**QUEEN'S
UNIVERSITY
BELFAST**

New is not always best

Peto, T., & Chakravarthy, U. (2019). New is not always best. *JAMA Ophthalmology*, 137(7), 838-839.
<https://doi.org/10.1001/jamaophthalmol.2019.1876>

Published in:
JAMA Ophthalmology

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights
Copyright 2019 American Medical Association. This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Title: New is not always best

Authors: *Tunde Peto , MD, PhD and *Usha Chakravarthy MD, PhD

*Center for Public Health, Queen's University of Belfast

Correspondence:

Usha Chakravarthy, MD. FRCOphth, PhD. Professor of Ophthalmology and Vision Sciences, Queen's University of Belfast. Consultant in Ophthalmology, Belfast Health and Social Care Trust. Center for Public Health, Institute of Clinical Sciences, Grosvenor Road, Belfast BT12 6BA

Dr Peto reports no recent relevant conflicts of interest. Professor Peto reports lecture fees from Novartis, Optos and Heidelberg Engineering in the past year. Professor Chakravarthy reports no recent relevant conflicts of interest. Professor Chakravarthy has received personal fees from Allergan, Apellis and Novartis in the past year.

Word count = 870

The advent of anti-vascular endothelial growth factor therapy has ushered in an era of optimism and hope in the management of many maculopathies including diabetic macular edema (DME). Ranibizumab and aflibercept have been shown in major clinical trials that enrolled patients with center-involved DME to yield both superior visual outcomes and improvements in diabetic retinopathy severity after two years of treatment compared with macular laser.¹⁻² More recently, the Diabetic Retinopathy Clinical Trials Retina Network investigators conducted a randomized clinical trial comparing ranibizumab, aflibercept and bevacizumab, a compounded, less expensive, but unlicensed product. They reported for eyes with center-involved DME and slightly impaired vision, defined as a Snellen equivalent of 20/32-20/40, no differences in visual acuity outcomes at one or over two years across all three agents.³ These studies have underpinned present treatment algorithms and current guidelines from across the world using anti-VEGF agents as standard care in eyes with center-involving DME when the visual acuity (VA) is 20/32-2.40 .

However, controversy remains on whether anti-VEGF therapies should be administered to patients who have center-involved DME but visual acuity defined as good (better an ETDRS letter score of 79 equivalent to a Snellen acuity of 20/25 or better) as this level of visual acuity had been an exclusion criterion in all clinical trials prior to the Network's Protocol V. A high proportion of patients have eyes with center-involved DME and excellent VA,⁴ evoking the question of whether observation, macular laser or anti-VEGF is the most appropriate strategy. Arguments for the use of anti-VEGF therapies in eyes with excellent VA include data that show progression over time to VA loss.⁴ Commencing eyes with DME and excellent VA on anti-VEGF therapies creates burden and inconvenience of high frequency review and intravitreal drug injections with their attendant risk of endophthalmitis, along with mounting costs to patient and payers.

In this issue of *JAMA Ophthalmology*, Network investigators report findings from Protocol V, the first major randomized clinical trial that specifically sought to address the timing of initiation of treatment for patients with good VA and center-involved DME, enrolling participants into 3 arms, observation, prompt thermal laser or

prompt aflibercept.⁵ The study design permitted those assigned to observation or thermal laser to receive aflibercept should BCVA reduce from baseline by 10 letters at any visit or by 5 to 9 letters at two consecutive visits.

Protocol V has now revealed that two years after entry into the trial, the proportion of eyes experiencing a 5-letter decrease in BCVA was not statistically significantly different across all 3 groups. Protocol V tells us that deferring treatment in eyes with good VA as defined in this trial and center-involved DME does not result in worse outcomes compared to prompt initiation of anti-VEGF therapy. Some two-thirds of the observation group never experienced this 5- or more letter decline in visual acuity over the two-year period, confirming the robustness of the original observations from the ETDRS.⁴ Data from Protocol V also suggests prompt treatment with aflibercept does not reduce the risk of ≥ 5 letter loss as 33 of the 205 eyes in this category experienced this end point at 2 years, a finding that was not significantly different among the prompt laser and observation groups with deferred aflibercept treatment. A finding of marginal significance was a small difference in favor of aflibercept in the proportions that experienced at least two-step worsening in diabetic retinopathy severity level on color photography compared to the observation group. In addition, some 10% of those in the observation group showed two-step improvements which was not dissimilar to that seen in the other groups (prompt aflibercept 14% and laser 12%). Given these lack of differences in the various groups in both visual acuity reductions and improvements in retinopathy severity, the clinical relevance of the finding of a marginal worsening in diabetic retinopathy severity in favor of prompt aflibercept is debatable.

What Protocol V has not addressed is the effect of the three regimens on the patient's quality of life. It would be important to understand the effect of the visit schedules which differed between groups and the challenge of high frequency visits and injections in the prompt aflibercept group given that those with DM already have systemic co-morbidities that often contribute to a burden of hospital visits. Prompt initiation of treatment with aflibercept almost certainly results in considerable excess costs which if implemented into routine clinical practice would

add to a strain and burden on both the patient and over-stretched health economies.

It is worth noting that participants in Protocol V had good control of diabetes and blood pressure and attended visits frequently and thus may not necessarily reflect the profile of patients with DM in routine care. However real world data from the OBTAIN study, which included patients with excellent VA, has reported that follow-up is maintained in untreated eyes with DME over a period of 1 year.⁶ Protocol V now gives us the confidence to manage our patients with DME and excellent VA conservatively at least until there is documented reduction in VA. Such a management strategy would avoid potentially unnecessary introduction of anti-VEGF therapies at a stage of disease which may be amenable to alternative non-invasive strategies such as good systemic control.

References

1. Nguyen QD¹, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012 Apr;119(4):789-801.
2. Brown DM¹, Schmidt-Erfurth U², Do DV³, Holz FG⁴, Boyer DS⁵, Midena E⁶, Heier JS⁷, Terasaki H⁸, Kaiser PK⁹, Marcus DM¹⁰, Nguyen QD³, Jaffe GJ¹¹, Slakter JS¹², Simader C², Soo Y¹³, Schmelzer T¹⁴, Yancopoulos GD¹³, Stahl N¹³, Vitti R¹³, Berliner AJ¹³, Zeitz O¹⁵, Metzger C¹⁴, Korobelnik JF¹⁶. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. *Ophthalmology*. 2015 Oct;122(10):2044-52.
3. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW. *New England Journal of Medicine*. 2015; 372:1193-1203

4. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol. 1985;103:1796–1806.

5. Protocol V

6. Busch C, Fraser-Bell S, Zur D, Rodríguez-Valdés PJ, Cebeci Z, Lupidi M, Fung AT, Gabrielle PH, Giancipoli E, Chaikitmongkol V, Okada M, Láíns I, Santos AR, Kunavisarut P, Sala-Puigdollers A, Chhablani J, Ozimek M, Hilely A, Unterlauff JD, Loewenstein A, Iglicki M, Rehak M; International Retina Group. Real-world outcomes of observation and treatment in diabetic macular edema with very good visual acuity: the OBTAIN study. Acta Diabetol. 2019 Mar 22. doi: 10.1007/s00592-019-01310-z.