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Use of optical coherence tomography angiography for the diagnosis of age-related macular degeneration

Andreas Abou Taha[1], Daniel Lazar[2], Clara Julin[3] & Torben Lykke Sørensen[3, 4]

1) Department of Ophthalmology, Zealand University Hospital, Roskilde, 2) Department of Ophthalmology, University Hospital of Southern Denmark, Vejle, 3) Faculty of Health and Medical Sciences, University of Copenhagen, 4) Clinical Eye Research Division, Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark

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ABSTRACT

INTRODUCTION. Age-related macular degeneration (AMD) causes approximately 9% of all blindness worldwide. The introduction of optical coherence tomography angiography (OCT-A) has revealed a potential for non-invasive diagnosis of neovascular AMD (nAMD), but has yet to be proven an accurate method for nAMD diagnosis. The purpose of this study was to map the clinical use of OCT-A in nAMD diagnosis and to investigate the agreement between two consultants in diagnosing nAMD.

METHODS. A survey was administered to assess Danish ophthalmologists in nAMD diagnostic modalities. Furthermore, a prospective observational cohort study was conducted in which two consultants graded Triton and Heidelberg OCT-A in patients with suspected nAMD.

RESULTS. A total of 21 ophthalmologists completed the survey. OCT-A combined with structural OCT was the first choice for the majority (81%), whereas dye-based ophthalmic angiography was used when in doubt of the diagnosis. OCT-A was used to guide treatment decisions in 64% of patients. Some ophthalmologists (48%) had no formal OCT-A training. In the second part of the study, an agreement was recorded between the two consultants in 86% of the cases with Triton OCT-A and 66% with Heidelberg OCT-A.

CONCLUSIONS. OCT-A with structural OCT has become a primary diagnostic method of nAMD, but national guidelines are lacking. Future implementation of new diagnostic technology of nAMD should include trial-based guidelines and physician training.

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Age-related macular degeneration (AMD) affects the retina, is a leading cause of irreversible visual impairment and causes approximately 9% of all blindness worldwide [1]. AMD involves macular structure and function deterioration with distinguishable findings that become evident when patients exceed 55 years of age. AMD may be divided into dry and wet AMD; the latter is characterised by retinal neovascular complications that may lead to leakage of either intra- or subretinal fluid, haemorrhage and scarring of the retina, resulting in loss of vision [1, 2]. A structural optical coherence tomography (OCT) can only confirm and monitor fluid in the retina. To

confirm clinical suspicion of neovascular AMD (nAMD), the invasive procedure of fundus fluorescein angiography (FFA)/indocyanine green angiography (ICGA), is performed. This procedure is the current imaging gold standard [2-4]. An increased risk was recorded of allergy, nausea, vomiting, urticaria and - in severe cases - anaphylaxis due to the injection of fluorescein dye [5]. A recent and adopted neovascularisation imaging method is the non-invasive image-device optical coherence tomography angiography (OCT-A) [6]. OCT-A instrument manufacturers employ a unique algorithm and scanning protocol to acquire images of blood vessels [7-9]. Current OCT-A devices use their own algorithm to reduce artefacts in the imaging process. However, correction software still represents a significant interpretation challenge [7, 9, 10].

OCT-A reflects the movement of red blood cells, thereby depicting blood vessels. Unlike FFA/ICGA, OCT-A cannot show leakage. Therefore, OCT-A has not yet been proven as an accurate method for nAMD diagnosis [5, 11].

In Denmark, the implementation of OCT-A has been fast with little uniformity and employing a range of OCT-A devices, which resulted in a lack of practice knowledge about OCT-A interpretation for nAMD.

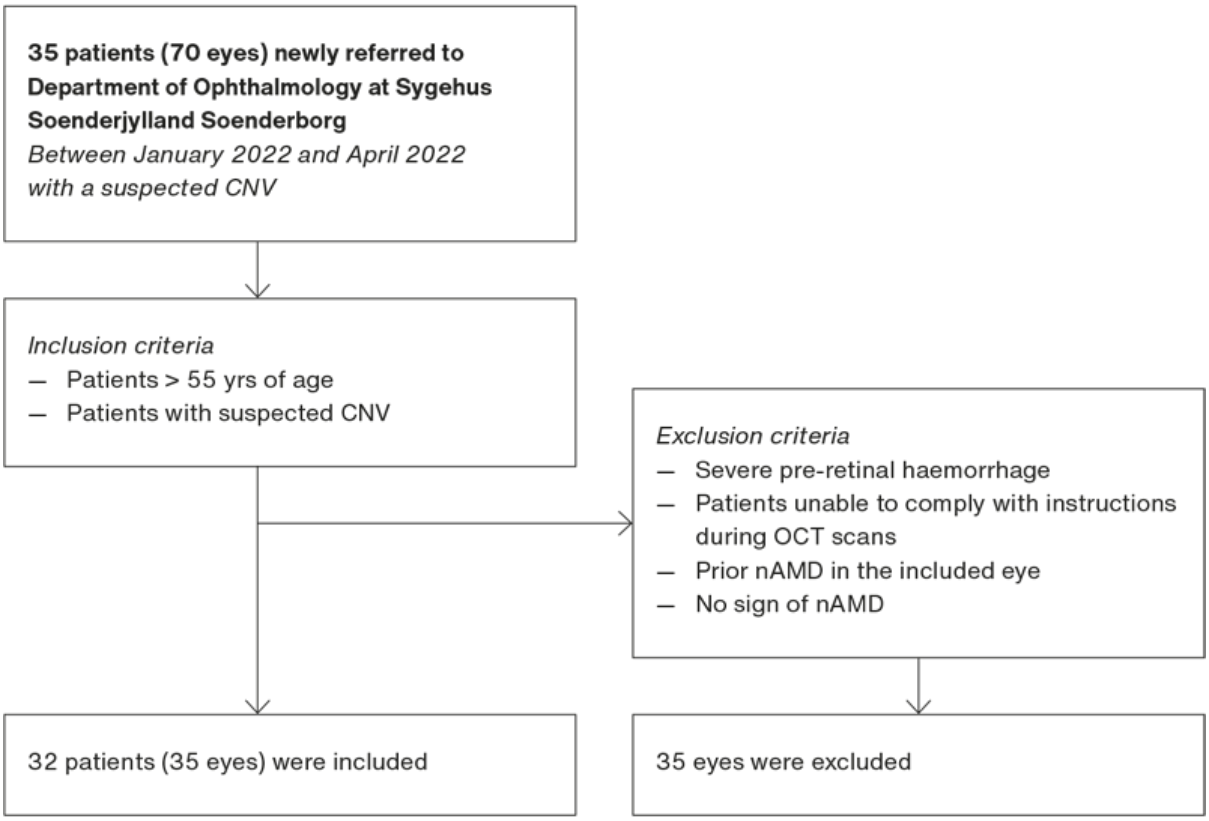
The aim of this study was to map the clinical use of OCT-A in nAMD diagnosis in Denmark and investigate the agreement between two consultants regarding the diagnosis of active choroidal neovascularisation (CNV) based on OCT-A.

METHODS

Study design and participants: Initially, a cross-sectional study was conducted in which an online self-administered questionnaire from SurveryXact with open- and close-ended questions was constructed. In total, 25 hospital ophthalmologists were invited to participate. General information about the participants was obtained, including healthcare region of employment and position, nAMD diagnostic experience in years, anti-vascular endothelial growth factor (anti-VEGF) treatment initiation and OCT-A usage. Information regarding FFA/ICGA usage, implemented OCT-A guidelines, interpretation training and usage for nAMD were noted. The survey sought to quantify the diagnostic methods based on the participant's latest ten patients with suspected nAMD for whom anti-VEGF treatment was considered. The open-ended questions enquired about the participants' reasoning in relation to choosing OCT-A and/or FFA/ICGA, their experienced limitations and their general opinion of the diagnostic methods. The questionnaire is presented in supplementary table 1 (https://content.ugeskriftet.dk/sites/default/files/2023-07/a12220780-supplementary.pdf).

Subsequently, a prospective observational cohort study was conducted assessing a total of 70 eyes in 35 patients with nAMD for eligibility. nAMD patients newly referred to the Department of Ophthalmology, Hospital Soenderjylland Soenderborg, underwent standard investigation with Triton OCT-A. Additionlly, an Heidelberg OCT-A was performed. The inclusion and exclusion criteria are shown in **Figure 1**.

FIGURE 1 Flow chart of included and excluded patients.



CNV = choroidal neovascularisation; nAMD = neovascular age-related macular degeneration; OCT = optical coherence tomography.

Image acquisition: A swept-source OCT device (Triton SS-OCT, Topcon, Tokyo, Japan) with a light source (1,050 nm) and an A-scan rate (100,000 scans per second) was used. Cube scans of 6 × 6 mm were acquired using automated layer segmentation. Patients had an additional OCT-A performed on a spectral domain OCT device (Heidelberg Engineering Spectralis HRA-2 SD-OCT-A, Heidelberg, Germany) with a 4.5 × 4.5 mm cube and a resolution of 512 × 265 mm.

Image grading and analysis: The treatment decision was made by the primary consultant who had access to all patient data and images. No grading of the primary consultant was used in this study. Two independent senior medical retina consultants graded the Triton OCT-A (the device they used in their daily practice), structural OCTs and fundus photo, while being blinded to all patient data. Three weeks after the initial grading, the same task was given for Heidelberg OCT-A, structural OCT and fundus photo. Prior to the grading, both consultants received one hour of training and instructions in the use and interpretion of Heidelberg OCT-A in relation to CNV. The grading consisted in determining whether CNV was present or not.

Approvals and ethics: Under Danish law, questionnaire survey studies are not notifiable to the National Committee on Health Research Ethics. This study was conducted in accordance with the Tenets of the Declaration of Helsinki. All participants in the second part of the study were informed verbally and in writing.

Statistical analysis

The interrater reliability between the two secondary consultants was tested by Cohen's Kappa test using Microsoft Excel 2016 Version 16.61 (22050700).

Trial registration: not relevant.

RESULTS

A total of 21 respondents in all health regions of Denmark completed the survey. All respondents had access to either Triton or Heidelberg OCT-A. Details about the respondents are provided in Supplementary table 2. Most (57%, n = 12) had no local nAMD treatment guidelines with anti-VEGF using OCT-A, whereas some (33% n = 7) had adopted local guidelines. Furthermore, a small portion (10%, n = 2) were unaware if local guidelines existed. Almost half, i.e. 48% (n = 10), had no training, 43% (n = 9) had sufficient training, 5% (n = 1) had insufficient training in OCT-A interpretation, whereas 5% (n = 1) did not answer the question. Through open-ended questions, the respondents were asked to elaborate on their use of OCT-A and/or FFA/ICGA when making treatment decisions about nAMD patients. The preferred diagnostic methods consisted mostly (81%, n = 17) of OCT-A and only FFA/ICGA as a supplementary diagnostic method, whereas some (14%, n = 3) preferred FFA/ICGA as their first choice and OCT-A as a supplementary method. One respondent had no preferred method. The majority used structural OCT to monitor activity. Reported OCT-A limitations included lack of personal experience and identification of neovascular leakage. Subpar image quality was noted due to artefacts, geographic atrophy, large retinal pigment epithelial detachments, cataract, haemorrhage and poor patient cooperation. Limitations for FFA/ICGA were reported as time-consuming, invasive, risk of side effects and the need for patient cooperation. A total of 20 out of 21 respondents had diagnosed more than ten nAMD patients in total. The preferred diagnostic methods for the responders' recent ten nAMD patients where anti-VEGF was considered was a combination of OCT-A and OCT clinical findings (49%), FFA/ICGA and OCT (24%), OCT (12%), FFA/ICGA, OCT-A and OCT (12%), OCT-A (2%) or FFA/ICGA (1%).

In the second part of this study, a total of 35 eyes (32 patients) were included among which women (62.5%) comprised the majority. The mean age was 80 years (range: 70-91 years). With Triton OCT-A, the consultants agreed 83% of the times (Cohens' kappa coefficient 0.79) and only 63% of the times (Cohens' kappa coefficient 0.57) when using Heidelberg OCT-A. The number of times that the two secondary consultants agreed on the presence of CNV are summarised in **Table 1**.

TABLE 1 Answers between two senior medical retina consultants for the presence of choroidal neovascularisation or not. Values are n.

	Consultant 2	
Consultant 1	**CNV**	**no CNV**
Triton OCT-A		
CNV	26	2
No CNV	4	3
Heidelberg OCT-A		
CNV	20	3
No CNV	10	2

CNV = choroidal neovascularisation; OCT-A = optical coherence tomography angiography.

DISCUSSION

OCT-A is a new technology with clear advantages owing to its quick and non-invasive properties. It has been suggested that applying OCT-A in combination with structural OCT and funduscopy may suffice as the primary diagnostic method [12]. Due to its limitations, OCT-A has also been suggested as a diagnostic tool complementary to FFA/ICGA [5].

This survey-based study among ophthalmologists in Denmark sought to map the use of OCT-A in diagnosis of nAMD. The results indicate that OCT-A has become widely applied in clinical practice to guide treatment decisions in a significant portion of patients with suspected nAMD. Most ophthalmologists in our study expressed that OCT-A was their primary method for deciding whether to treat suspected nAMD patients, whereas FFA/ICGA was used as an additional tool in case of doubt. Structural OCT was used to monitor nAMD, which is sensitive in illustrating the activity of CNV indirectly based on retinal fluid, but the findings are not specific to nAMD [13]. According to the Danish National Guidelines for the treatment of nAMD, CNV activity signs are required before anti-VEGF treatment.

A limitation to OCT-A is the inability to identify and diagnose CNV activity through leakage [2]. Some studies have found a correlation between the morphological appearance of CNV on OCT-A and CNV activity, whereas others found no clear correlation [3, 4]. A review found that the sensitivity and specificity of OCT-A compared with FFA/ICGA varied 50-100% and 67-100%, respectively [6]. This correlates with another study that found a high sensitivity (85-100%) and specificity (78-96%) using triton OCT-A in nAMD diagnosis, whereas another study compared Heidelberg OCT-A and OCT with FFA/ICGA and achieved a high sensitivity (89%) and specificity (87%) [2, 10]. Using a diagnostic strategy with OCT-A and structural OCT as the primary diagnostic methods and supplementing with FFA/ICGA in uncertain cases will likely lower the number of false negatives. Other

limitations to OCT-A include common image artefacts that may lead to misinterpretation, a limited field of view and the inability to visualise vessels with a slow blood flow [10, 11]. In our survey, some participants mentioned that OCT-A is performed in both eyes in all patients with suspected nAMD, even with a fellow symptom-free eye, which may lead to identification of subclinical CNV. These findings may potentially result in overdiagnosis and inappropriate treatment. Recommendations have been made for more rigorous evaluation and implementation of technology, along with its increased use, whereas a Spanish review found that the ophthalmological community has thought little about the risk of overdiagnosis [14, 15]. The high image quality of OCT-A has broadened the understanding of retinal vascular diseases. This includes identification of subclinical non-exudative CNV that is not associated with loss of visual acuity but seems to be a predictor of later development of nAMD [16]. In fact, subclinical CNV seems to have a protective effect on progression of geographic atrophy. It has therefore been suggested that treatment with anti-VEGF is not recommended until symptomatic nAMD develops [16].

The response rate was favourable compared with similar online surveys among physician specialists [17]. The geographical distribution and different levels of experience among respondents of the survey provided a representation of the population of ophthalmologists diagnosing nAMD in Denmark. The use of a self-administered online questionnaire increased the risk of non-response selection bias. It is hard to predict in which direction this influenced the results. However, it is likely that ophthalmologists with strong viewpoints for or against the use of OCT-A would want to express their opinion. The risk of recall bias was a major limitation to quantifying the exact proportion of patients diagnosed with the different diagnostic methods. To reduce this bias, the participants were solely asked about their last ten patients.

Our survey found disagreement among ophthalmologists on whether hospital departments have issued guidelines on the use of OCT-A in nAMD diagnosis. The current guidelines for anti-VEGF treatment are based on FFA/ICGA findings. Moreover, to our knowledge, clinical trials with OCT-A-based endpoints have yet to be published. More trials to establish the patient outcome of using OCT-A in the diagnosis of nAMD should be conducted to ensure best practice and define OCT-A-based guidelines. The need for standardised protocols of OCT-A image acquisition and interpretation has also been suggested [5, 11]. Our survey found that almost half of the ophthalmologists had no formal training in operating and interpreting OCT-A. A future focus should not only be on developing new technology but also on how to implement it appropriately, including the development of evidence-based guidelines and training of physicians.

In the second part of our study, the two senior medical retina consultants agreed 29 out of 35 times using Triton OCT-A and 22 out of 35 times using Heidelberg OCT-A; both supplemented by structural OCT and fundus photo. The reliability of agreement was near strong using Triton OCT-A and near moderate using Heidelberg OCT-A, respectively [18]. Both consultants agreed that their education in relation to OCT-A Heidelberg was sufficient. This indicates that some interpersonal variation of interpreting OCT-A exists and that the variation is higher if individuals have less experience with the OCT-A device. A limitation to this study was the small sample size of eligible and included patients. By blinding both secondary consultants to all patient data and separating the time at which the grading of the two OCT-A images took place, the strength was increased and bias reduced. All OCT-As were performed by the same two investigators to overcome interindividual variation in scan performance.

CONCLUSIONS

This survey mapped the use of OCT-A in Denmark and investigated the agreement between two consultants in detecting CNV in OCT-A. Despite a lack of research into the patient outcome of nAMD diagnosis from OCT-A and known limitations to the technology, this study found that OCT-A plus structural OCT has become the primary diagnostic method for guiding nAMD treatment decisions in Denmark. OCT-A plus structural OCT has become

widespread due to the convenience of a diagnostic method that is non-invasive and faster than the existing dye-based angiographies. The future focus on the implementation of new diagnostic technology like OCT-A should include trial-based guidelines and training of physicians.

Correspondence *Andreas Abou Taha*. E-mail: moskio2000@hotmail.com

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