIDE + RESOLVE

- RBZ 0.5mg vs RBZ 0.3mg vs Sham
- Mixed results re whether 0.3mg or 0.5mg RBZ more effective
- BCVA significantly improved in RBZ compared to sham.

READ-2 + REVEAL + RESTORE

- RBZ alone vs Laser alone vs RBZ+Laser
- BCVA significantly improved in RBZ compared to laser.
No added benefit to RBZ+laser

RISE & RIDE → VIVID & VISTA

RISE & RIDE

- These are the landmark clinical trials of RBZ in diabetic maculopathy that led to US FDA approving RBZ.

VIVID & VISTA

- Are the 'equivalent' Aflibercept (AFL) trials of RISE & RIDE which led to FDA approval of AFL

Aflibercept for DMO

- **VIVID & VISTA**
- Phase 3 double masked RCTs
- Laser alone vs 2mg AFL every 4 weeks vs 2mg AFL every 8 weeks after 5 initial monthly injections
- Results after 2 years:
- Mean change in BCVA (approx +11.4 letter vs +0.8 letter) and CST values significantly better in AFL vs laser
- Similar efficacy in monthly vs 2-monthly AFL
- Improvement in ETDRS diabetic retinopathy severity scale in AFL groups vs laser (as was the case in RISE & RIDE studies)

Intravitreal steroids for DMO

- Fluocinolone (Iluvien) insert
 - FAME A + FAME B study (n=953) Double masked Phase 3 RCTs
 - At 2 years, Fluocinolone showed a statistically significant improvement in mean BCVA compared to sham.
- Dexamethasone implant (Ozurdex)
 - MEAD Trial (n = 1048) Double masked Phase 3 RCT
 - At the end of 3 years: % patients who achieved BCVA gain of ≥ 15 letters from baseline and mean reduction in CRT higher in Dex implant group compared to sham.
- FAME & MEAD trials: Significantly higher rate of cataract and glaucoma in steroid groups compared to sham groups.

Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119:2125–32.

Boyer DS, Yoon YH, Belfort R, Jr, Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1904–14

DRCR.net

If you have time, it is worth having a glance at the findings of the diabetic retinopathy clinical research network study findings:

[http://drcrnet.jaeb.org/ViewPage.aspx?
PageName=Presentations](http://drcrnet.jaeb.org/ViewPage.aspx?PageName=Presentations)

GLAUCOMA

Collaborative NTG study

- One eligible eye of 145 subjects with NTG randomized to no treatment or 30% IOP reduction from baseline.
- VF loss progression 12% in treated group vs 35% in controls at 5 years
- Without treatment, 50% of NTG patients show no progression of VF loss at 5 years
- RF for progression:
 - Female gender
 - Migraine headaches
 - Optic disc haemorrhage at diagnosis

OHTT

- 1636 participants with no evidence of glaucomatous damage, aged 40 to 80 years, and with an IOP between 24 mm Hg and 32 mm Hg in one eye and between 21 mm Hg and 32 mm Hg in the other eye
- Randomized to either observation or treatment with topical ocular hypotensives.
- The goal in the medication group was to reduce the IOP by 20% or more and to reach an IOP of 24 mm Hg or less.

OHTT findings

- Mean IOP reduction in medication group was 22.5%.
- At 5 years, the cumulative probability of developing POAG was:
 - 4.4% in the medication group
 - 9.5% in the observation group
- Little evidence of increased systemic or ocular risk associated with ocular hypotensive medication.

OHTS

Risk factors for conversion of OHT to glaucoma:

- Older age
- Larger C:D ratio
- Higher IOP
- Greater PSD
- Thinner CCT

Tube VS Trab Study

- Multicentre RCT: Baerveldt tube shunt (n=107) vs trabeculectomy with MMC (n=105).
- **NOTE: All patients enrolled had undergone previous intraocular surgery (cataract surgery and/or previous failed trabeculectomy)**
- At 5 years, mean IOP was 14.4 mmHg in the tube group and 12.6 mmHg in the trabeculectomy group (P = .12).
- Mean number of glaucoma medications was 1.4 in the tube group and 1.2 in the trabeculectomy group (P = .23).
- The cumulative probability of failure during 5 years of follow-up was 29.8% in the tube group and 46.9% in the trabeculectomy group (P = .002; hazard ratio = 2.15).
- The rate of reoperation for glaucoma was 9% in the tube group and 29% in the trabeculectomy group (P = .025).

Primary Tube Versus Trabeculectomy Study

- Purpose:

To compare the long-term safety and efficacy of nonvalved tube shunt surgery to trabeculectomy with mitomycin C in eyes that have NOT had previous ocular surgery.

- Results:

NO RESULTS PUBLISHED YET (OCT 2016)

Keep on your radar, but unlikely to feature in exam if study results not published at least a month before the exam date.

Early Manifest Glaucoma Trial

- RCT of 255 patients with early glaucoma. Median IOP 20mmHg.
- Groups: laser trabeculoplasty plus topical betaxolol hydrochloride (n = 129) or no initial treatment (n = 126).
- Median follow up of 6 years.
- Glaucoma progression (VF + Optic disc progression) was less frequent in the treatment group (58/129; 45%) than in controls (78/126; 62%) (P = .007)
- The median time to progression was 18 months longer in the treatment group than the control group.
- Increases in clinical nuclear lens opacity gradings were significantly associated with treatment (P = .002).

The Advanced Glaucoma Intervention Study (AGIS)

- 581 patients (776 eyes) with advanced POAG who could not be managed by maximum tolerated medical therapy alone.
- Randomised between two groups:
 - Argon laser trabeculoplasty, followed by trabeculectomy if needed and then by a 2nd trabeculectomy (ATT)
 - Trabeculectomy , followed by argon laser trabeculoplasty if needed and then trabeculectomy (TAT)
- **Results: Eyes with IOP under 18mmHg at all visits over 6 years did not show an increase of their initial visual field defect.¹**
- For a 7-year follow up, eyes assigned to initial trabeculectomy showed a greater mean decrease IOP and smaller cumulative probability of failure of the first intervention than eyes assigned to initial argon trabeculoplasty.
- In black patients the average % of eyes with VF loss was less in the ATT sequence than in the TAT sequence, a difference that is NOT statistically significant at any visit.
- In white patients, the average % of eyes with VF loss was less in the TAT sequence at 18 months, a difference that increases and is statistically significant in years 8 to 10. ²
- Younger age and higher preoperative IOP were associated with increased failure rates for ALT and Trabeculectomy.³
- Trabeculectomy failure was also associated with diabetes, and one or more postop complications.³
- Trabeculectomy increased the rate of cataract formation to 78%.⁴

¹ The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol. 2000 Oct;130(4):429-40. ² Ederer F, Gaasterland DA, Dally LG, Kim J, VanVeldhuisen PC, Blackwell B, Prum B, Shafranov G, Allen RC, Beck A; AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. Ophthalmology. 2004 Apr;111(4):651-64. ³ AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. Am J Ophthalmol. 2002 Oct;134(4):481-98. ⁴ AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study: 8. Risk of cataract formation after trabeculectomy. Arch Ophthalmol. 2001 Dec;119(12):1771-9.

The Collaborative Initial Glaucoma Treatment Study (CIGTS)

- RCT of 607 patients with newly diagnosed POAG initially treated with either medication or trabeculectomy
- 6 Monthly follow up for minimum of 4 years. VF loss was the primary outcome variable in CIGTS.
- VF loss did not differ significantly by initial treatment after up to 5 years of follow up.
- When aggressive treatment aimed at substantial reduction in IOP from baseline is used, loss of VF can be seen to be minimal in general.
- IOP in medicine group averaged 17 to 18 mmHg, in surgery group averaged 14 to 15 mmHg.
- The rate of cataract requiring removal was 3x greater in the surgically treated group.
- Over the entire period of follow-up, surgical patients had a greater risk of substantial VA loss compared with medical patients, even with adjustment for cataract-induced loss.

Glaucoma laser trial (GLT) & Glaucoma laser trial follow up study

- Multicentre RCT, 203 patients, median follow up from diagnosis of POAG was 7 years
- As compared to eyes treated initially with medications, laser trabeculoplasty showed:
 - 1.2 mm Hg greater reduction in intraocular pressure ($P < .001$)
 - 0.6 dB greater improvement in the visual field ($P < .001$)
 - increase in ratio of optic cup area to optic disc area of -0.01 ($P = .005$)
- I.E. STATISTICALLY SIGNIFICANT BUT CLINICALLY SIMILAR
- BEFORE ADVENT OF PROSTGLANDIN ANALOGUES, CARBONIC ANYHYDRASE INHIBITORS & ALPHA AGONISTS.

The Low-Pressure Glaucoma Treatment Study

- Double masked multicentre RCT. NTG patients (IOP ≤ 21).
- Comparing brimonidine 0.2% (n=99) to timolol 0.5% (n=79).
- Mean follow up 30 months.

RESULTS:¹

- Mean IOP: Similar at all time points.
- Visual fields progression in
 - 9.1% Brimonidine patients (Drop out 28.3%)!
 - 39.2% Timolol patients (Drop out 11.4%)
 - Drop-out due to Drug-related side effects

RISK FACTORS:²

Older age, systemic anti-hypertensives, lower ocular perfusion pressure

- ?Neuroprotective effect of alpha2 agonists
- ?High dropout rate skewed results
- ?detrimental effect of timolol – paradoxical to other research findings

¹ De Moraes CG, Liebmann JM, Greenfield DS, Gardiner SK, Ritch R, Krupin T; Low-pressure Glaucoma Treatment Study Group. Risk factors for visual field progression in the low-pressure glaucoma treatment study. *Am J Ophthalmol.* 2012 Oct;154(4):702-11.

² Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S; Low-Pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. *Am J Ophthalmol.* 2011 Apr;151(4):671-81. Erratum in: *Am J Ophthalmol.* 2011 Jun;151(6):1108.

Optic Neuritis

ONTT

- Subjects: 389 subjects with acute optic neuritis
- The cumulative probability of developing MS by 15 years was 50%
- 25% of patients with no baseline brain MRI lesions developed MS
- 72% of patients with one or more lesions developed MS.
- In absence of MRI lesions, the following are associated with low risk of developing MS:
 - male gender
 - optic disc swelling
 - atypical clinical features of optic neuritis

ONTT

- Most patients experienced rapid visual recovery within 2 weeks after onset of symptoms
- Complete recovery often occurred by 4 to 6 weeks
- High-dose intravenous methylprednisolone followed by oral prednisone accelerated visual recovery but did not improve the 6-month or 1-year visual outcome compared with placebo
- Within the first 5 years of follow-up, the probability of a recurrence in either eye was almost 2-fold higher in the prednisone group than in either the placebo group ($P = .004$) or the intravenous group ($P = .003$).
- By 5 years, IV methylprednisolone treatment had no significant effect on the development of MS compared to no treatment.

Endophthalmitis

EVS

- 420 patients with endophthalmitis within 6 weeks of cataract surgery or secondary IOL implantation
- Randomised to immediate 3-port PPV or Vitreous tap & inject
- 9 months evaluation of VA + media clarity

Results:

- If initial VA was HM or better: No difference in visual outcome whether or not an immediate PPV was performed
- If initial VA was PL or worse: PPV produced a 3x increase in the frequency of achieving 20/40 or better acuity (33% vs 11%)
- Systemic antibiotics made no difference to final VA or media clarity

Herpes Simplex Keratitis

HED STUDY: Epithelial keratitis

For patients with HSV epithelial keratitis treated with topical trifluridine:

No apparent benefit of a 3-week course of oral acyclovir in preventing HSV stromal keratitis or iritis was seen during 12 months follow up.

HEDS: Stromal keratitis

- No statistically or clinically significant beneficial effect of oral acyclovir in treating HSV stromal keratitis in patients receiving concomitant topical corticosteroids & trifluridine
- Compared with placebo, corticosteroid therapy reduced the risk of persistent or progressive stromal keratouveitis by 68%.
- At 6 months after randomization, no clinically or statistically significant differences in visual outcome or recurrent herpetic eye disease were identified between the steroid and placebo groups.

HEDS: Prevention

- HEDS investigated efficacy of oral acyclovir (400mg BD) VS placebo in preventing ocular HSV recurrences (total 703 patients)
- Long-term oral acyclovir therapy reduces the rate of recurrent HSV epithelial keratitis and stromal keratitis.
- Probability of recurrence of HSV disease during the 1-year treatment period was 19% in the acyclovir group compared with 32% in the placebo group.
- No statistical difference in recurrences between the two groups in the 6 months after cessation of treatment.

- Many corneal specialists still give oral aciclovir because they do not believe the HEDS trial was powered for

Melanoma

Melanoma

- Uveal melanoma can occur in iris (best prognosis), ciliary body (worst prognosis) or choroid.
- 10 year metastasis rate: 7% for iris melanoma, 25% for choroidal melanoma, 33% for ciliary body melanoma.²
- Tumour size one of most important prognostic features of uveal melanoma.

COMS Melanoma trials

- 3 large multicentre choroidal melanoma trials:
- Small melanoma:
Observe natural history
- Medium melanoma
Compare enucleation versus plaque radiotherapy
- Large melanoma
Compare Enucleation vs Enucleation preceded by
external beam radiotherapy

***This table below was asked about in detail to a candidate in the 2016 OSCE.
Tip: Learn the suspicious features (e.g. overlying lipofuscin) suggestive of choroidal melanoma on examination.***

COMS Summary

Melanoma size	Treatment arms	Melanoma Specific Mortality
Small ≤ 2.4 mm thickness < 10 mm largest basal diameter	Observation only	1% at 5 years
Medium 2.5-10mm thickness basal diameter < 16 mm	Plaque brachytherapy VS enucleation	No significant difference at 10 years (17-18%)
Large > 10 mm thickness OR > 2 mm thickness AND ≥ 16 mm basal diameter	1. Enucleation or 2. External beam radiotherapy preceding enucleation	No significant difference (40-45% at 10 years)