Objective evaluation of proliferative diabetic retinopathy using optical coherence tomography

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ABSTRACT

Purpose: To present the routine use of optical coherence tomography (OCT) and OCT angiography (OCTA) for the objective diagnosis and monitoring of proliferative diabetic retinopathy (PDR).

Design: Retrospective observational case series.

Subjects: Patients with diabetic retinopathy imaged using a standardized PDR-protocol

Methods: Patients routinely imaged with a standardized PDR-protocol between March 2017 and January 2019 were included. This included a 12x9 mm structural OCT volume centered on the macula and a 6x6 mm OCTA scan centered on the optic nerve head obtained using a Topcon swept-source system (DRI OCT-1 Triton, Topcon, Tokyo, Japan). Ultra-widefield fluorescein angiography (FA) was also performed when clinically indicated. The ground truth for each case was determined by merging the findings from biomicroscopy and imaging modalities to generate the maximum level of detection for each finding.

Main outcome measures: Detection rates of new-onset, regression and reactivation of neovascularization of the disc (NVD) and neovascularization elsewhere (NVE) using different modalities (biomicroscopy/color photography, structural OCT, B-scan OCTA, *en face* OCTA). Detection of progression of tractional retinal detachment (TRD).

Results: 383 eyes of 204 patients were evaluated. After excluding patients without PDR or with insufficient image quality, 47 eyes of 35 patients were included. For the detection of new-onset NVD and NVE, structural OCT had the highest detection rate (100%) of all modalities. However, for the detection of regression or reactivation of neovascularization, B-scan OCTA had the highest detection rate (100%), as structural OCT detected regression only in 45.5% of cases, resulting in a low detection rate of reactivation (12.5%). Among 10 eyes with TRD, OCT detected fovea-threatening TRD during follow-up in 7 eyes, resulting in vitrectomy.

Conclusion: This study demonstrates the utility of novel multimodal imaging in the daily management of patients with PDR. Posterior pole structural OCT had the best detection rate for neovascularization, while B-scan OCTA showed the most potential for objective monitoring of disease following treatment.

Proliferative diabetic retinopathy (PDR) is characterized by neovascularization that occurs at the vitreoretinal interface that may cause vitreous hemorrhage (VH), tractional retinal detachment (TRD), and neovascular glaucoma, thereby significantly increasing the risk of vision loss.[1] Patients with PDR may sometimes present a diagnostic and management challenge. First, the sensitivity of fundus biomicroscopy for distinguishing neovascularization from intraretinal microvascular abnormalities (IRMAs) is not high.[2] Smaller lesions may be missed by the examiner, especially when not accompanied by more pronounced signs of severe retinopathy. Another challenge is related to post-treatment monitoring. Clinical examination may show signs of a residual neovascular complex following panretinal photocoagulation (PRP) or intravitreal injection treatment - it may sometimes be difficult to tell whether this is still “active”. In such cases, fluorescein angiography (FA) may still show signs of leakage despite resolution or stability of neovascularization, and may also show leakage with other vascular lesions, including IRMAs, dilated capillaries, and microaneurysms.[3] FA is also time consuming and carries the risk of side effects, and therefore cannot be repeated frequently.[4] Finally, there are challenges related to surgical decision making, both for TRD and non-clearing VH. Traditionally, one of the indications for surgery is those TRDs which threaten or involve the macula, as – in some cases – extramacular TRDs can remain stable for years without the need for vitrectomy. [5] However, there is no accepted standard for the assessment of the TRD progression of a TRD, a problem which may lead to unnecessary surgical intervention or delays in treatment. A further indication for vitrectomy is recurrent or non-clearing VH. This can present a diagnostic challenge in as much as a decision needs to be made whether the hemorrhage is due to leakage and bleeding from active neovascularization or a tractional event from fibrotic complexes. Whereas disease activity suppression, whether via PRP or an anti-vascular endothelial growth factor (VEGF) agent, is indicated in the former case, a vitrectomy will be of best use in the latter scenario.

In recent years the treatment paradigm for PDR has seen the beginning of a shift from PRP to intravitreal anti-VEGF therapy, based on the results of the DRCR.net Protocol S and CLARITY studies.[6,7] However, in both studies, retreatment criteria were based on investigator assessment of neovascularization on ophthalmoscopy and any available retinal images. So far, no objective tool has been suggested for the assessment of neovascularization response to treatment, although such tools have been used routinely for the assessment of retreatment of macular edema both in clinical practice and in clinical trials for more than a decade, starting with the PrONTO trial.[8] Modern imaging modalities such as widefield optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) may serve as objective tools in the assessment of neovascularization both in the clinical setting and in the context of clinical trials.

Previous studies have demonstrated the use of spectral domain optical coherence tomography (SD-OCT) in the detection of neovascularization in PDR.[3,9,10,11] Current devices allow for a wider-field scan than is available with SD-OCT, reaching the retinal midperiphery - “posterior pole” OCT. Swept-source optical coherence tomography (SS-OCT) uses a wavelength-tunable laser and dual-balanced photodetector offering higher imaging speeds in comparison with SD-OCT.[12] Studies have demonstrated its ability to better visualize the posterior vitreous and vitreoretinal interface.[13] Optical coherence tomography angiography (OCTA) is a novel and non-invasive technique for demonstrating the microvascular blood flow.[14] It produces a depth-resolved evaluation of the reflectance data from retinal tissue, providing a three-dimensional volume of information. A number of preliminary studies have begun to describe the characteristics of retinal neovascularization on OCTA.[15,16,17,18]

In our clinical practice, we use a combination of these tools. Posterior pole SS-OCT is used to diagnose neovascularization and SS-OCTA provides information about the activity of the vessels. We also use posterior pole SS-OCT to help guide referrals for surgical intervention

in patients with TRD. Given the experience we have accumulated in the use of these imaging modalities in the management of patients with PDR, we herein present a series of patients to demonstrate how we use these tools at different stages in disease management.

METHODS

Data Collection:

This was a retrospective observational case series. In our practice, we acquire posterior pole OCT and OCTA in all patients with severe non-proliferative diabetic retinopathy (NPDR) and with any stage of PDR. For the evaluation of retinal neovascularization, eyes with a diagnosis of PDR and existing images according to our PDR protocol (see below) between March 2017 and January 2019 were included. For the evaluation of TRD, eyes with posterior pole OCT images were included. Eyes were excluded if they had severe media opacities preventing a clear scan, or if image quality was otherwise judged insufficient to allow clinical assessment (e.g., due to poor fixation or image artefacts). Demographic and clinical data were collected for all patients. Clinical data included best-corrected visual acuity (BCVA), color fundus photography, B-scan (structural) OCT, OCTA, and FA in selected cases. Approval for data collection and analysis was obtained from the Institutional Review Board at Moorfields (ROAD17/031). The study adhered to the tenets set forth in the Declaration of Helsinki.

Image Acquisition Protocol:

OCT scans were obtained using a single Topcon OCT instrument (DRI OCT-1 Triton, Topcon, Tokyo, Japan). It uses a wavelength of 1050 nm with a scan speed of 100,000 A-scans per second, providing a lateral resolution of 20 μm and an in-depth resolution of 2.6-8 μm. As per the scanning protocol in our clinic, for each patient a high-definition 12 mm line scan, a 12 x 9 mm volume scan centred on the macula, and a 6 x 6 mm OCTA scan centered on the optic

nerve head were acquired. In selected cases, a 6 x 6 mm OCTA scan centered over areas of NVE was acquired. The decision to perform this targeted scan of suspected neovascularization was based on previous history, clinical examination and/or conventional OCT/FA imaging.

FA photographs were acquired using the Optos 200TX (Optos Plc, Dunfermline, Scotland) ultra-widefield system.

Definition of Diagnostic Reference Standards and Ground Truth:

Due to the lack of an unequivocal gold standard for the diagnosis of active neovascularization, we adopted a pragmatic approach to detection representative of real-world clinical practice. The ground truth for each case was determined by merging the findings from biomicroscopy/color fundus photography with both FA and OCT/OCTA to generate the maximum possible level of detection for each finding. This approach was particularly helpful in cases where findings were equivocal on one modality - e.g., in FA imaging where it was difficult to distinguish between an IRMA and NVE but where structural OCT clearly showed presence of a lesion in the preretinal space.

We used the following methods to determine the presence of neovascularization: (1) The presence of a clearly formed neovascular complex (NVE or NVD) on biomicroscopy or color fundus photography; (2) The presence of a clear NVD on *en face* OCTA; (3) the presence of a preretinal hyperreflective material (PRHM) on structural OCT - in which case an OCTA scan is done in that location. If a flow signal is present on the B-scan OCTA or a clear NVE is seen on *en face* OCTA a diagnosis of neovascularization is made. (4) The presence of leakage on FA. FA is done in cases when the other modalities are not sufficient for the diagnosis of neovascularization: a suspected peripheral NVE in which the diagnosis on biomicroscopy/colour photography is unclear, the presence of new preretinal hemorrhage or

vitreous hemorrhage in the absence of clear neovascularization detected using the other modalities, or in cases of progressing severe diabetic retinopathy.

Similarly, we used these methods to determine the activity of neovascularization: (1) On biomicroscopy/color fundus photography: the presence of neovascularization that was not documented before or apparent growth of a previous lesion that was previously documented. Alternatively, neovascularization that remains constant after treatment, associated with progression of diabetic retinopathy, suggests its activity; (2) On FA: The presence of florid leakage. However, as previously mentioned, such leakage may result from other microvascular changes (e.g., IRMA) or may persist despite treatment; (3) Structural OCT: the presence, persistence or growth of a PRHM; (4) B-scan OCTA: the presence of a flow signal in the PRHM; (5) *en face* OCTA: the presence of a clear neovascular complex, either new or that has not changed or has grown since last documentation.

Image Grading:

Two masked, trained retina specialists (R.S., H.K.) independently reviewed the OCT, OCTA, and FA images for existence of neovascularization as seen on each image modality. For posterior pole OCT, the presence of any PRHM was noted on careful scrutiny of individual OCT B-scans within the volume. Assessment of retinal neovascularization on OCTA involved a two-step process. First, the presence of flow within the PRHM on B-scan OCTA was recorded. The presence of flow within any areas of PRHM was then further scrutinized using the vitreoretinal segmentation slab as delineated automatically by the device. The slab's location was manually adjusted in order to provide the best view of the neovascularization (this process was done during the clinical consultation and typically took an average of 10 seconds). Then, the *en face* OCTA images of the superficial retinal slab and vitreoretinal slab were examined for obvious delineation of the retinal neovascular network. The superficial retinal slab was defined as the

volume between the internal limiting membrane (ILM) and the outer boundary of the inner plexiform layer (IPL). The vitreoretinal interface (VRI) slab was defined with an inner boundary 100 μm above the ILM and an outer boundary at the ILM. For FA grading, the presence of leakage in foci suspected to be neovascularization by clinical examination and OCT were recorded. Disagreements between graders were adjudicated by a senior retina specialist (P.A.K.).

Statistical analysis

Inter-rater agreement was calculated using kappa statistics, wherein a Kappa (K) value of less than 0.2 means poor agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 good agreement, and 0.81-1.00 very good agreement. Statistical analyses were performed by MedCal version 19.0.5 (MedCalc Inc., Mariakerke, Belgium).

RESULTS

A total of 383 eyes of 204 patients with diabetic retinopathy were imaged using a standard posterior pole OCT and OCTA protocol. Of those, 169 eyes of 98 patients were diagnosed with PDR. Of eyes with PDR, 93 eyes of 60 patients had both imaging modalities performed on the same visit. Of those, 46 eyes of 30 patients were excluded: 5 eyes had media opacity precluding proper interpretation of the scan, 15 had peripheral NVE which could not be detected using our protocol, and 26 with previous treatment for PDR and no visible neovascularization at the time of the scan (no PRHM on OCT). Therefore, 47 eyes of 35 patients were included in the study. For TRD follow-up, a total of 10 eyes of 10 patients met the inclusion criteria and were included in the study. The inter-rater agreement was 0.85 for B-scan OCTA, 0.88 for *En Face* OCTA, 1.0 for structural OCT, and 1.0 for FA.

Detection of new-onset neovascularization

Detection of retinal NVD

Forty-one eyes of 32 patients had NVD which was detected using the scanning protocol. Posterior pole structural OCT detected the NVD in 41/41 eyes (100%). OCTA B-scans detected flow in 34/41 eyes (82.9 %). *En face* OCTA images detected NVD in 22/41 eyes (53.7 %). Of note, all cases with detected NVD on *en face* OCTA demonstrated flow on B-scan OCTA, but only 22/34 cases (64.7 %) with detectable flow on OCTA B-scan were discoverable on *en face* OCTA. Of the 19 undetected cases by *en face* OCTA, four were of poor quality or suffered from motion artifacts. *En face* structural OCT was also reviewed in these cases and detected an NVD in 19/41 cases (46.3 %). Review of color fundus photographs and biomicroscopy examination revealed that an NVD could only be detected in 23/41 eyes (56 %). Of these, three showed clear signs of fibrosis, however, OCTA B-scans still demonstrated clear evidence of flow (Table 1, Figure 1-2).

Detection of posterior pole retinal NVE

Eleven eyes of ten patients had an NVE which was detected using the scanning protocol. Of those five were macular and six outside the arcades. Posterior pole OCT detected 11/11 (100%) of the NVE, OCTA B-scan detected flow in 11/11 (100%), and *en face* OCTA detected an NVE in 8/11 eyes (72.7%) (Table 2, Figure 3-4). Of note, on examination, and confirmed on color fundus photographs, NVE was detected in 8/11 (72.7 %) since in three eyes detection of the NVE was not possible due to retinal and preretinal hemorrhages.

Detection of Disease Activity Following Treatment

Seventeen eyes of 13 patients had sequential images and were followed up for progression or regression in response to treatment (Table 3). Of those, over the study period, 11 eyes showed

signs of regression (resolution or diminished activity), eight showed signs of reactivation of previously inactive neovascularization, and three showed signs of resistance to treatment.

Regression of neovascularization following treatment

Eleven eyes showed signs of regression during follow-up. Clinical examination and color photographs detected regression in 9/11 (81.8%) cases. In the other two cases the appearance of a fibrous band prevented a clear decision regarding the activity of NV. Posterior pole OCT detected regression in 5/11 (45.5%) of cases. Flow signal on B-scan OCTA showed regression in 11/11 (100%) of cases. *En-face* OCTA showed regression in 9/11 (81.8%) cases. In the other two cases no NV was seen previously, and therefore no regression could be detected.

Reactivation of neovascularization following treatment

Eight eyes showed signs of reactivation of previously inactive neovascularization. Funduscopy and color photographs detected 4/8 (50%) of those. Of note, in one of these cases the lesion looked active previously (despite having no flow on OCTA B-scan), and so reactivation could not be detected. OCT detected reactivation only in one case (12.5%). In all other cases PRHM was seen before and after the activation, unchanged. B-scan OCTA detected reactivation in 8/8 (100%) of cases. En-face OCTA detected reactivation in 5/8 cases (62.5%) (Figure 5).

Resistance of neovascularization to treatment

Three eyes showed signs of resistance to treatment. This was expressed as no difference in the detection of neovascularization from before to after the treatment, and was the same on all examination modalities.

Table 4 summarizes the detection rates for each examination technique for each of the previously mentioned stages.

Monitoring of TRD Progression

Ten eyes of 10 patients had evidence of TRD on OCT scans. Seven of those had signs of fovea-threatening detachment as detected using OCT during follow-up and were sent for vitrectomy. The other cases included nasal traction not threatening the macula and stable on follow-up, and two cases threatening an atrophic or scarred fovea and therefore not indicated for surgery (Figure 6).

DISCUSSION

In this paper, we present our routine usage of PDR-protocol swept source imaging in patients with diabetic retinopathy and describe the utility of different detection techniques in managing these patients. Posterior pole OCT and the flow signal on B-scan OCTA were the most useful for detection of newly formed neovascularization. However, for the detection of regression and reactivation of neovascularization, B-scan OCTA proved most useful. In cases with TRD, posterior pole OCT served as an objective tool in deciding on the proper timing for surgical intervention.

For the detection of NVD, widefield OCT was the most useful modality, with a detection rate of 100%, followed by B-scan OCTA with a detection rate of 82.9%. For the detection of NVE up to the equator, both widefield OCT and B-scan OCTA had a detection rate of 100%. Notably, *en face* OCTA was less sensitive in detecting new-onset neovascularization. All cases identified using this modality were also positive on B-scan OCTA, but the opposite was not true, further showing that B-scan OCTA may be a more reliable method for the detection of new vessels than *en face* OCTA. It is worth mentioning structural *en face* OCT. We found that once positive it can be a useful tool in confirming the diagnosis of NVD, as its appearance is clearer on this modality in many cases and is likely pathognomonic (Figure 1).

Several factors may explain the lower detection rate of funduscopy and color photography (56% for NVD, 72.7% for NVE). First, the presence of fibrosis may make the distinction between an active an inactive lesion on both mediums more difficult, as was seen in several of our cases. Second, the presence of hemorrhage may mask details of neovascularization, as was also seen here. Third, the distinction between an IRMA and neovascularization may be difficult without the assistance of OCT to show the exact location of the vessel within the retinal layers. Finally, some vessels may be too fine to detect without the use of high-resolution imaging. However, imaging devices have their limitations as well. *En face* OCTA is prone to various artifacts,[19] which accounted for some of the misdetections of NV in our cohort, further signifying the need to inspect the accompanying B-scan flow signal. The presence of hemorrhage may lead to a false-positive diagnosis of NV (Figure 4), which can be avoided by looking at the combination of flow data and *en face* OCTA for that area.

Our findings show that for the follow-up of NV, the detection rates change considerably. While structural OCT proved very sensitive in the detection of new vessels, its high sensitivity was to its detriment. It failed to detect their regression (detection rate of 45.5%), a fact which then prevented it from detecting their reactivation (detection rate of 12.5%) (Figure 2). Its counterpart, the B-scan OCTA, proved to be the most useful in this regard, detecting regression and reactivation in 100% of cases. While being more useful for these aims than structural OCT, clinical examination and color photographs proved unreliable in comparison with B-scan OCTA, detecting regression in 81.8% of cases (due to fibrotic changes) and reactivation in only 50% of cases. These findings suggest that structural OCT should not be used as a single modality in cases of neovascularization with no activity, especially in eyes with burnt out PDR.

For the detection of resistance all modalities proved useful, with a detection rate of 100%. However, there were very small numbers of patients in this group, and larger studies are needed to confirm these findings.

The timing of referral of patients for vitrectomy and delamination currently varies significantly between clinicians and the decision to proceed with surgery is often subjective. Our findings begin to establish an objective means of triaging appropriate candidates for surgery in cases of recurrent or non-clearing VH. This relies on observed diminution of flow in established PRHM or lack of flow in newly-observed PRHM on B-scan OCTA, thereby implicating a tractional mechanism for the VH, which is amenable to a surgical solution. In cases of diabetic TRD, OCT is an established tool for progression monitoring in the clinic, although this particular application is not widely described in the literature. Our study demonstrates its useful role and highlights the advantages conferred by widefield OCT, which facilitates single-scan monitoring of much of the posterior pole. Early detection of progression on serial scans gives the opportunity for earlier intervention, before pre-operative foveal involvement limits postoperative visual recovery. Furthermore, with some surgeons favouring the use of pre-operative anti-VEGF agents in active PDR days or weeks prior to a vitrectomy, our imaging protocol provides a way to assess the response to an intravitreal injection in this scenario.

The data presented here describe the use of posterior pole SS-OCT and OCTA in supporting real-life decision-making in patients with PDR. Previous papers discussing the use of OCTA in PDR patients included either case reports or descriptive series[20,21,22,23] or descriptors of morphological features of neovascularization as seen using this device.[15] Despite the limitations of current commercial OCTA devices, limiting the field of view to the posterior pole and its proximity, we have shown here that they can aid in the management of PDR patients where routine funduscopy failed, as is often the case in clinics. While new devices will allow

montaging of several OCTA scans to provide a wide-field view in the near future,[24,25] the findings presented herein will still apply to these devices, further emphasizing the promise behind them and possibly changing the diagnosis paradigm currently in use by most clinicians.

Our study has some limitations and this area of clinical research has a number of unresolved issues. First, as discussed, the OCTA device used in this study does not provide wide-field imaging of the whole retinal area. However, the concepts and findings here should apply to these devices once they are more widely available. Furthermore, prior studies have shown that the majority of neovascularization in PDR are located in the posterior pole. [26-28] Second, a number of patients were excluded due to insufficient image quality limiting the assessment of neovascularization. Third, the existing standards for detection and monitoring of neovascularization in PDR are imperfect, as there is no conclusive definition for the activity of neovascularization, and it is currently based on the assumption that the existence of blood flow within a neovascular complex necessarily represents activity. It is possible that blood flow may remain in stable mature complexes. It is therefore unclear whether all neovascularization detected to be active on these imaging modalities should be treated and that all neovascularization that are found to be inactive should be left untreated. Further longitudinal studies are required to compare the complication rates of PDR based on treatment decisions made on multimodal imaging versus current practice.

In summary, in this study structural OCT and B-scan OCTA had the highest detection rates for new-onset neovascularization. However, for follow-up, B-scan OCTA showed higher detection rates, mostly due to the persistence of PRHM on OCT. OCT is useful as an objective tool in timing surgery for patients with TRD and VH. Our findings suggest that a multimodal imaging approach for the detection of neovascularization and for determining its activity may be a useful alternative to current practice, particularly once wider-field versions of OCT and OCTA

devices become more readily available. Further longitudinal studies are required to validate these findings.

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FIGURE LEGENDS

Figure 1 – Detection of neovascularization of the disc (NVD) in three patients with proliferative diabetic retinopathy. A: Right eye (RE) of a 57 year-old female patient. B: RE of a 58 year-old male patient. C: RE of a 33 year-old female patient. 1: fundus color photograph. 2: 6 x 6 mm en face optical coherence tomography angiography (OCTA) scan centered over the disc depicting new vessels. 3: Structural en face optical coherence tomography (OCT). 4: B-scan OCTA demonstrating flow-signal as a sign of NVD activity. We show a spectrum of disease, ranging from a large lesion with significant elevation above the surface [A], to smaller lesions which may be easily mistaken for a small disc hemorrhage on clinical examination [B] or where detection may be difficult as the lesion is contained within the physiological optic disc cup [C]. In each case, there is clear detection of PRHM on structural OCT B-scans with superimposed flow signals from OCTA. In [A] the neovascular complex is not seen on *en face* OCTA due to segmentation error, but the lesion is clearly seen on *en face* structural OCT.

Figure 2 – detection of neovascularization of the disc (NVD) in the right eye of a 45 years-old male patient with proliferative diabetic retinopathy. A: Baseline visit. B-scan optical coherence tomography angiography (OCTA) (left) shows the presence of preretinal hyperreflective material (PRHM) with an overlying flow signal consistent with active NVD. *En face* OCTA (right) demonstrates NVD, although without very clear delineation of the complex. The patient had coexisting diabetic macular edema and so underwent three sessions of panretinal photocoagulation (PRP) and five-monthly injections of aflibercept to this eye. B: Follow-up visit seven months later. There is an absence of flow on B-scan OCTA (left) despite the persistence of PRHM. En face OCTA (right) no longer shows NVD. This demonstrates the potential false positive nature of structural OCT in the follow-up of regressed neovascularization.

Figure 3 – Detection of neovascularization elsewhere (NVE) in the left eye of a 36-year-old male patient with proliferative diabetic retinopathy. A: Color fundus photography showing NVE inferior to the superior temporal arcade (arrow). B: Near infra-red image depicting the same NVE (arrow). C: Wide-field optical coherence tomography (OCT) line scan through the lesion, showing preretinal hyperreflective material (PRHM). D: A 4.5 x 4.5 mm *en face* optical coherence tomography angiography (OCTA) scan demonstrating the NVE. E: B-scan OCTA showing flow in the NVE as a sign of activity. OCTA can be directed to an area of a suspected NVE and confirm the diagnosis, while also providing information about its activity.

Figure 4 – detection of neovascularization elsewhere (NVE) in the left eye of a 33-year-old male patient with proliferative diabetic retinopathy. A: Color fundus photography showing a suspected area of NVE (arrowhead) and preretinal haemorrhage (arrow). B: Optical coherence tomography angiography (OCTA) B-scan demonstrating preretinal hyperreflective material (PRHM) with superimposed flow signals, confirming the presence of NVE. C: 6 x 6 mm *en face* OCTA scan centred on the NVE at the level of the superficial capillary plexus, showing an NVE (arrow). D: The same scan at the level of the vitreoretinal interface better demonstrating the NVE (arrow). The preretinal haemorrhage can also be seen (arrowhead) but is easily differentiated from the NVE. E: B-scan OCTA at the level of the preretinal haemorrhage also shows PRHM (arrow). However, minimal flow is seen, and there is shadowing underneath the PRHM, suggestive of a hemorrhage. This demonstrates the importance of combining OCT with OCTA, as in our protocol, for the distinction between NVE and other preretinal changes.

Figure 5 – regression and reactivation of neovascularization of the disc (NVD) in the left eye of a 42-year-old female patient with proliferative diabetic retinopathy. This patient was

previously treated with panretinal photocoagulation (PRP). A: Baseline. Active NVD as seen on color photograph (left), B-scan optical coherence tomography angiography (OCTA) (middle), and *en face* OCTA (right). The patient also had diabetic macular edema (DME). Further panretinal photocoagulation was added and a course of five-monthly aflibercept injections was administered. B: Follow up six months later. The color photograph no longer shows activity. B-scan OCTA shows significant reduction of flow. *En face* OCTA does not show any sign of NVD. C: Follow up 3 months later. Reactivation of NVD was evident in the color photograph, on B-scan OCTA and on en face OCTA. As the patient also developed recurrent DME, a course of three bimonthly aflibercept injections was started. This figure demonstrates the utility of the suggested imaging protocol in the objective evaluation of regression and recurrence of neovascularization.

Figure 6 – Follow-up in two cases of tractional retinal detachment (TRD) in patients with proliferative diabetic retinopathy, showing the usefulness of posterior pole OCT as an objective decision-making tool when considering surgery in patients with proliferative diabetic retinopathy. A: Left eye (LE) of a 58-year-old female patient with TRD. Top row: Color fundus photograph (left) and wide-field optical coherence tomography (OCT) (right) showing perimacular TRD. Bottom row: While having surgery in her right eye, the left eye was observed. On follow-up 6 months later, visual acuity was unchanged and the color photograph looked similar. However, OCT showed that the fovea was threatened and the patient was referred for surgery. B: LE of a 65 year-old female patient with a lower nasal TRD. Top row: scan at the level of the fovea. Bottom row: Scan at the lower macular level. Middle: OCT scan taken at baseline visit. Right: OCT scan taken after a year of follow-up, showing stability of the TRD, and therefore the patient was observed.

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Figure 1

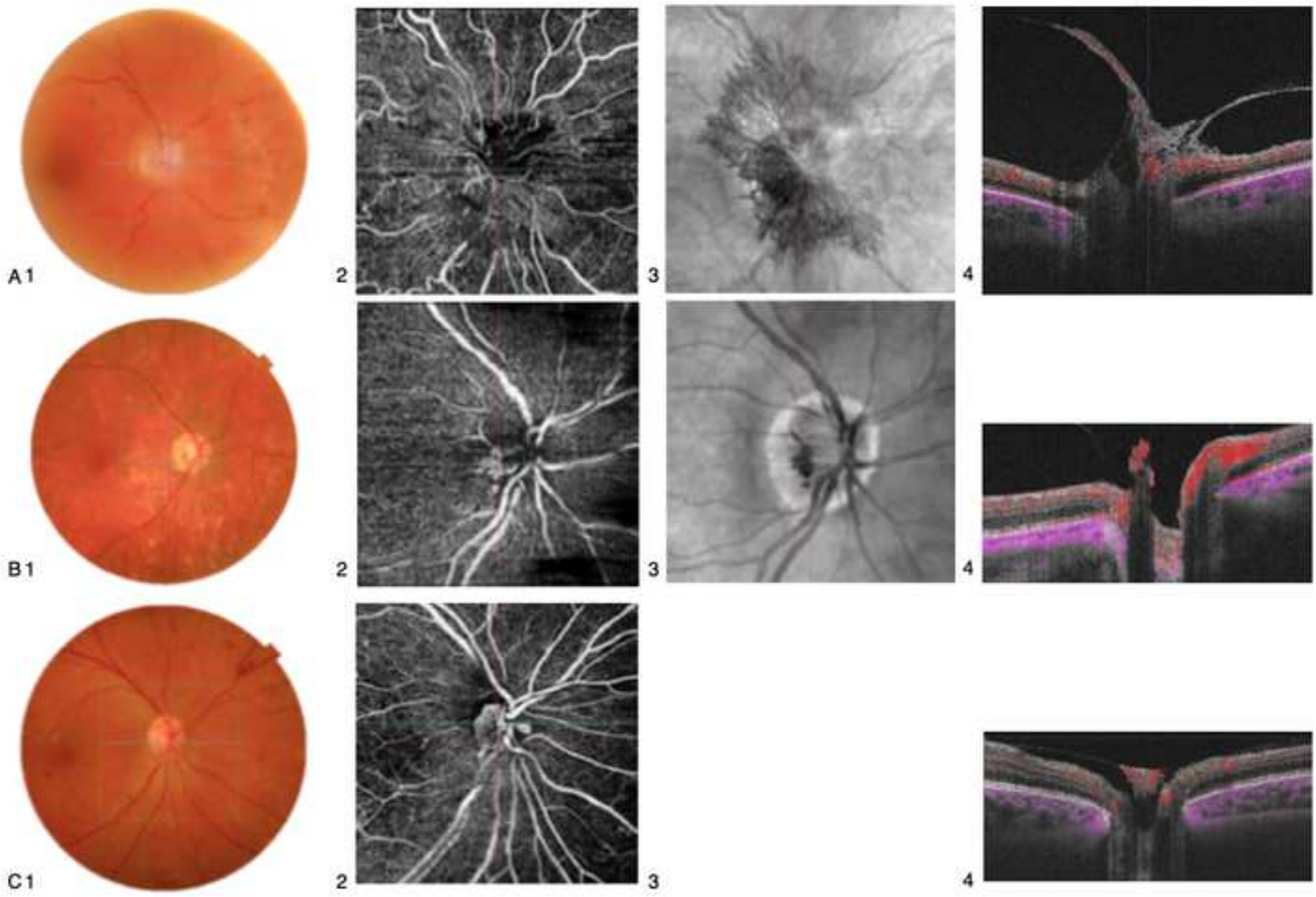

Figure 2

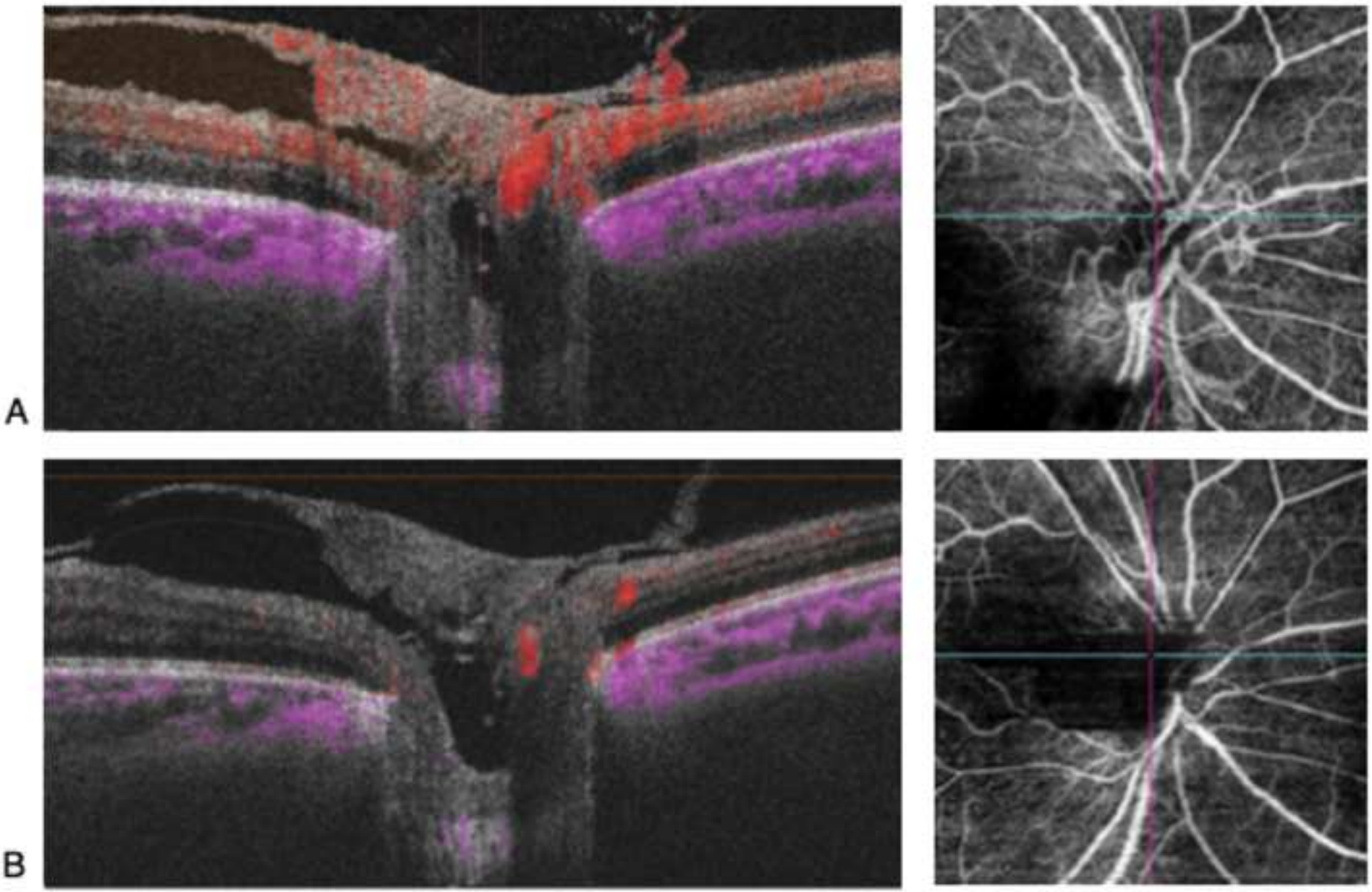

Figure 3

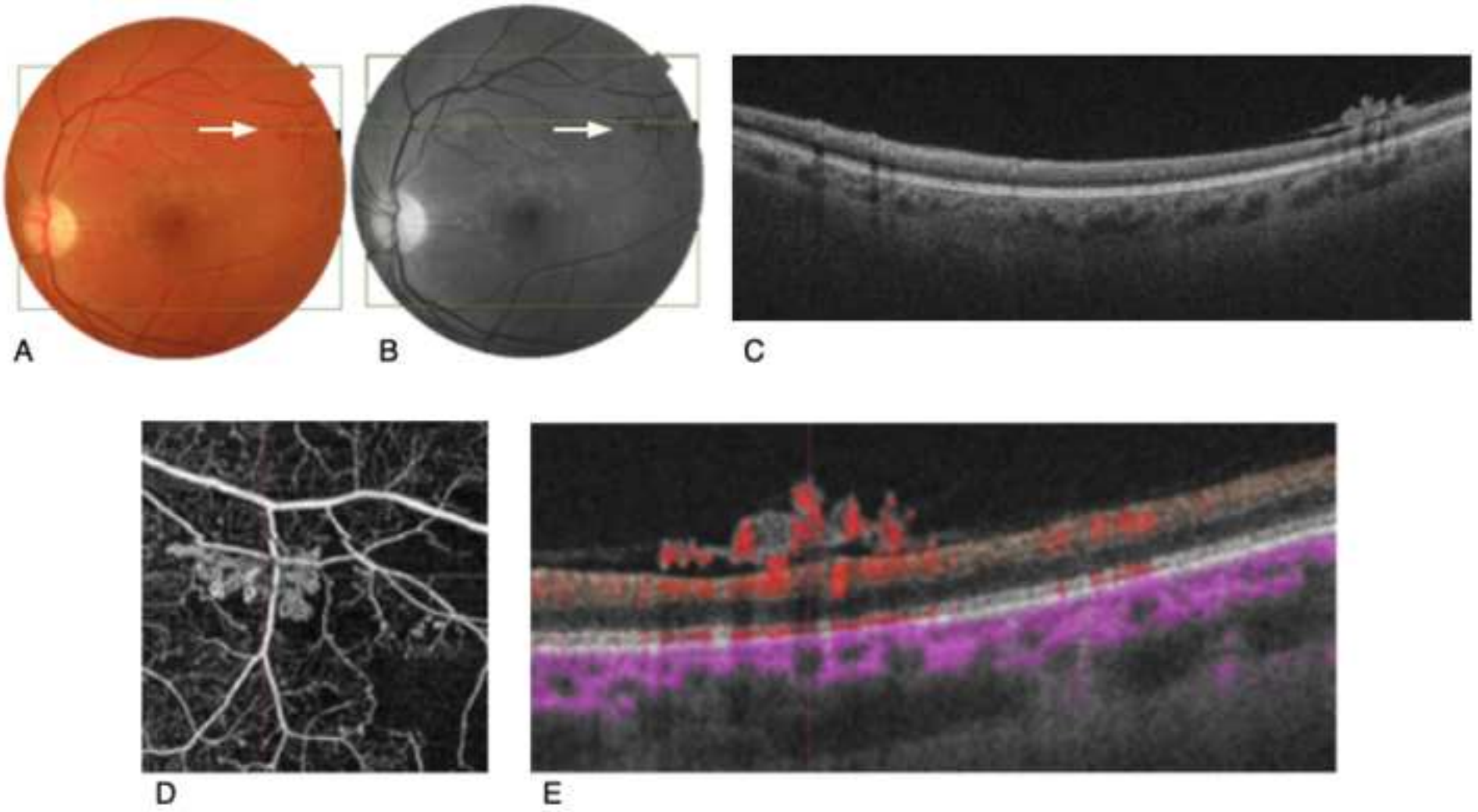

Figure 4

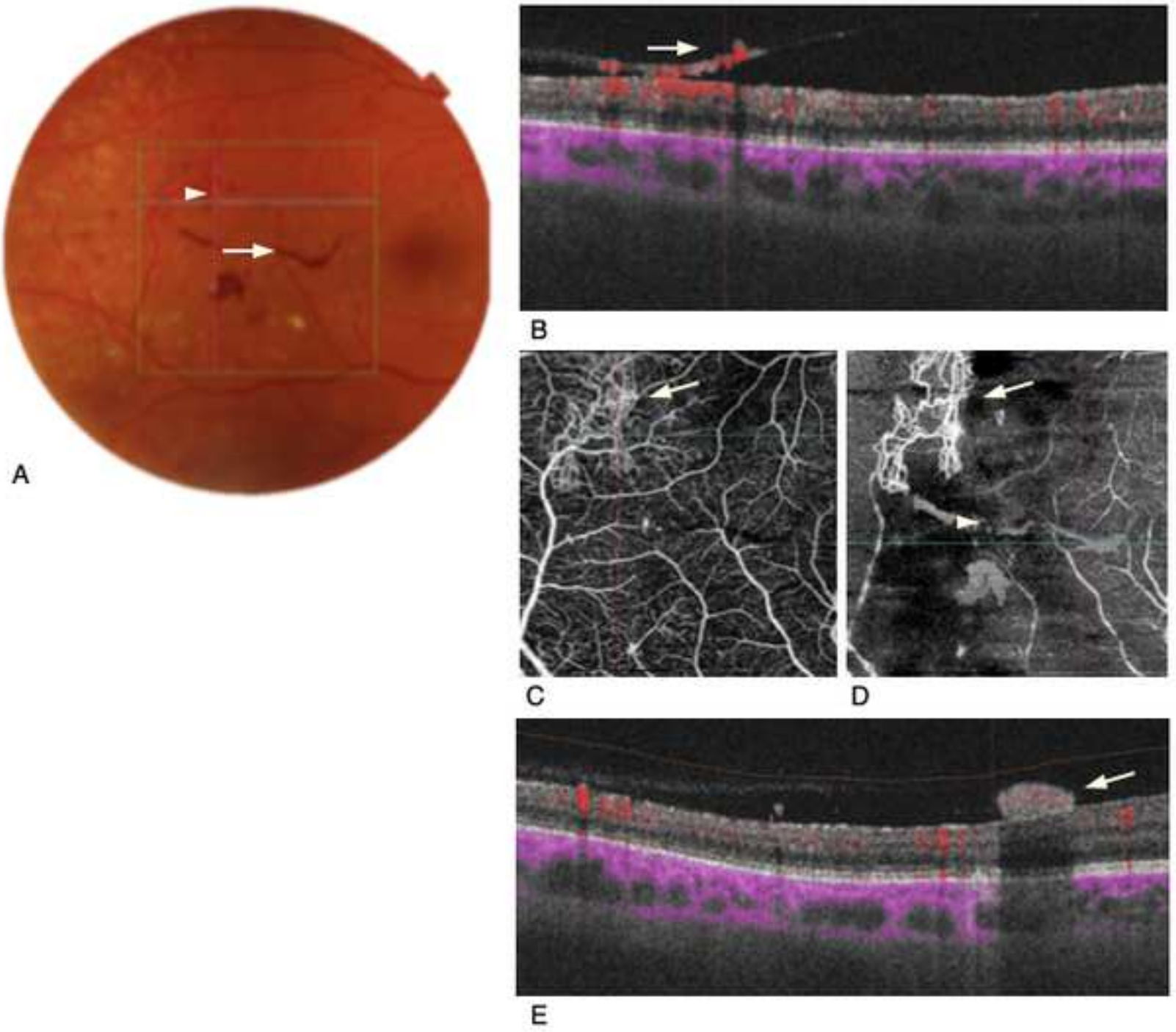

Figure 5

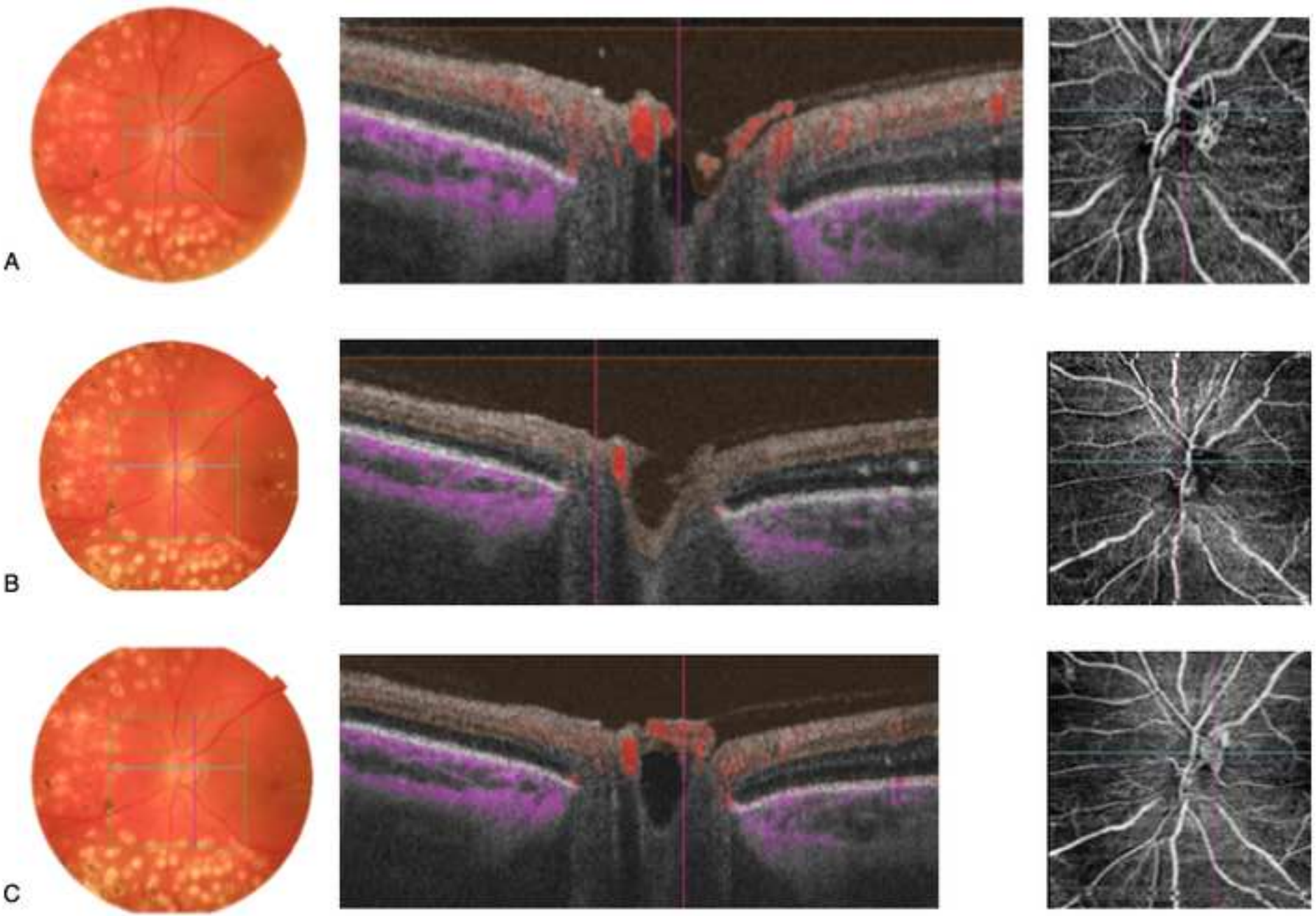

Figure 6

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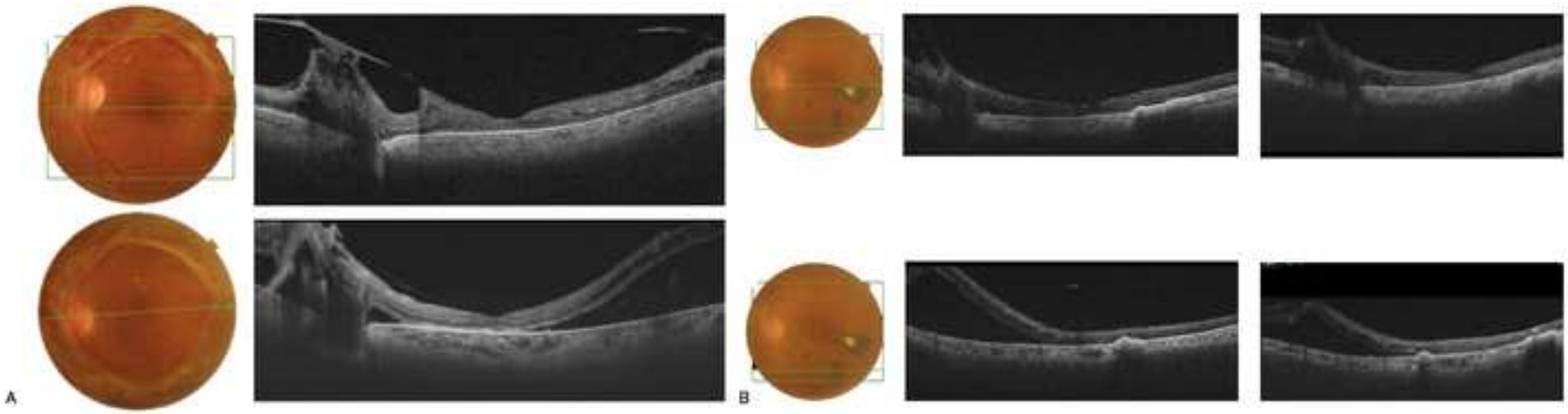

Table 1 - Detection of neovascularization of the disc using multimodal imaging

Patient	Eye	CP/biomicroscopy	OCT	Flow on B-scan OCTA	En-face OCTA	Enface structural OCT	FA
1	L	Y	Y	Y	Y	Y	NA
2	R	Y	Y	Y	Y	Y	NA
	L	Y	Y	Y	Y	Y	NA
3	R	Y	Y	Y	Y	Y	NA
	L	N	Y	N	N	N	NA
4	L	Y (signs of fibrosis)	Y	Y ^	N	Y	NA
5	L	Y	Y	Y	Y	Y	NA
6	R	N	Y	N	N	N	NA
	L	Y	Y	Y	N	Y	NA
8	R	Y	Y	Y	Y	Y	NA
	L	Y	Y	Y	Y	Y	NA
9	R	Y	Y	Y	Y	Y	NA
	L	Y	Y	Y	Y	Y	NA
10	R	Y	Y	Y ^	N *	N	NA
	L	Y	Y	Y	Y	N	NA

11	R	Y	Y	Y	Y	Y *	NA
12	L	Y	Y	Y	Y	Y	NA
13	L	Y (signs of fibrosis)	Y	Y ^	N	Y	NA
14	R	Y	Y	Y	Y	Y	NA
15	R	Y	Y	Y	Y	Y	NA
16	R	Y	Y	Y	Y	Y	NA
17	R	N	Y	Y	Y	N	Y
	L	Y	Y	N	N	N	NA
18	R	N	Y	Y	N	N	Y
19	R	N	Y	Y	Y	Y	NA
20	R	N	Y	Y ^	Y	N	NA
	L	N	Y	Y ^	Y	N	NA
21	R	N	Y	Y ^	N	N	NA
22	R	N	Y	Y	N *	N *	NA
23	R	N	Y	Y	N	N	NA
24	R	N	Y	Y	N *	N *	NA
	L	N	Y	Y	N *	N *	NA
25	R	N	Y	N	N	N	NA
26	R	N	Y	N	N	N	NA

27	R	N	Y	N	N	N	NA
28	L	N	Y	N	N	N	NA
29	R	Y (signs of fibrosis)	Y	Y ^	N	N	NA
30	L	Y	Y	Y	Y	Y	Y
31	R	N	Y	Y ^	N	N	NA
32	R	N	Y	Y	Y *	N *	NA
	L	Y	Y	Y	Y *	N *	NA

* Artifacts or poor quality

^ Minimal flow detected

CP = color photograph, OCT = optical coherence tomography, OCTA = optical coherence tomography angiography, FA = fluorescein angiography, R = right, L = left, Y = yes, N = no, NA = not available

Table 2 - Detection of neovascularization elsewhere using multimodal imaging

Patient	Eye	Location	CP/biomicroscopy	OCT	Flow on B-scan OCTA	En-face OCTA	FA
1	L	Macular	Y	Y	Y	Y	NA
2	R	Extra-macular	N	Y	Y	Y	NA
3	R	Macular	Y	Y	Y	Y	NA
	L	Extra-macular	Y	Y	Y	Y	NA
4	L	Extra-macular	N	Y	Y	N	NA
5	R	Extra-macular	Y	Y	Y	N	NA
6	L	Macular	Y	Y	Y	N	NA
7	R	Macular	Y	Y	Y	Y	NA
8	R	Extra-macular	Y	Y	Y	Y	NA
9	R	Extra-macular	N	Y	Y	Y	NA
10	L	Macular	Y	Y	Y	Y	Y

CP = color photograph, OCT = optical coherence tomography, OCTA = optical coherence tomography angiography, FA = fluorescein angiography, R = right, L = left, Y = yes, N = no, NA = not available

Table 3

Table 3 – Detection of disease activity following treatment using multimodal imaging

Patient	Eye	CF/bio-microscopy	OCT	Flow on B-scan OCTA	En-face OCTA	Time since last examination (weeks)	Treatment	Response
1	L	+	+	+	+		Fill-in PRP	
		-	-	-	-	22		Regression
2	R	+	+	+	+		Fill-in PRP + aflibercept x2	
		-	+	-	-	14		Regression
		-	+	+/-	-	35		Reactivation
	L	+	+	+	+		Fill-in PRP + aflibercept x3	
		-	+	+/-	-	14		Regression
		-	+	+	-	35		Reactivation
3	L	+	+	+	-		Fill-in PRP + bevacizumab	
		-	+	-	-	5		Regression
4	R	+	+	+	+		aflibercept x5	
		Fibrous band	+	-	-	25		Regression
	L	+	+	+	+		PRP + aflibercept x5	
		-	-	-	-	25		Regression
5	R	+	+	+	+		PRP + aflibercept x4	
		Fibrous membrane	+	-	-	30		Regression
6	R	-	+	+/-	+/-			
		-	+	+	+	41	Fill-in PRP	Reactivation
	L	-	+	-	-			
		+	+	+	+	5	PRP	Reactivation
		+/-	+	+/-	+/-	5		Regression

7	L	+	+	+	+		Fill-in PRP	
		-	-	-	-	5		Regression
8	R	-	+	-	-			
		+	+	+	+	22		Reactivation
	L	-	+	-	-			
		+	+	+	+	22		Reactivation
9	L	+	+	+	+		Fill-in PRP	
		+	+	+	+	8		Resistance
10	L	+	+	+/-	+		PRP	
		↓	+/-	+/-	+/-	31		Regression
		+	+	+	+	18		Reactivation
11	R	+	+	+	+		Previous full PRP	
		+	+	+	+	14		Resistance
12	L	+	+	+/-	+			
		+	+	+	+	18	Fill-in PRP	Reactivation
		-	-	-	-	5		Regression
13	R	+/-	+	+	+		Aflipercept x1	
		+/-	+	+	+	6		Resistance

12 – Small tuft of NVD stable for years treated previously with PRP

13 – Previous full PRP and stable NV

- = Resolution of signs of activity, + = Signs of activity, +/- = minimal flow detected, CF = Color photograph, OCT = optical coherence tomography, OCTA = optical coherence tomography angiography, PRP = pan retinal photocoagulation

Table 4 – Detection rate of different examination techniques for several stages in the management of patients with proliferative diabetic retinopathy

Stage	CP/BM	OCT	OCTA B-scan flow	En face OCTA
Detection of NVD	56%	**100%**	82.9%	53.7%
Detection of NVE	72.7%	**100%**	**100%**	72.7%
Detection of NV regression	81.8%	45.5%	**100%**	81.8%
Detection of NV reactivation	50%	12.5%	**100%**	62.5%
Resistance to NV	100%	100%	100%	100%

Bold = modality with highest detection rate for the aim

CP = color photograph, BM = biomicroscopy, OCT = optical coherence tomography, OCTA = optical coherence tomography angiography