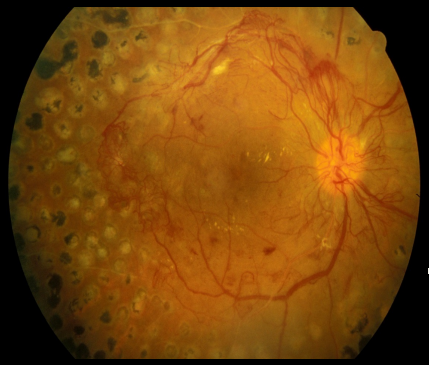

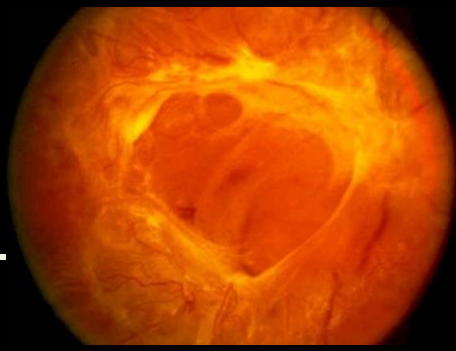

Update on intravitreal treatments for diabetic retinopathy

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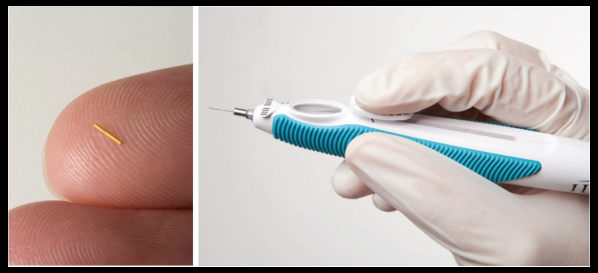
Introduction

- Significant developments in treatment options
- The current RCOphth guidelines on diabetic retinopathy are now out of date (written 2013)
- NICE guidelines: in consultation stage
- In the meantime:
- Consensus UK document 2020: EYE 34 : 1-51

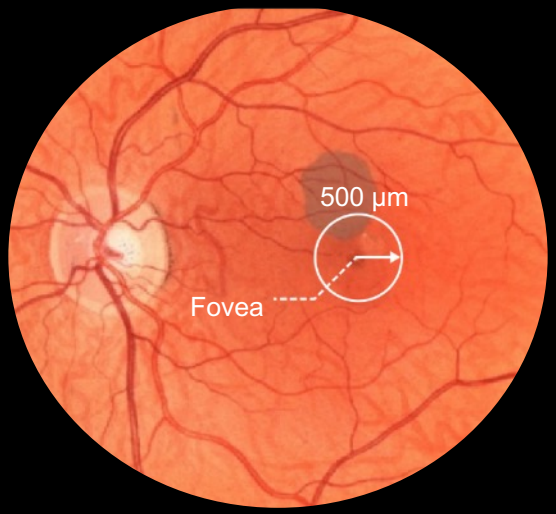
Diabetic macular oedema

Importance of glycaemic and blood pressure control

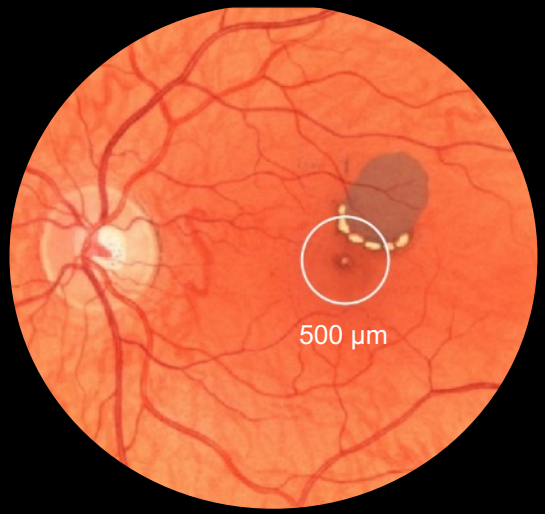


Clinically significant macular oedema

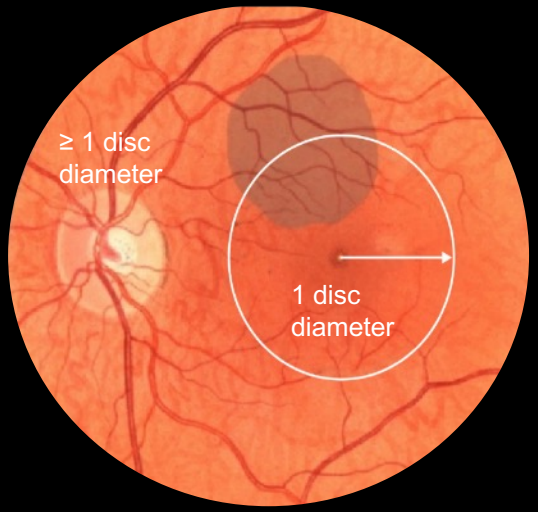
- CSMO is diagnosed if any of the following parameters are met:



1. Retinal thickening within 500 µm of the centre of the macula

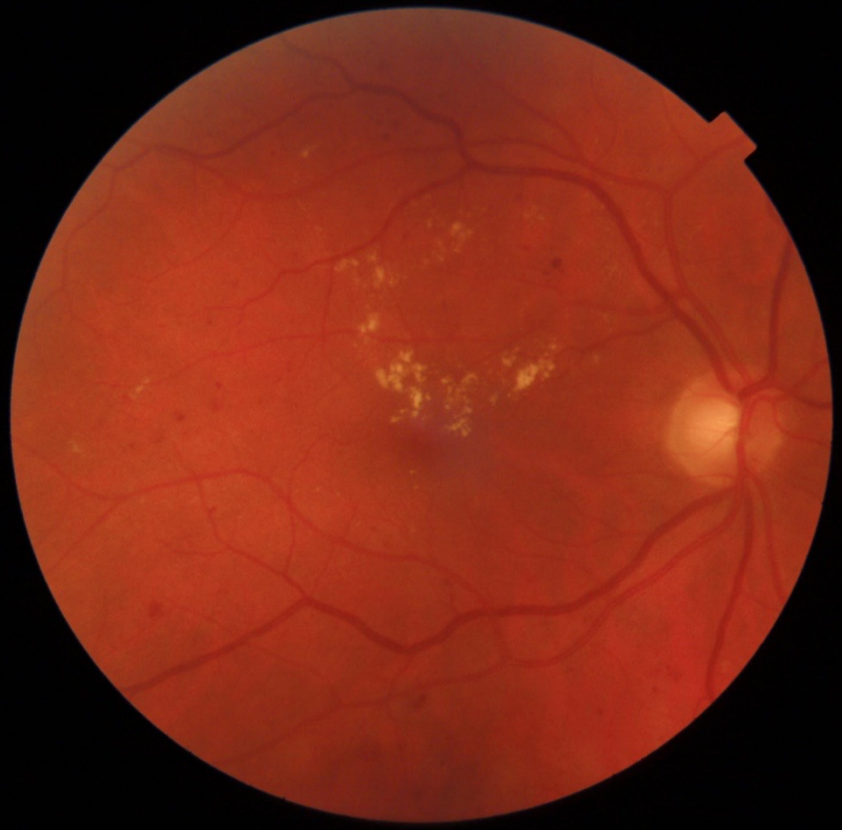


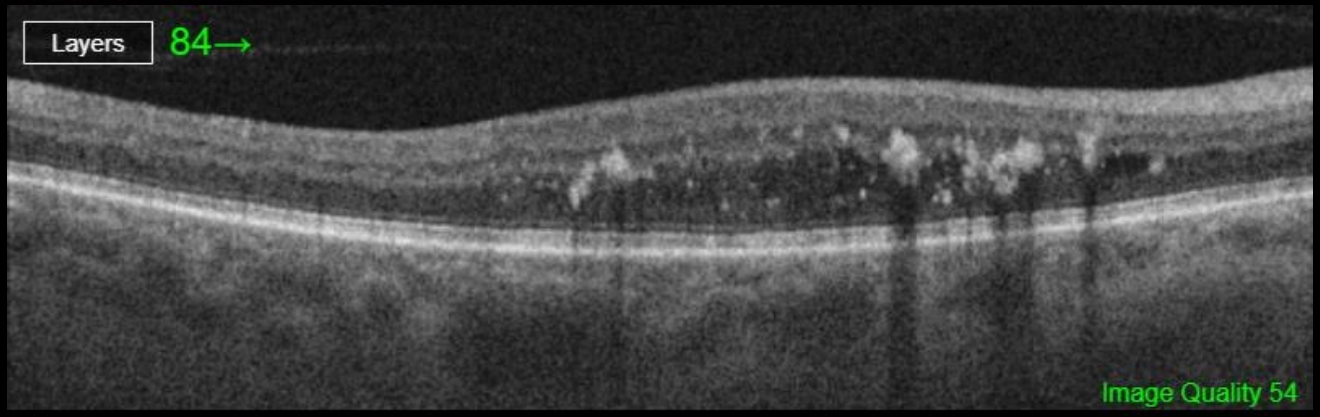
2. Hard exudates within 500 µm of the centre of the macula, if associated with thickening of the adjacent retina



3. Retinal thickening of >1 disc area in size, any part of which is located within 1 disc diameter of the centre of the macula

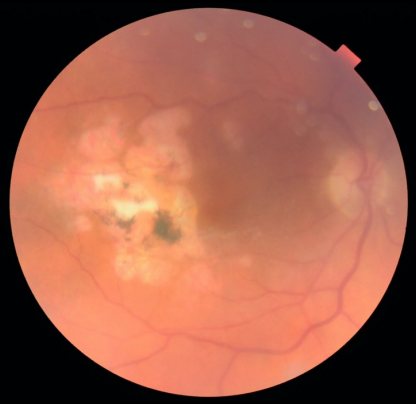
1. ETDRS Research Group. *Arch Ophthalmol.* 1985;103:1796–1806;
2. Bandello F, et al. *Eye (Lond).* 2012;26(4):485–493.

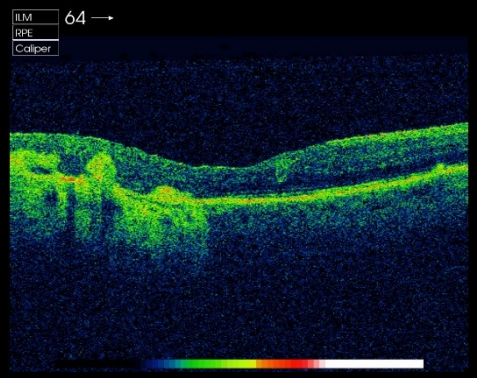



Layers
84→
Image Quality 54

Effects of Macular Laser treatment

- Laser scars enlarge over time
- Caution if treatment close to fovea
- Enlarging scotomata may occur/ERM
- Secondary choroidal neovascularisation may develop
- Role is now mainly for non-centre involving CSMO, or occasionally adjunctively after anti-VEGF
- Subthreshold laser can be used in some units





Anti-VEGF: NICE guidance for DMO

- **Ranibizumab: recommended as an option for treating visual impairment due to DMO if the eye has a central retinal thickness of 400 µm or more at the start of treatment.**

  RESTORE study: 7.9 letters mean change in BCVA at 1 yr, 8 letters at 3 years

  RISE and RIDE: 12.5 and 11.9 mean change in BCVA at 2 years

- **Aflibercept : Recommended for eyes with visual impairment due to DMO with more than 400 µm central retinal thickness at the start of treatment**

  VIVID and VISTA studies: Mean gain 1 year 10.5-12.5 letters, 9.4-11.5 letters year 2, 10.4 -11.7 letters : range depending on study/treatment regime (2mg monthly, or 2mg every 2 months after five monthly doses)

Anti-VEGF: NICE guidance for DMO

- **FARICIMAB**: recommended as an option for treating visual impairment due to DMO if the eye has a central retinal thickness of 400 µm or more at the start of treatment . Yosemite and Rhine Studies

- **BROLUCIZUMAB**: recommended as an option for treating visual impairment due to DMO if the eye has a central retinal thickness of 400 µm or more at the start of treatment.

- Brolucizumab has been found to be associated with intraocular inflammation and occlusive vasculitis, rarely used now

Beovu for AMD
Inflammation, retinal vasculitis, occlusion in 1088 treated eyes in Hawk and Harrier
Safety committee review of data

- Fifty brolucizumab-treated eyes were considered to have definite/probable drug-related events within the spectrum of IOI, retinal vasculitis

IOI (definite/probable	**4.6%**
IOI plus vasculitis	3.3%
IOI + vasculitis + occlusion	2.1%
Moderate visual loss (15 letters) with IOI + vasculitis +occlusion	0.74%
Severe visual loss (30 letters) with IOI + vasculitis +occlusion	0.5%

Faricimab in Diabetic Macular Oedema

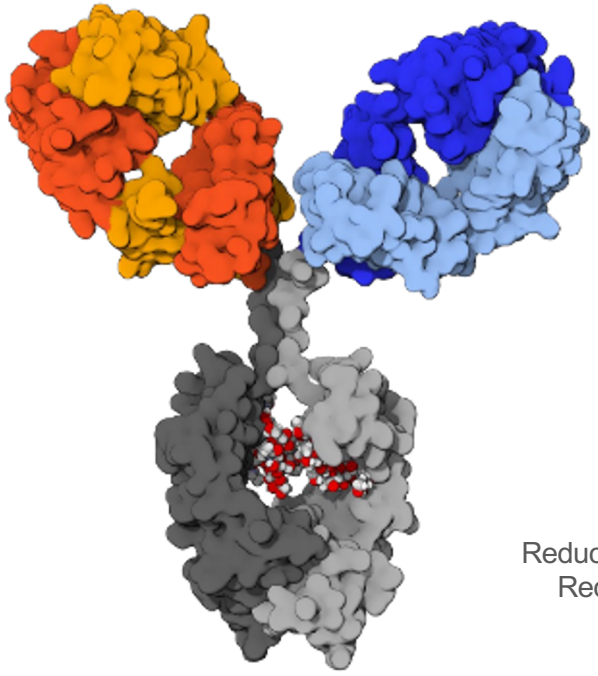
YOSEMITE AND RHINE Study Results

Phase 3, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Studies to Evaluate the Efficacy and Safety of Faricimab with extended dosing up to 16 weeks in Patients With Diabetic Macular Edema

Published in Lancet online 24 Jan 2022 C Wykoff et al

Faricimab Is the First Bispecific Antibody Designed for Intraocular Use: 1 Molecule, 2 Targets

Anti–Ang-2 Fab
Enhances vascular stability
Reduces inflammation and vascular leakage



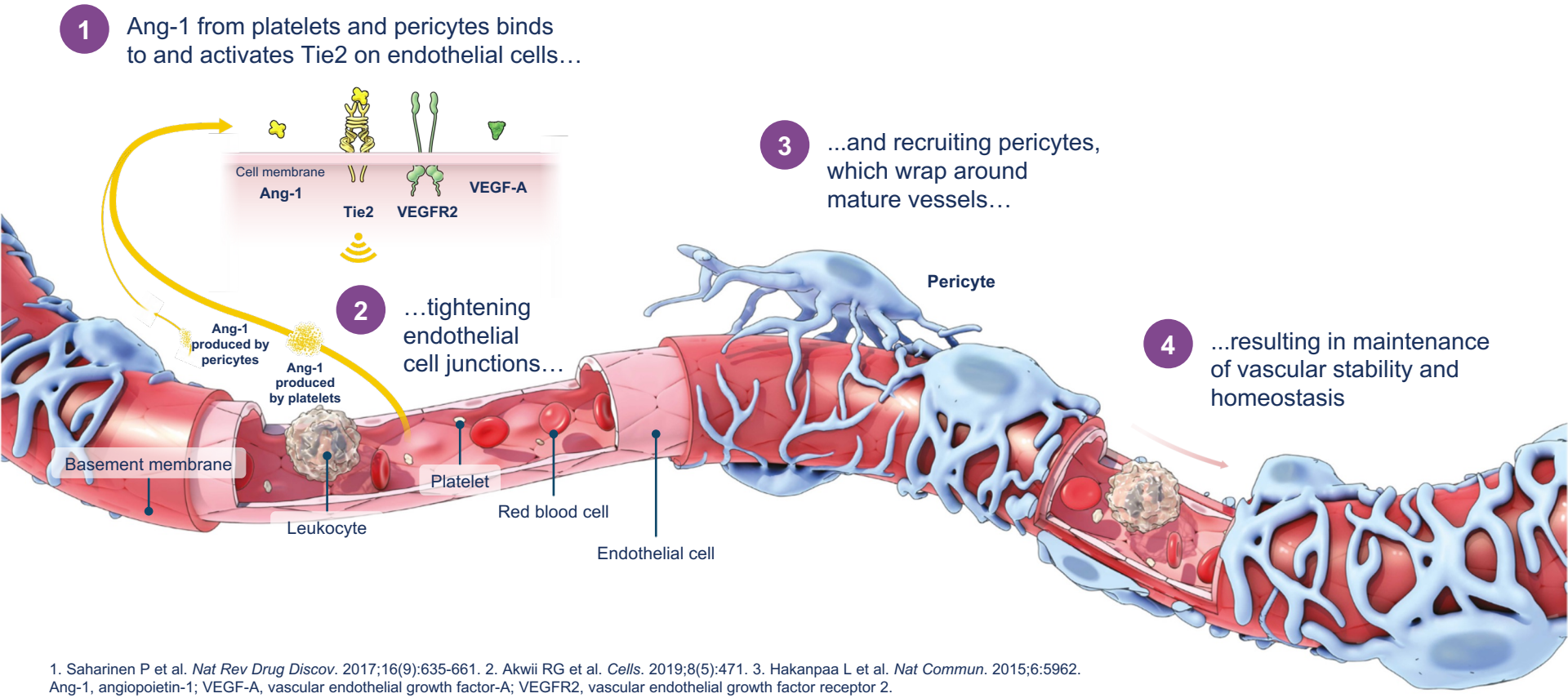
Anti–VEGF-A Fab
Inhibits vascular leakage and neovascularization

Modified Fc
Reduces systemic exposure
Reduces inflammatory potential

CrossMAb molecule representative of faricimab.
Regula JT et al. *EMBO Mol Med*. 2016;8(11):1265-1288, with correction in Regula JT et al. *EMBO Mol Med*. 2019;11(5):e10666.
Ang-2, angiopoietin-2; Fab, fragment antigen binding; Fc, fragment crystallizable; VEGF-A, vascular endothelial growth factor-A.

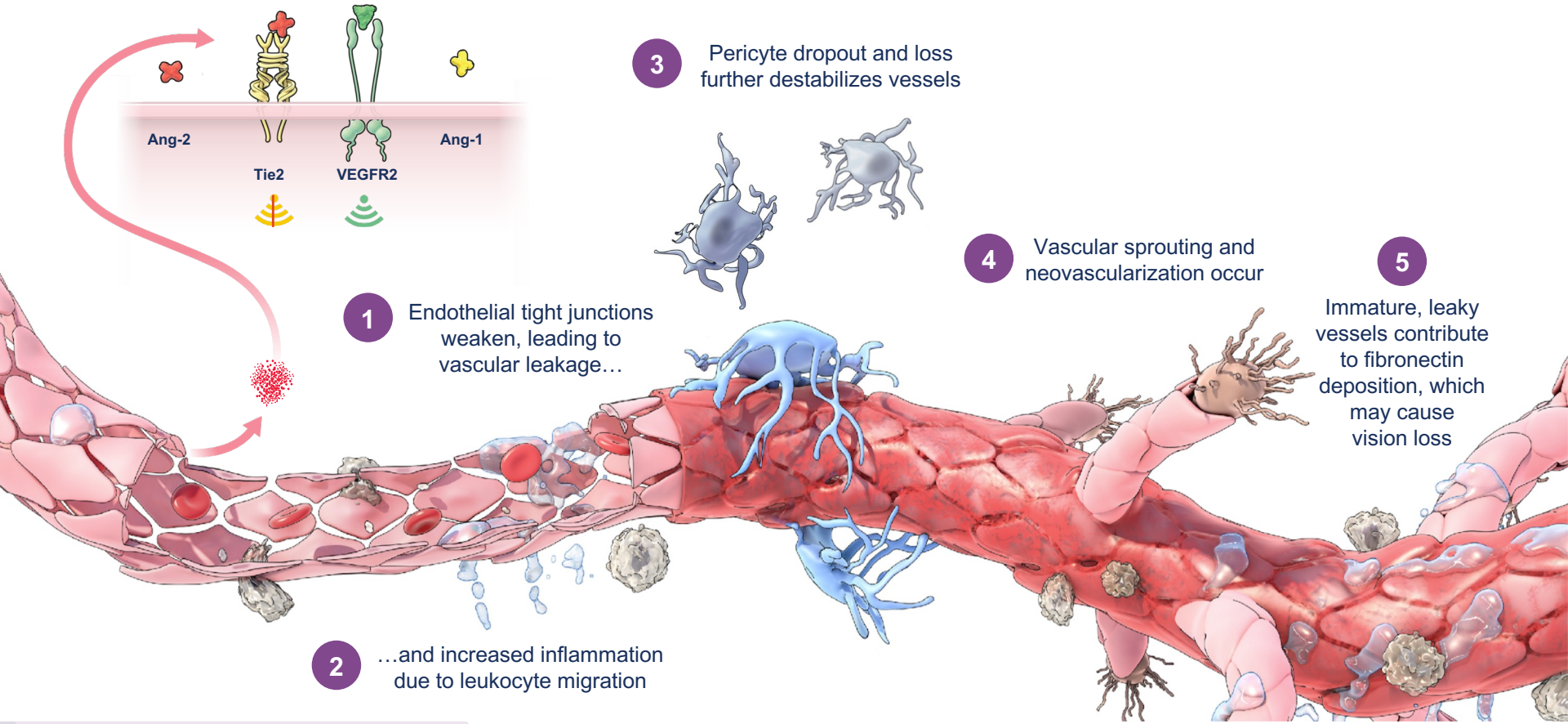
YOSEMITE RHINE

The Angiopoietin Pathway Maintains Vascular Stability and Homeostasis Under Physiological Conditions1-3

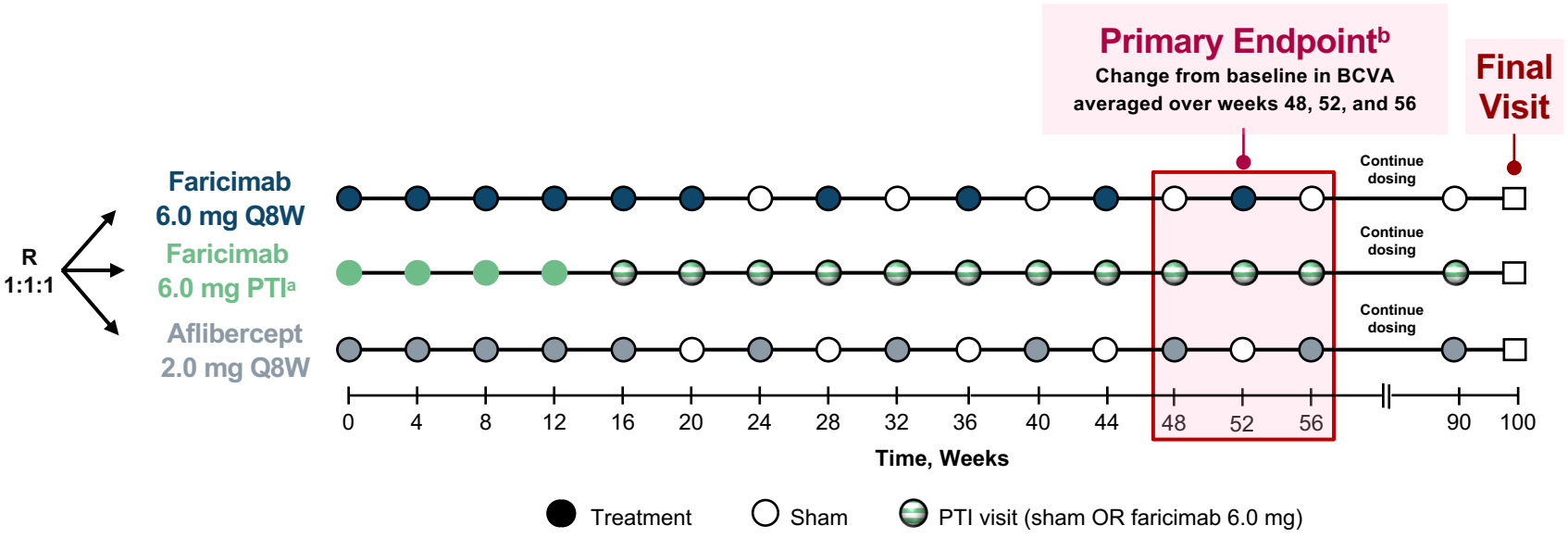


1. Saharinen P et al. *Nat Rev Drug Discov*. 2017;16(9):635-661. 2. Akwii RG et al. *Cells*. 2019;8(5):471. 3. Hakanpaa L et al. *Nat Commun*. 2015;6:5962.
Ang-1, angiopoietin-1; VEGF-A, vascular endothelial growth factor-A; VEGFR2, vascular endothelial growth factor receptor 2.

Ang-2 Promotes Vascular Instability in Disease by Blocking Ang-1–Tie2 Signaling



YOSEMITE and RHINE

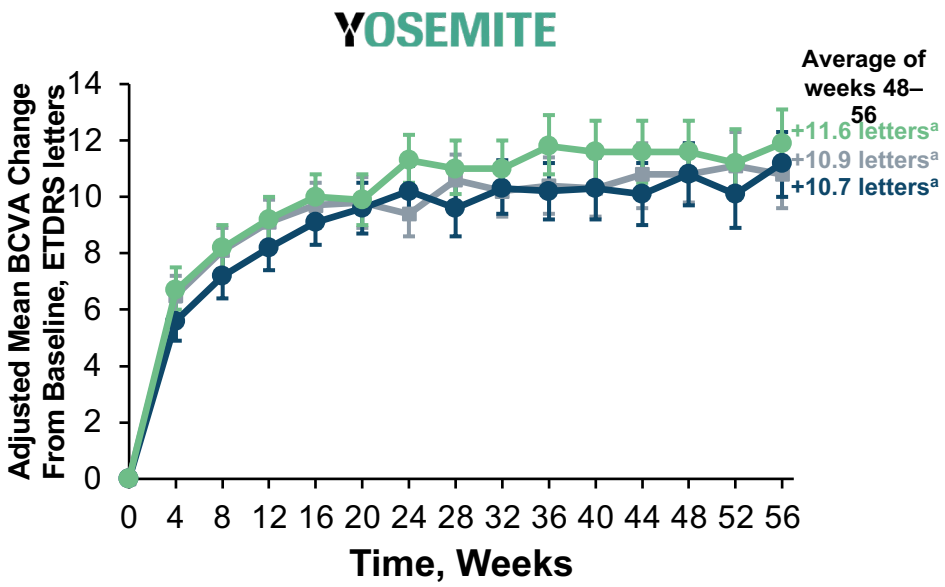


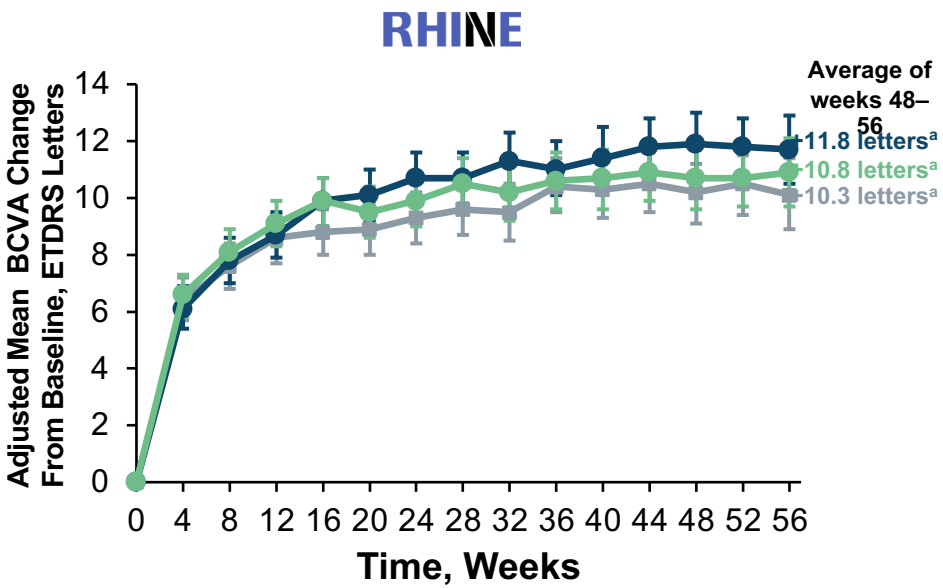
Treatment naïve and **previously treated with anti-VEGF** agents (cap of 25% at enrollment)

ClinicalTrials.gov identifiers: NCT03622580 (YOSEMITE); NCT03622593 (RHINE).
[a] The PTI algorithm is a protocol-driven regimen based on the treat-and-extend concept. [b] BCVA was measured using the Early Treatment Diabetic Retinopathy Study visual acuity chart at a starting distance of 4 m.
BCVA, best-corrected visual acuity; PTI, personalized treatment interval; Q8W, every 8 weeks; R, randomization; VEGF, vascular endothelial growth factor.

YOSEMITE RHINE

Changes in mean BCVA



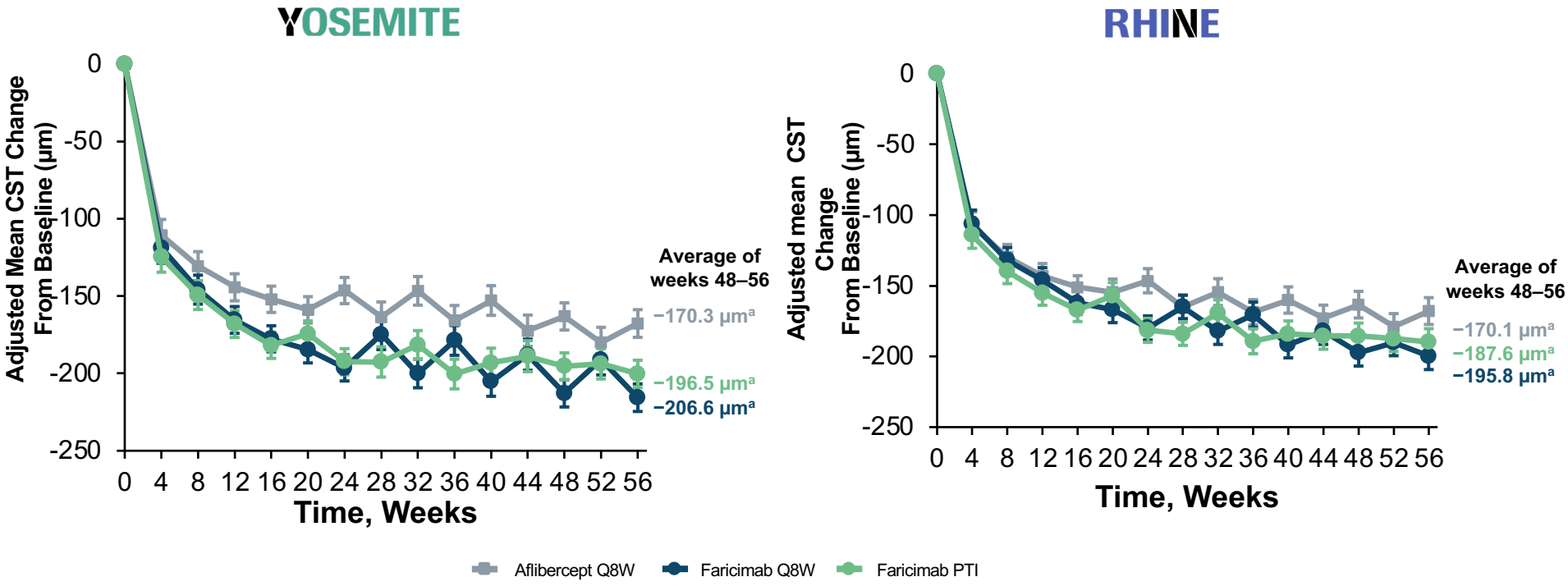


[a] Adjusted mean BCVA change from baseline at 1 year, averaged over weeks 48, 52, and 56

Aflibercept Q8W Faricimab Q8W Faricimab PTI

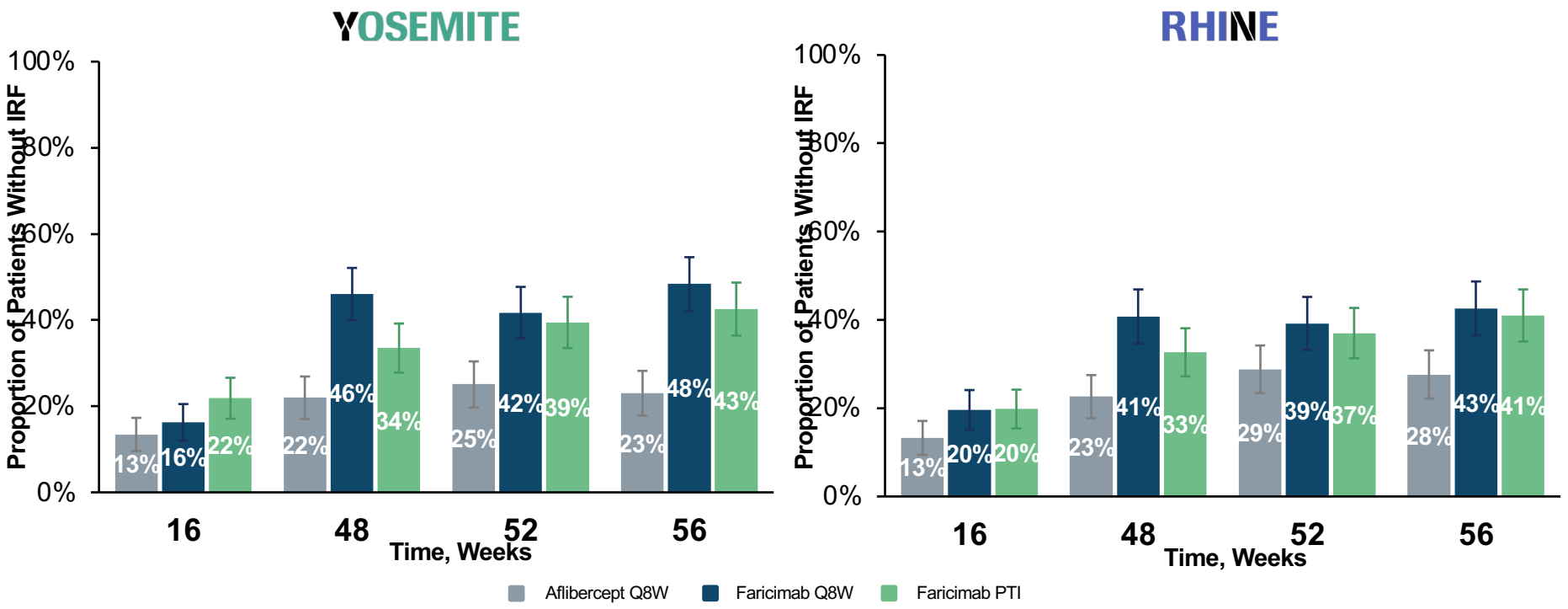
Results are based on a mixed-model repeated-measures analysis. 95% CIs are shown.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention-to-treat; PTI, personalized treatment interval; Q8W, every 8 weeks.

Change in CST



[a] Adjusted mean CST change from baseline at 1 year, averaged over weeks 48, 52, and 56. Results are based on a mixed model for repeated measures analysis. 95% CI are shown.
CST, central subfield thickness; ITT, intent-to-treat; PTI, personalized treatment interval; Q8W, every 8 weeks.

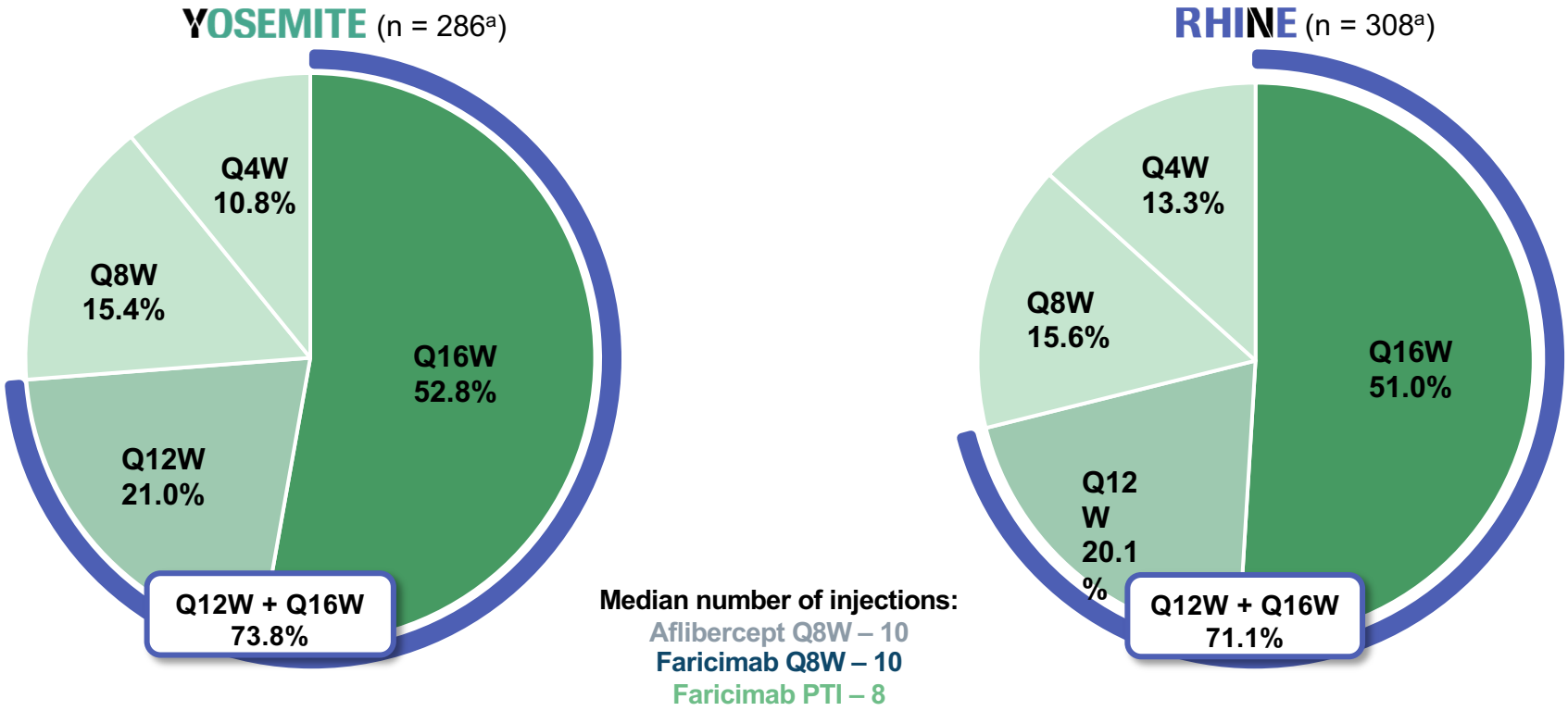
More Patients Treated With Faricimab Had Absence of intraretinal fluid Versus Aflibercept Through Week 56



Proportion of patients in each treatment group after baseline was estimated using the CMH method. Adjusted for baseline characteristics. The weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada vs the rest of the world). Asia and rest of the world regions are combined due to a small number of enrolled patients. Weighted % for aflibercept arm presented for the faricimab Q8W versus aflibercept comparison. 95% CIs are shown. BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; IRF, intraretinal fluid; ITT, intent-to-treat; PTI, personalized treatment interval; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.

YOSEMITE
RHINE

Strong Durability With Faricimab: >70% of Patients On At Least Q12W Dosing Intervals at Week 52 (ITT Population)



[a] Number of patients in PTI arm with evaluable data at week 52. Treatment interval at a given visit is defined as the treatment interval decision made at that visit. Percentages are based on the number of patients who have not discontinued the study at the visit

BCVA, best-corrected visual acuity; ITT, intent-to-treat; PTI, personalized treatment interval

Steroid: NICE guidance

- **Fluocinolone acetonide (Iluvien)** Option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies in pseudophakic eyes. Iluvien: FAME studies, 34% ≥ 15 letter gain at 3 years vs 13.4% in sham group

- **Dexamethasone implant (Ozurdex)**
- the diabetic macular oedema does not respond to non-corticosteroid treatment, or such treatment is unsuitable
- Ozurdex : MEAD study 22% vs 12% sham ≥ 15 letter gain at 3 years

When to consider steroid treatment

- Insufficiently responsive to anti-VEGF treatment : Or ‘frequent flyers’ eg Vitrectomised eye
- Ozurdex generally lasts for a few months
- Iluvien may act for up to 3 years

Treatment pathways

- Depends on local commissioning arrangements
- Some units start patients on faricimab (Vabysmo) when meets NICE guidance, other units only use this in switch patients
- Biosimilar ranibizumab now available, less expensive per vial but Ranibizumab has been shown to be less effective than aflibercept in patients with reduced vision in the DRCR-net Protocol T study
- Consider intravitreal steroid if poor response after 6-12 months

Centre involving oedema not meeting NICE guidance threshold

- Observe
- Consider clinical trial
- May consider laser if appropriate to do so
- Some units have access to anti-VEGF for this group

Summary: DMO treatment decision

- Multiple treatment options for DMO
- Choice depends on several factors:
- VA: may affect choice of anti-VEGF
- CSMO: centre involving or not /location of microvascular changes/leakage (Laser vs anti-VEGF as first line option)
- Duration of DMO
- Central macular thickness (availability of anti-VEGF treatment on NHS)
- ? Pseudophakic or vitrectomised eye
- Patient choice

Proliferative diabetic retinopathy: Panretinal photocoagulation

- Known efficacy: has been the standard of care since 1970s for PDR
- Durable results
- PRP-induced PDR regression typically lasts indefinitely
- May result in:
  - Visual field changes
  - Decreased night vision
- May exacerbate DME
- Patients may still require vitrectomy despite PRP

Possible Rationale for considering anti-VEGF over PRP

- Visual field changes
- Retinopathy severity score
- Rate of vitreous haemorrhage
- Rate of vitrectomy

Anti-VEGF monotherapy as a first step without PRP: issues

- Safety issues if there is delayed follow-up
- Cost-effectiveness (No NICE appraisal)
- Numbers of visits, duration of treatment
- Workload: capacity issues
- Adjunctive anti-VEGF could be given, if needed, in addition to PRP

Protocol S

- **Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial**

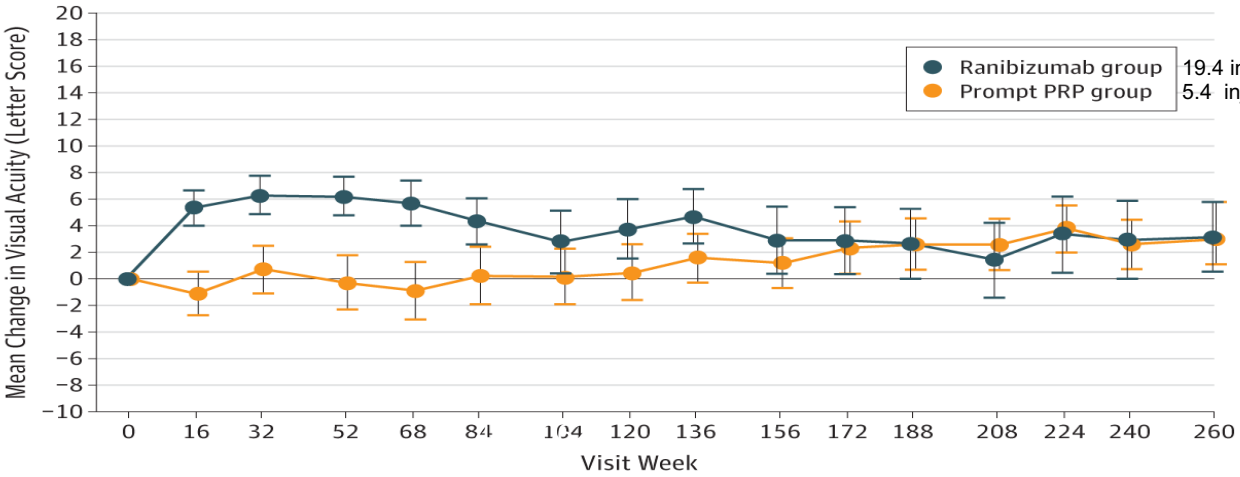
- **Jeffrey G. Gross, MD**, **Adam R. Glassman, MS**, **Lee M. Jampol, MD**, **Seidu Inusah, MS**, **Lloyd Paul Aiello, MD, PhD**, **Andrew N. Antoszyk, MD**, **Carl W. Baker, MD**, **Brian B. Berger, MD**, **Neil M. Bressler, MD**, **David Browning, MD**, **Michael J. Elman, MD**, **Frederick L. Ferris III, MD**1, **Scott M. Friedman, MD**, **Dennis M. Marcus, MD**, **Michele Melia, ScM**, **Cynthia R. Stockdale, MSPH**, **Jennifer K. Sun, MD, MPH**, **Roy W. Beck, MD, PhD**, and **Diabetic Retinopathy Clinical Research Network**

- 2 year results JAMA 2015; 314: 2137-2146
- 5 year results JAMA 2018; 136: 1138-1148

Protocol S

- **Primary outcome**: Mean visual acuity change at 2 years: Ranibizumab was non-inferior to PRP
- Rates of ≥15 letter improvement were similar between the groups
- Rates of ≥15 letter, or ≥10 letter worsening were similar between the groups
- Planned follow-up to 5 years
- Included eyes with DME as well as no DME at baseline
- Eyes in the PRP group could be given Ranibizumab for DME, but **not** if there was vitreous haemorrhage

Protocol S: Visual acuity at 5 years



No. of eyes					
Ranibizumab group	191	160	139	124	117
Prompt PRP group	203	168	146	134	123
Change in visual acuity, mean (SD)					
Ranibizumab group		2.8 (15.2)	2.9 (14.9)	1.4 (15.7)	3.1 (14.3)
Prompt PRP group		0.2 (13.7)	1.2 (11.4)	2.6 (11.0)	3.0 (10.5)
Adjusted difference (95% CI)		2.2 (-0.5 to 5.0)	1.6 (-1.1 to 4.3)	-0.7 (-4.0 to 2.5)	0.6 (-2.3 to 3.5)
P value		.11	.24	.66	.68

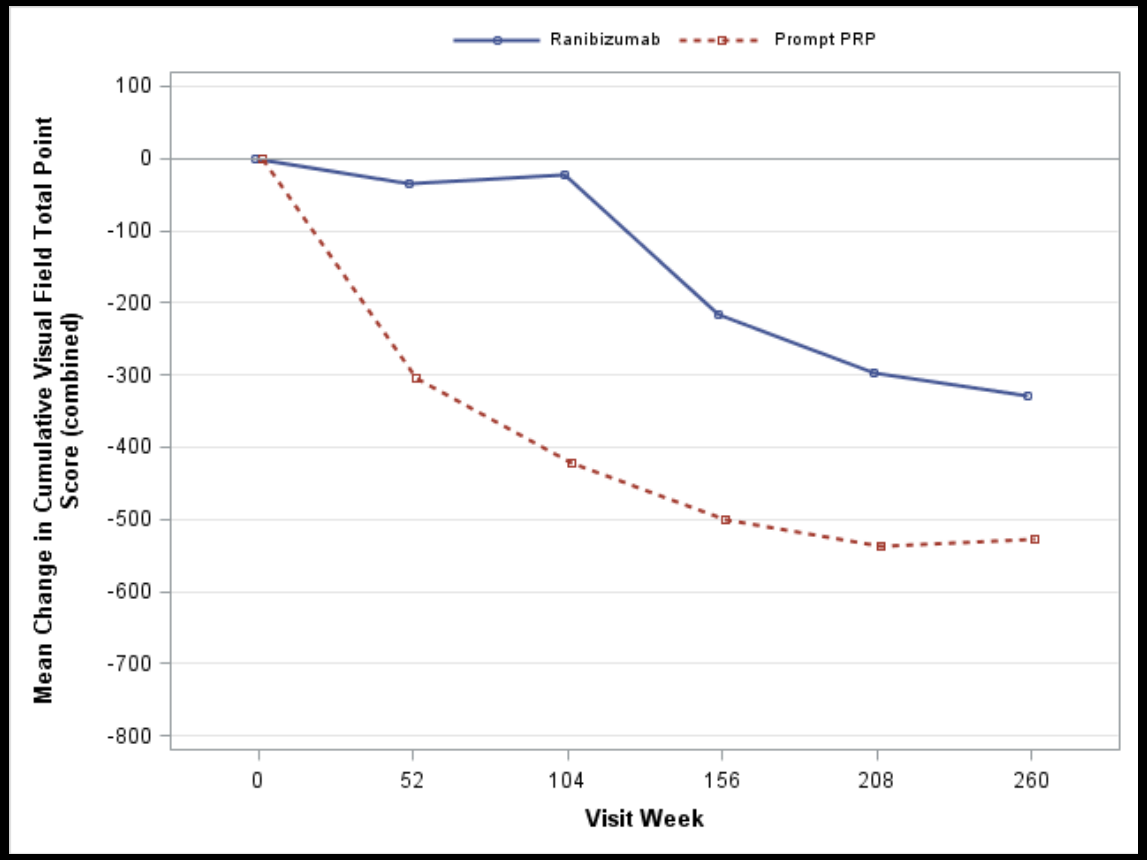
	Ranibizumab group	**Prompt PRP group**
DME at baseline	+2.5 (n=20)	+4.6 (n=24) (p = 0.48)
No DME at baseline	+3.2 (n=96)	+2.4 (n=98) (p = 0.98)

Ranibizumab injection rate

	Median Injections by 2 years Ranibizumab group	Median Injections by 5 years Ranibizumab group (60% follow-up)	Median Injections by 5 years prompt PRP group (60% follow-up)
PDR without DME (n=133)	10	15 (mean 18.0)	0 (mean 3.4)
PDR with DME (n=36)	14	24 (mean 25.3)	10 (mean 14.2)

Ranibizumab group: mean of 3 injections per year in each of years 2-5

Changes in Cumulative Visual Field Total Point Score for the Overall Cohort



NEI VFQ-25 No significant differences in any aspect between the groups

	Baseline		**104 weeks**		**Changes from baseline**	
	Ranibizumab	PRP	Ranibizumab	PRP	Ranibizumab	PRP
Driving Mean +/- SD	79 ± 18	78 ± 15	82 ± 15	79 ± 14	3 ± 16	0 ± 15
					P = 0.17	
Peripheral vision Mean +/- SD	85 ± 22	77 ± 28	82 ± 25	76 ± 26	-2 ± 20	-1 ± 31
					P = 0.38	

CLARITY

CLinical efficacy of intravitreal Aflibercept versus panRetinal photocoagulation for best corrected visual acuity In patients with proliferative diabetic reTinopathY without macular oedema at 52 weeks: a multicentre, single-blinded, randomized, controlled, phase 2b, non-inferiority trial

Sobha Sivaprasad,
Philip Hykin, Toby Prevost, Joana Vasconcelos, Amy Riddell, Caroline Murphy, Joanna Kelly & Jim Bainbridge on behalf of the CLARITY Study Group, UK

KING'S College LONDON

CLARITY

Funded by NHS National Institute for Health Research

FIAT LUX

Moorfields Eye Hospital

Clarity

- The primary outcome at 52 weeks showed aflibercept was non-inferior and superior to PRP for best corrected visual acuity
- Both treatment groups showed progression in capillary non perfusion

- Anti-vascular endothelial growth factor therapy can improve diabetic retinopathy score without change in retinal perfusion. RETINA 39:426–434, 2019

- Sophie Bonnin MD, Benedicte Dupas MD, Carlo Lavia MD, Ali Erginay MD, Myriam Dhundass MD, Aude Couturier DM, Alain Gaudric DM, Ramin Tadayoni MD PhD

Cost-effectiveness

- Clarity: ICER of £1392.99 per 1 letter change in BCVA score at list price for Aflibercept.
- Protocol S 2 year data: JAMA Ophthalmol. 2017;135(6):576-584
- Those with PDR without vision-impairing DME at baseline assigned to ranibizumab incurred costs of $22 576 compared with $7445 for those given PRP. This was **$662 978/QALY**
- This would not be cost-effective at the £50,000 /QALY for NICE approvals

Capacity

- In the UK, and some other countries, having the workforce needed to deliver care is a major issue
- Patients given PRP for PDR that has fully regressed may ultimately only require annual review
- Median 3 injections in each of years 2-5 in Protocol S, so it is anticipated that ongoing regular review with periodic injections is needed long term
- Many units would struggle to deliver this additional number of treatments even if funding were approved

Summary

- Anti-VEGF therapy for PDR has a significantly greater cost and treatment burden
- No quality of life differences between the groups were shown in any measure in Protocol S or Clarity
- Visual acuity were outcomes the same at 5 years in Protocol S in both groups, mean of 19.4 injections in the ranibizumab group vs 5.4 injections in the prompt PRP group

Proliferative retinopathy: Summary

- PRP is highly durable and there is less risk to patients if they have gaps in follow-up due to intercurrent illness etc.
- Many treatment naïve eyes will respond well to PRP monotherapy
- Anti-VEGF could be used as an adjunct to PRP if needed

Summary

- Period of rapid change in treatment options for diabetic retinopathy
- Importance of blood pressure and glycaemic control
- Several different anti-VEGF treatments have been approved by NICE
- Intravitreal steroid treatment can be considered for poor responders