ABSTRACT.
This work is a systematic review and meta-analysis to evaluate the diagnostic accuracy of optical coherence tomography angiography (OCTA) in the identification of choroidal neovascularization due to age-related macular degeneration (AMD) in comparison with fluorescein angiography (FA). A systematic search of the literature was carried out on Medline, EMBASE, Web of Science, Cochrane Library and Center for Reviews and Dissemination. Studies comparing OCTA with FA for the diagnosis of choroidal neovascularization due to AMD that included data on the diagnostic validity of the test or the data necessary for its calculation were selected. The QUADAS-2 tool was used to assess the risk of bias in selected studies. The quantitative analysis of the results was performed by meta-analysis. Seven primary studies were included. The quality of the evidence was good. The total population included in the meta-analysis comprised 553 eyes, with a cumulative sensitivity and specificity of 85.9% (95% CI 81.9–89.3%) and 89% (95% CI 83.5–93.2%), respectively, cumulative positive and negative likelihood ratios of 8.36 and 0.15, respectively (95% CI of 3.05–22.890 and 0.09–0.24, respectively), and a cumulative diagnostic odds ratio of 67.21 (95% CI 22.58–200.05). The evidence obtained does not demonstrate the superiority of OCTA over FA. Its use as a support technique could improve patient flow and reduce the number of FA.

Key words: age-related macular degeneration – angiography – choroidal neovascularization – optical coherence tomography

Introduction
Age-related macular degeneration (AMD) is the leading cause of blindness in people over 50 in developed countries (Pascolini et al. 2004). The EUREYE study (Augood 2006), which used a population of more than 4000 participants aged over 65 from seven European countries, reported a prevalence of 3.32%.

Wet, exudative or neovascular AMD, currently classified as late AMD, appears in 15% of AMD-diagnosed patients, in most cases accompanied by vision loss (Ardourel 2000). In this scenario, as a response to the pathological process, excessive vascularization occurs in the choroid, which can be effectively treated through intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) (Ruiz Moreno 2014). Therefore, its correct early diagnosis and follow-up are particularly relevant.

The two imaging techniques most widely used for the identification and monitoring of choroidal neovascularization (CNV) are fluorescein angiography (FA) and optical coherence tomography (OCT). Fluorescein angiography (FA) is considered the gold standard in the diagnosis of late AMD and requires the administration of intravenous contrast (sodium fluorescein), allowing two-dimensional images to be obtained in which blood flow can be dynamically visualized. It is associated with a risk of adverse reactions and anaphylaxis (López-Sáez et al. 1998). Optical coherence tomography (OCT) is a non-invasive technique based on interferometry that offers structural information from images obtained in the ocular fundus (Sánchez González 2015).

Optical coherence tomography angiography (OCTA) is an evolved form of OCT, in which computer algorithms are used to decorrelate the signals caused by tissue from those produced by moving cells, and in a
series of consecutive OCT scans at the same point, a blood flow image is generated (de Carlo et al. 2015). Therefore, like OCT is a non-invasive and fast technique, but it does not provide merely structural information. Instead, it offers an angiographic image of the fundus and has been presented as a tool with great potential for the identification and post-treatment follow-up of CNV.

The objective of this systematic review and meta-analysis was to evaluate the efficacy, in diagnostic validity terms, of OCTA in the identification of CNV due to AMD.

Methods

Systematic review and meta-analysis of the literature following the recommendations included in the PRISMA declaration (Urrutia & Bonfill 2010).

Bibliographic search

A systematic search was carried out divided into two parts: a manual search on the websites of national and international health technology assessment agencies; and a structured search in reference databases: Medline, EMBASE, Web of Science, Cochrane Library and Center of Reviews and Dissemination (the search strategy is shown in the Appendix S1). A secondary review was carried out by going through the references in the selected studies for their final analysis.

Selection criteria

The inclusion criteria were based on the PICOD (population, intervention, comparison, outcome and design) structure:

Population: Patients with suspected or confirmed diagnosis of exudative AMD.

Intervention: Optical coherence tomography angiography (OCTA).

Comparison: Fluorescein angiography (FA) or indocyanine green angiography (IGA).

Results: Efficacy (in diagnostic validity terms relating to sensitivity, specificity, predictive values and likelihood ratios, as well as the possibility of obtaining $2 \times 2$ contingency tables).

Design: Studies of diagnostic tests.

Non-original studies such as narrative reviews, letters to the editor, editorials, research notes or protocols, studies with a case-control design, abstracts from conferences and studies in languages other than Spanish, English or French were excluded.

Study selection and data extraction

Two independent reviewers performed the title and abstract screening and carried out the full-text analysis. Discrepancies were resolved by consensus. These two researchers also extracted the data, including among the variables collected general information such as the author, country, year of publication, design, inclusion and exclusion criteria, patient characteristics, as well as the intervention and comparator. Specific variables included data to construct the contingency tables, which were then used to calculate the diagnostic validity parameters with a 95% confidence interval (CI). Thus, the sensitivity, specificity, predictive values and likelihood ratios were either calculated or extracted directly from the text.

Assessment of methodological quality and synthesis of results

Methodological quality was assessed independently by two researchers, and any disagreements were resolved by consensus. The QUADAS-2 tool (Whiting et al. 2011) and Review Manager (RevMan), version 5.4 (The Cochrane Collaboration 2020, London, UK) software were used to assess bias risk.

The results of the studies were presented qualitatively and quantitatively, if cumulative results could be presented. Statistical data pooling was carried out using MetaDiSc version 1.4 statistical software. Values of $p < 0.05$ were considered statistically significant, with 95% confidence intervals and using the DerSimonian Laird random-effects method. Pooled sensitivity, specificity, positive and negative likelihood ratio and diagnostic odds ratio (DOR) values were calculated. The SROC (summary of ROC) curve was represented by the DerSimonian Laird method, and the area under the curve (AUC) was calculated.

To estimate the existence of a threshold effect, Spearman’s correlation coefficient was evaluated, and the sensitivity and specificity values of the different studies were represented in the ROC space.

The likelihood ratio test was applied to evaluate the heterogeneity of pooled sensitivity and specificity. The Cochran $Q$ test was employed to calculate the pooled likelihood ratios and pooled DOR. The inconsistency test ($I^2$) was performed for all parameters.

Results

Selection and characteristics of the studies

From a total of 770 references, 676 documents without duplicates were identified. Six hundred and twenty (620) documents were initially excluded for not meeting the inclusion criteria or for meeting any of the exclusion criteria. Of the 56 documents read in full text, seven studies of diagnostic tests were finally selected (Coscas et al. 2015; Faridi et al. 2017; Gong et al. 2016; Nikolopoulou et al. 2018; Told et al. 2018; Ahmed et al. 2019; Usman et al. 2019) for analysis (Fig. 1), four were prospective cohort studies (Faridi et al. 2017; Nikolopoulou et al. 2018; Told et al. 2018; Usman et al. 2019) and the other three were retrospective cross-sectional studies (Coscas et al. 2015; Gong et al. 2016; Ahmed et al. 2019) (Table 1).

Two of the studies were conducted in Asia, one in Pakistan (Usman et al. 2019) and the other in China (Gong et al. 2016). One more was carried out in the United States (Faridi et al. 2017). The remaining four were performed in Europe, two in Austria (Told et al. 2018; Ahmed et al. 2019), one in Italy (Nikolopoulou et al. 2018) and another in France (Coscas et al. 2015) (Table 1).

The inclusion criterion in all the studies was AMD diagnosis, with the exception of Gong et al. (2016), who used the mere suspicion of AMD without confirmatory diagnosis as an inclusion criterion. In all studies, the diagnosis had to be exudative or neovascular AMD, or there had to be at least a suspicion or signs of CNV (Usman et al. 2019), (Gong et al. 2016). Except for Ahmed et al. and Faridi et al. (Faridi et al. 2017; Ahmed et al. 2019), prior treatment of exudative AMD was not considered an exclusion criterion. Other ocular pathologies were treated as exclusion criteria, especially those associated with the presence of CNV not due to AMD (Gong et al. 2016; Nikolopoulou...
et al. 2018; Usman et al. 2019), non-exudative AMD (Usman et al. 2019) or Type 3 neovascularization in exudative AMD (Ahmed et al. 2019) (Table 1).

The mean age of the population included in the analysed studies ranged between 58.5 ± 5.05 and 77 ± 6.4 years; in several studies, the criterion for inclusion was that the patients had to be over 50 years of age (Coscas et al. 2015; Gong et al. 2016; Nikolopoulou et al. 2018; Usman et al. 2019).

All the selected studies used FA as the reference test. In two studies (Faridi et al. 2017; Ahmed et al. 2019), diagnosis was established through the combined use of FA and OCT (Table 1).

The OCTA technology used in the different selected studies covered the different options on the market. Four of the studies (Gong et al. 2016; Faridi et al. 2017; Nikolopoulou et al. 2018; Ahmed et al. 2019) were performed with Avanti® SD-OCT equipment from Optovue (Fermont, CA), which used the SSADA (Split-spectrum amplitude-decorrelation angiography) decorrelation algorithm (Jia et al. 2012). Coscas et al. (2015) used an OCTA prototype based on the Spectralis® OCT-2 (Heidelberg Engineering), which used a different algorithm (Coscas et al. 2016). Usman et al. (Usman et al. 2019) used an RS 3000® device by Nidek (Gamagori, Japan), which used the OMAG (optical micro-angiography) algorithm (An & Wang 2008), and Told et al. (2018) employed the DRI Triton® device (Topcon, Tokyo, Japan), based on the OCTARA (OCTA ratio analysis) algorithm (Stanga et al. 2016) (Table 2).

All these devices offered angiographic images of the different layers of the retina and choroid, with differences in technical aspects such as the wavelength of the laser used, scanning speed or the macular area covered by a scan. There were also differences in the applications, such as the possibility of eliminating involuntary eye movement, only offered by the Spectralis and RS 3000 (Table 2).

**Description of the quality of the studies**

The quality analysis did not reveal a high bias risk in the domains analysed using the QUADAS-2 tool (Fig. 2). Undetermined bias risk was identified in selected patients in Gong et al. (2016) and Faridi et al. (2017) as it was not clear whether the selection of cases and controls had been avoided. Two studies (Usman et al. 2019; Ahmed et al. 2019) presented undetermined risk in the intervention and the
Table 1. Characteristics of included studies and population.

| Author year | Country      | Age (Mean ± SD) | Design           | Inclusion and exclusion criteria | Intervention | Comparator |
|-------------|--------------|-----------------|------------------|----------------------------------|--------------|------------|
| Usman et al. (2019) | Pakistan      | 58.5 ± 5.05-80   | Prospective cohort | I: AMD; suspect of CNV, >50 years. E: dry AMD, CNV due to other pathologies, patients with diabetic or hypertensive retinopathy, retinal vein occlusion or pathologic myopia. | OCTA         | Nidek RS 300008 |
| Nikolopoulou et al. (2018) | Italy        | 70.9 ± 10.27        | Prospective cohort | I: exudative AMD treated or not treated, ≥50 years, adequate pupillary dilation to permit high-quality imaging. E: CNV due to other pathology, allergy to contrasts. | OCTA         | AngioVue System, XR Avanti |
| Told et al. (2018) | Austria      | 77 ± 6.4 55        | Prospective cohort | I: Active type 1 or 2 AMD. E: Type 3 or mixed AMD, or any other pathology. | SD-OCTA      |            |
| Faridi et al. (2017) | USA          | 76.7 ± 8.9 50      | Prospective cohort | I: Treatment naive neovascular AMD. E: Poor quality images. | SD-OCTA (RTVue-XR Avanti) | FA + OCT  |
| Ahmed et al. (2019) | Austria      | 75.3 ± 9.17 64.3  | Cross-sectional   | I: Treatment naive and active neovascular AMD. E: Previous treatment. | Versión beta de DRI Triton SS OCTA | FA (Spectralis HRA-OCT) |
| Gong et al. (2016) | China        | 67              | Cross-sectional   | I: >50 years, clinical features of AMD, OCTA and FA results available performed within 7 days. E: CNV due to other pathologies or cataracts. | OCTA         |            |
| (AngioVue, Avanti SD-OCT) | France      | 74.1 ± 8.5 53.4  | Cross-sectional   | I: >50 years, exudative AMD, FA y IGA. E: Previous conditions that could confound the interpretation of images. | OCTA Spectralis | FA (Spectralis HRA-OCT) |

AMD = age-related macular degeneration, CNV = choroidal neovascularization, E = exclusion criteria, FA = fluorescein angiography, I = inclusion criteria, IGA = indocyanine green angiography, N = population size, OCT = optical coherence tomography, OCTA = OCT angiography, SD-OCT = spectrum decorrelation OCT, SS-OCT = split-spectrum OCT.

reference test as they did not specify whether or not the researchers responsible for interpreting test results had been masked. The undetermined risk was also assigned in the applicability of the reference test in two studies (Faridi et al. 2017; Ahmed et al. 2019), which based the diagnosis on the combination of GA and OCT.

**Diagnostic validity**

Sensitivity ranged between 75.7% (95% CI: 68.8–82.8) and 96.6% (95% CI: 88.3–99) and specificity between 80% (95% CI: 58.4–91.9) and 100% (95% CI: 92.7–100).

Positive predictive values ranged between 80.4% (95% CI: 68.2–88.7) and 100% (95% CI: 95.5–100) and negative values between 65.3% (95% CI: 54.1–75.1) and 90.5% (95% CI: 71.1–97.3) (Table 3).

As regards the positive likelihood ratio (LR+), the studies reported disparate results ranging from high relevance for its diagnosis (LR+ > 10) (Coscas et al. 2015; Faridi et al. 2017) to values that indicated regular relevance (LR+ between 2 and 5) (Gong et al. 2016; Usman et al. 2019). The negative likelihood ratio (LR−) presented the same disparity as the LR+ ratio, but in this case, most of the studies reported high relevance (LR− < 0.1) (Coscas et al. 2015; Usman et al. 2019) or good relevance (LR− between 0.1 and 0.2) (Gong et al. 2016; Faridi et al. 2017; Nikolopoulou et al. 2018; Told et al. 2018) (Table 3).

**Meta-analysis**

For the quantitative synthesis of the results, the data extracted from all the studies analysed in this review were included, except those corresponding to the study by Told et al. (2018), because no negative cases were reported by the latter. The total population included in the calculation comprised 553 eyes (Table 4).
The value of the Spearman correlation coefficient between sensitivity and specificity was 0.486, implying a poor but direct correlation, which would not indicate the existence of a threshold effect. When representing the ROC curve with the sensitivity and specificity values reported in the studies, a scatter plot was obtained in which a threshold effect was not observed, but heterogeneity was identified.

The following estimated pooled values were obtained: sensitivity, 85.9% (95% CI: 81.9–89.3); specificity, 89% (95% CI: 83.5–93.2); positive likelihood ratio, 8.36 (95% CI: 3.05–22.890); and negative likelihood ratio, 0.15 (95% CI: 0.09–0.24). Plotting the SROC curve gave an AUC result for all studies of 0.94 ± 0.02. The cumulative DOR yielded a result of 67.21 (95% CI: 22.58–200.05) (Table 4 and Figs 3 and 4).

Heterogeneity, measured using the likelihood ratio test for pooled sensitivity and specificity and the Cochrane Q test for pooled likelihood ratios and DOR, was detected in all tests (p < 0.05). However, the small number of studies included in this meta-analysis must be taken into account, as this reduced the robustness of these tests. More reliable was the heterogeneity measured by $I^2$, which was high for sensitivity, specificity and positive likelihood ratio (74.2%, 82.6% and 77.3%, respectively) (Table 4).

### Discussion

Optical coherence tomography angiography is a recent non-invasive technology that has only been used in clinical practice for a few years. The possibility of obtaining angiograms without the need for contrast and in a matter of seconds (Vallejo et al., 2018) makes OCTA a clear alternative for identifying exudative AMD compared with conventional OCT, which provides only structural information, or FA, an invasive technique with risks of adverse reactions (López-Sáez et al. 1998).

The relevance of this study lies in the fact that, to our knowledge, no previous structured review of evidence has been performed on the diagnostic validity of OCTA in the management of exudative AMD.

### Quality of the studies and validity of the results

This systematic review and meta-analysis included seven diagnostic validity studies (Coscas et al. 2015; Gong et al. 2016; Faridi et al. 2017; Nikolopoulou et al. 2018; Told et al. 2019)
2018; Ahmed et al. 2019; Usman et al. 2019). All the included studies had low or undetermined risk of bias due to specific problems in the masking of the test (Ahmed et al. 2019; Usman et al. 2019) or in the applicability of the OCT reference test (Faridi et al. 2017; Ahmed et al. 2019).

The populations studied followed similar inclusion and exclusion criteria. All of them reported confirmed or suspected diagnosis of exudative AMD. The study designs were also similar; hence, the clinical heterogeneity between the studies was low. No threshold effect was detected. For all these reasons, the decision was taken to carry out a quantitative synthesis of the results, despite the relatively small number of primary studies.

The meta-analysis revealed the good diagnostic capacity of OCTA to detect exudative AMD, with pooled values of 85.9% for sensitivity, 89% for specificity and 0.15 for positive and negative likelihood ratios, respectively. All these results were equivalent to those obtained for OCT in other studies in similar applications (National Institute for Health & Care Excellence (UK) 2018; Faes et al. 2019). Furthermore, the cumulative DOR value was high and significant, with a confidence interval far from unit (67.21; 95% CI: 22.58–200.05) (Table 4).

These results must be qualified by the presence of heterogeneity in the meta-analysis, detected by p-values of <0.05 in the chi-squared test in all the calculated parameters, as well as $I^2$ values $>$ 50% for DOR and pooled likelihood ratios and $I^2$ $>$ 75% for pooled sensitivity and specificity.
The sources of this heterogeneity can be traced across multiple items. An important source of diversity was the different devices and software that were used to perform OCTA: RS 3000/C210 (Usman et al. 2019), DRI Triton/C210 (Told et al. 2018), Avanti/C210 (Gong et al. 2016; Faridi et al. 2017; Nikolopoulou et al. 2018; Ahmed et al. 2019) and Spectralis/C210 (Coscas et al. 2015), with different scanning speeds or covered areas, which necessarily added dispersion as OCTA is more device-dependent than FA or OCT (Table 2).

Despite their similar clinical characteristics, there might be racial differences in CNV because the origin of the populations differed substantially, as several studies were carried out in Europe (Nikolopoulou et al. 2018; Told et al. 2018; Ahmed et al. 2019; Coscas et al. 2015), another in the United States (Faridi et al. 2017) and two more in Asia (Gong et al. 2016; Usman et al. 2019). One of the studies included in the analysis (Faridi et al. 2017) used combined FA and OCT as the reference test. Finally, two studies (Faridi et al. 2017; Told et al. 2018) excluded anti-VEGF-treated patients; the others included both treated and untreated patients. Anti-angiogenic treatment produces changes in the lesions detected; hence, these should be treated as different populations, or at least taken into account in the results.

The studies analysed were Sackett’s phase II or III diagnostic tests, which usually comprise a highly selected population suspected of suffering from the disease. Hence, the prevalences in the studied populations were very high, ranging between 44% and 82.5% (Table 1). These very high prevalences, in contrast with the general population but normal in these types of studies, can result in overestimation of the diagnostic validity parameters.

**Limitations of the technology**

False negatives were reported in all the studies and, with the exception of Ahmed et al. (2019), false positives were also observed due to the two main limitations of OCTA, namely the presence of artefacts in images and the impossibility of identifying leakage or detachment (Spaide, Klancnik, & Cocnay 2015; Vallejo et al. 2018). The presence of large haemorrhages, serous leakage or retinal pigment epithelium detachment can conceal the presence of CNV. In contrast, several studies reported false positives that turned

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**Table 4. Meta-analysis.**

| Pooled variable (N = 553) | Usman et al. | Nikolopoulou et al. | Faridi et al. | Ahmed et al. | Gong et al. | Coscas et al. |
|--------------------------|-------------|---------------------|--------------|-------------|-----------|--------------|
| Threshold effect: Spearman’s $r$ | 0.49 | 0.94 ± 0.019 | 0.86 (0.82-0.89) | 19.34; $p = 0.002$ | 0.89 (0.83-0.93) | 74.2% |
| Sensitivity (%) (CI 95%) | 82.6% | 77.3% | 82.6% | 77.3% | 82.6% | 77.3% |
| Heterogeneity Likelihood ratio test | Cochran Q test | Cochran Q test | Cochran Q test | Cochran Q test | Cochran Q test | Cochran Q test |
| Specificity (%) (CI 95%) | 82.6% | 77.3% | 82.6% | 77.3% | 82.6% | 77.3% |
| Heterogeneity Likelihood ratio test | Cochran Q test | Cochran Q test | Cochran Q test | Cochran Q test | Cochran Q test | Cochran Q test |
| LR+ | 21.3 | 8.36 (3.06-22.89) | 22.05; $p = 0.001$ | 19.5 | 8.73 | 23.94 | 17.70 |
| Weight (%) (95% CI) | 14.33 | 0.15 (0.097-0.24) | 12.38; $p = 0.03$ | 17.11 | 26.19 | 17.09 | 8.08 |
| LR− | 20.61 | 67.21 (22.58-200.05) | 11.54; $p = 0.042$ | 20.11 | 10.17 | 24.31 | 15.14 |
| LR+ | 20.61 | 67.21 (22.58-200.05) | 11.54; $p = 0.042$ | 20.11 | 10.17 | 24.31 | 15.14 |
| LR− | 20.61 | 67.21 (22.58-200.05) | 11.54; $p = 0.042$ | 20.11 | 10.17 | 24.31 | 15.14 |

AUC = area under the ROC curve, DOR = diagnostic odds ratio, LR+/LR− = likelihood ratio $+/−$, N = population size (number of eyes).
out to be CNV not detected by angiography and that had to be treated (Usman et al. 2019) or that corresponded to quiescent neovessels not detected by FA (Gong et al. 2016; Nikolopoulou et al. 2018).

Several studies used systems to reduce the presence of artefacts due to eye movement and projection of blood vessels (Coscas et al. 2015; Gong et al. 2016; Faridi et al. 2017; Told et al. 2018; Usman et al. 2019) (Table 2), although it must be highlighted that the use of these methods could result in the loss of information (Usman et al. 2019), and that the abundance of artefacts produced by differences in signal, projection of upper layers or eye movements required continuous manual corrections (Told et al. 2018) and that artefacts were, therefore, the main cause of false positives (Gong et al. 2016; Faridi et al. 2017).

Two studies (Nikolopoulou et al. 2018; Told et al. 2018) reported poorer diagnostic capacity of OCTA in the identification of type 1 exudative AMD.

Finally, as OCTA is an imaging technique, users are normally required to be very well trained to ensure its correct interpretation. Notwithstanding the foregoing, it is subject to significant subjectivity less present in more easily quantifiable techniques.

It is important to highlight certain limitations usually present in meta-analyses. The inclusion of only published studies could have favoured the location bias of the works as the journals not indexed in some of the main databases were not available. Moreover, among the published studies, those reporting significant results are more likely to be published in English, cited and published repeatedly, leading to bias in favour of the English language, citation bias and multiple publication bias. The small number of included studies precluded a study on publication bias.

In sum, the evidence does not demonstrate the superiority of OCTA over FA, and it has important limitations, such as the presence of abundant artefacts in images and the inability to detect fluids from haemorrhages, serious exudate or retinal pigment epithelium detachment, which compromise its usefulness as the only diagnostic technique in exudative AMD. However, OCTA has reached a level of technical development that offers seemingly proven effectiveness in the diagnosis of CNV in the context of AMD, and if used in combination with OCT and FA, which are both capable of overcoming the shortcomings of OCTA, it could be extremely helpful in the management of patients with neovascular lesions due to AMD and in making decisions to start or continue anti-angiogenic treatment. Optical coherence tomography angiography (OCTA) can be used in the follow-up of these patients to speed up patient flow and reduce the impact of tests in the latter. Also, OCTA could be useful in the detection of quiescent neovessels not detected by FA, and its potential relevance in the identification of this entity has not been explored.

More evidence would be needed on the diagnostic capacity of OCTA in treated and untreated populations, analysed separately. Likewise, it would be important to study the capacity of OCTA to differentiate between different types of exudative AMD. The impact of concomitant and potentially interfering diseases with AMD has not been sufficiently studied.
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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategies