Ophthalmologica

Review Article

Ophthalmologica 2021;244:387–395
DOI: 10.1159/000513591

Received: August 31, 2020
Accepted: December 3, 2020
Published online: December 7, 2020

Use of Composite End Points in Early and Intermediate Age-Related Macular Degeneration Clinical Trials: State-of-the-Art and Future Directions

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Keywords
Age-related macular degeneration · Composite end points · Trial outcomes

Abstract
The slow progression of early age-related macular degeneration (AMD) stages to advanced AMD requires the use of surrogate end points in clinical trials. The use of combined end points may allow for shorter and smaller trials due to increased precision. We performed a literature search for the use of composite end points as primary outcome measures in clinical studies of early AMD stages. PubMed was searched for composite end points used in early/intermediate AMD studies published during the last 10 years. A total of 673 articles of interest were identified. After reviewing abstracts and applicable full-text articles, 33 articles were eligible and thus included in the qualitative synthesis. The main composite end point categories were: combined structural and functional end points, combined structural end points, combined functional end points and combined multicategorical end points. The majority of the studies included binary composite end points. There was a lack of sensitivity analyses of different end points against accepted outcomes (i.e., progression) in the literature. Various composite outcome measures have been used but there is a lack of standardization. To date no agreement on the optimal approach to implement combined end points in clinical studies of early stages of AMD exists, and no surrogate end points have been accepted for AMD progression.

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Introduction

Age-related macular degeneration (AMD) is one of the major causes of visual loss in the elderly worldwide, impairing physical, emotional and social well-being of those affected [1–3]. Due to population aging, patient numbers are expected to increase significantly over the next decades [4, 5]. While people with early stages of AMD are often asymptomatic under everyday lighting conditions, individuals with advanced AMD may develop irreversible central scotoma due to atrophy of outer retinal layers or choroidal neovascularization [2, 6, 7]. At present, therapies are only available for neovascular AMD. However, new therapies preventing nonadvanced disease from progressing are required to reduce the global burden of blindness due to AMD.

No clinical trial end points have been developed for this indication yet. In neovascular AMD trials, high luminance high contrast best-corrected visual acuity (BCVA) is an end point accepted by the regulatory authorities but BCVA is not sensitive enough to measure the functional deficit specific to early and intermediate AMD. Those are stages in which BCVA is largely unaffected but the visual deficit is prominent under low luminance or low contrast conditions [6, 7]. Progression from early AMD stages to advanced AMD is a slow process [8]. Thus, new surrogate end points for the progression of early and intermediate AMD to advanced AMD are needed [9].

Various end points, including structural, functional and patient-reported variables, have been implemented in previous studies of early AMD stages [10–19]. Composite end points summarize single end points across these different categories, increasing the overall sensitivity of the end point for reaching accepted outcomes (i.e., progression). If used in clinical trials, more sensitive composite end points would thus allow for smaller and shorter trials to be performed, without a reduction in statistical power [20, 21]. Sophisticated composite end points have been proposed for longitudinal studies in glaucoma but their relevance to current AMD research is unclear [22]. In order to assess the current state of relevant available research we reviewed the literature for the use of composite end points as primary outcome measures in clinical studies of early AMD stages.

Methods

PubMed was searched in August 2020 using the following search terms: age-related macular degeneration, early, intermediate, nonexudative, nonadvanced, Age-Related Eye Disease Study (AREDS) 2/3, end point, outcome and biomarker. All relevant abstracts were reviewed, and full-text articles were downloaded when indicated. Inclusion criteria were interventional or longitudinal studies on early or intermediate AMD including primary composite end points. Only studies published within the last 10 years were considered. Exclusion criteria were articles dealing primarily with neovascular AMD, geographic atrophy or diseases other than AMD, articles focusing mainly on serum biomarkers as well as articles in languages other than English.

Results

Our initial search yielded a total of 673 articles of interest. After screening the abstracts, 601 articles did not meet the inclusion criteria and were therefore excluded. We thus assessed 72 full-text articles for eligibility. Thirty-nine of these articles were excluded based on full-text assessment. Reasons for exclusion were: 25 studies did not implement composite end points, 4 investigated a healthy cohort, 3 were cross-sectional studies, 2 included participants with only late AMD, 2 were reviews, 1 was focused on serum biomarkers, 1 was focused on device-related instead of disease-related outcomes, 1 investigated single cases only. Thus, we included 33 articles in the qualitative synthesis. Twenty-two of these articles were published between 2016 and 2020 while 11 articles were published between 2010 and 2015.

Combined Structural and Functional Outcomes

Our search revealed 8 articles (7 studies) that implemented combinations of structural and functional outcome measures (Table 1); 4 of the studies were interventional [10–15, 19, 23]. Chew et al. [10, 12] combined fundus photography-based structural outcome measures providing evidence of progression to late AMD with BCVA loss in follow-up reports of the AREDS. Nittala et al. [14] combined thickness assessment of the retinal pigment epithelium (RPE)-drusen complex on optical coherence tomography and low luminance visual acuity in a longitudinal cohort study of 85 fellow eyes of neovascular AMD eyes. Robinson et al. [13] used onset of late AMD, increase in drusen volume and changes in the cone time constant in adaptometry as primary co-outcome measures in a randomized trial of light therapy with 60 participants [23]. Guymer et al. [11] investigated the primary outcome measures BCVA, drusen area and macular sensitivity on flicker perimetry in a pilot trial on nanosecond laser therapy with 50 participants. Recently, Saßmannshausen et al. [15] investigated point-wise sensitivity changes and retinal thickness changes as main outcome measures in a longitu-

Table 1. Composite end points identified in systematic literature search (2010–2020)

Authors	Year	Composite outcomes	Study type	Sample
Combined structural and functional outcomes				
Chew et al. [10]	2013	Progression to nvAMD, progression to central GA, visual acuity loss ≥15 letters	RCT	10-year follow-up of 4,757 AREDS participants
Chew et al. [12]	2014	Progression to nvAMD, progression to central GA, visual acuity loss ≥15 letters	RCT	10-year follow-up and risk factor assessment of 4,757 AREDS participants
Guymer et al. [11]	2014	Best-corrected VA, drusen area, macular sensitivity in flicker perimetry	Interventional	1-year pilot study on nanosecond laser therapy in 50 participants with bilateral iAMD
Robinson et al. [13]	2018	Progression to nvAMD, increased drusen volume, change in time constant of cone dark adaptation	RCT	1-year phase I/IIa study on light therapy in 60 early AMD eyes with nvAMD fellow eyes
Nittala et al. [14]	2019	Retinal layer thickness change, VA change	Natural history	2-year study of 85 eyes with nvAMD fellow eyes
Saßmannshausen et al. [15]	2020	Point-wise correlation of retinal sensitivity to corresponding standardized point-wise retinal thickness	Natural history	3-year structure-function correlation study of 59 iAMD eyes
Saßmannshausen et al. [15]	2020	Point-wise correlation of retinal sensitivity to corresponding standardized point-wise retinal thickness	Natural history	3-year structure-function correlation study of 30 iAMD eyes with predominantly reticular pseudodrusen
Combined structural outcomes				
Alexandre de Amorim Garcia Filho et al. [37]	2013	Changes in drusenoid pigment epithelial detachment area, progression to nvAMD, progression to GA	Natural history	Longitudinal study of drusenoid pigment epithelial detachments in 186 eyes with nonadvanced AMD
Guymer et al. [24]	2013	Progression to nvAMD, progression to GA, progression to higher severity scores of non-advanced AMD	RCT	3-year study on simvastatin use in 114 participants with iAMD
Seddon et al. [38]	2013	Progression to nvAMD, progression to GA	Validation	5- and 10-year analysis of 2,914 AMD participants and predictive modeling
Myers et al. [32]	2014	Progression on the 3 continent AMD consortium age-related macular degeneration severity scale	Natural history	20-year analysis of 4,439 participants from the Beaver Dam Eye Study, focusing on cigarette smoking
Wu et al. [17]	2014	Subsidence of the OPL and inner nuclear layer, development of a hyporeflective wedge-shaped band within the limits of the OPL	Validation	Retrospective analysis of 16 AMD eyes before development of geographic atrophy
Joachim et al. [34]	2015	Progression to nvAMD, progression to GA	Natural history	15-year analysis of 2,474 population-based participants of the Blue Mountains Eye Study
Abdelfattah et al. [36]	2016	Progression to nvAMD, progression to GA	Validation	Retrospective 2-year analysis of 89 early/iAMD eyes with nvAMD fellow eyes focusing on drusen volume
Folgar et al. [25]	2016	Progression to nvAMD, progression to GA	Validation	2-year analysis of RPE-DC including 345 AMD eyes from the AREDS 2 ancillary SD-OCT study
Liew et al. [35]	2016	Progression to nvAMD, progression to GA	Natural history	5- and 10-year analysis of 3,640 participants from the AREDS and the Blue Mountains Eye Study

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Table1 (continued)

Authors	Year	Composite outcomes	Study type	Sample
Veerappan et al. [18]	2016	Pre-atrophic OCT findings, progression to (central) GA, progression to nvAMD	Validation	3-year analysis of reflective drusen substructures including 349 AMD eyes from the AREDS 2 ancillary SD-OCT study
Burlina et al. [33]	2018	Progression to nvAMD, progression to GA	Validation	5-year analysis of fundus photographs and risk of progression using a deep learning approach in 4,613 AREDS participants
Joachim et al. [28]	2018	≥1-step/≥2-step progression on the 3 continent AMD consortium 5-step severity scale	Natural history	10-year analysis of 835 participants at early AMD stages from the Blue Mountains Eye Study and Rotterdam Study
Schmidt-Erfurth et al. [26]	2018	Progression to nvAMD, progression to GA	Validation	2-year analysis of quantitative OCT features preceding progression in 495 iAMD eyes
Chiang et al. [30]	2020	Modified AREDS severity scale	Validation	Includes a 4-year analysis of macular thickness in 77 eyes with no to intermediate AMD
Kim et al. [41]	2020	Drusen area, pigment epithelial detachment height	Interventional	12-month report of efficacy and safety of laser photocoagulation and antivascular endothelial growth factor in 20 patients with drusenoid pigment epithelial detachments
Nassisi et al. [40]	2019	Progression to nvAMD, progression to GA	Validation	2-year post hoc analysis of 501 early/iAMD fellow eyes of nvAMD eyes included in the HARBOR study
Piatti et al. [27]	2020	Macular hemorrhage, progression of atrophic areas	RCT	2-year nutritional supplementation study in 74 participants with iAMD
Sitnilska et al. [39]	2020	Progression to nvAMD, progression to GA	Validation	Longitudinal study of CFP, SD-OCT and IR imaging in 232 early/iAMD participants
Thiele et al. [29]	2020	Progression to nvAMD, progression to GA	Validation	6-year study of retinal layer thicknesses in 91 early/iAMD eyes
Waldstein et al. [31]	2020	Progression to nvAMD, progression to macular GA	Validation	2-year analysis of quantitative OCT features preceding progression in 309 early/iAMD eyes with nvAMD fellow eyes included in the HARBOR study
Combined functional outcomes				
Wu et al. [6]	2015	Retinal sensitivity (microperimetry), low-luminance VA	Natural history	1-year study of 41 participants with iAMD and 8 participants with extrafoveal GA
Hsu et al. [42]	2019	Multiple functional assessments	Natural history	1-year study including 66 early/iAMD participants
Combined multicategorical outcomes				
Finger et al. [43]	2019	Multiple structural, functional and patient-reported assessments	Natural history	3-year study of 650 early/iAMD participants (*description of study protocol*)
Curcio et al. [45]	2020	Multiple structural, functional and patient-reported assessments	Natural history	3-year study of 480 normal aging changes/early AMD participants (*description of study protocol*)

AREDS, Age-Related Eye Disease Study; CFP, color fundus photography; GA, geographic atrophy; iAMD, intermediate age-related macular degeneration; IR, infrared; nvAMD, neovascular age-related macular degeneration; OPL, outer plexiform layer; RCT, randomized, controlled trial; RPE/DC, retinal pigment epithelium-drusen complex; SD-OCT, spectral-domain optical coherence tomography; VA, visual acuity.

dinal study of 54 patients with intermediate AMD and in 25 patients with intermediate AMD and predominantly subretinal drusenoid deposits [19].

Combined Structural Outcomes

We identified 20 articles focusing on combined structural outcome measures (Table 1), 3 of which were interventional [17, 18, 24–41]. Twelve of these 20 articles included progression to late-stage AMD (development of choroidal neovascularization or geographic atrophy) as a composite end point [25–27, 29, 31, 33–36, 38–40]. Four of the articles reported the use of specific severity scales based on the anatomical AMD classification and implementing an additive structure (including increased drusen size and/or pigmentation as well as progression to late AMD) as the main outcome measure [24, 28, 30, 32]. Four other reports combined structural outcome measures different from the ones described. Wu et al. [17] defined 2 optical coherence tomography-based biomarkers (subsidence of the outer plexiform layer and inner nuclear layer and development of a hyporeflective wedge-shaped band within the limits of the outer plexiform layer) and combined them to the outcome measure "nascent geographic atrophy" in their analysis of 181 participants. Veerappan et al. [18] used a set of pre-atrophic findings (including RPE-drusen complex thinning, RPE disruption, photoreceptor layer thinning) and progression to late-stage AMD as primary outcome measures in their analysis of 349 participants of the ARED Study 2 ancillary spectral-domain optical coherence tomography study. Alexandre de Amorim Garcia Filho et al. [37] combined progression to late AMD with changes of the area of pigment epithelial detachments on optical coherence tomography to a main outcome measure. Kim et al. [41] combined drusen area on fundus photography and pigment epithelial detachment height on optical coherence tomography as primary co-outcomes.

Combined Functional Outcomes

Two studies combined different functional outcomes (Table 1). Wu et al. [6] described pointwise sensitivities obtained from fundus-controlled perimetry (microperimetry) as well as low luminance visual acuity (LLVA) in a longitudinal study of 49 participants with nonadvanced AMD. Hsu et al. [42] investigated several functional end points (BCVA, LLVA, low luminance deficit, percent-reduced threshold and average threshold from fundus-controlled perimetry as well as cone contrast tests) in 85 participants with early/intermediate AMD and healthy control participants longitudinally.

Combined Multicategorical Outcomes

In addition, we identified 3 reports that included end points from more than 1 of the outcome categories mentioned above (Table 1). Two reports described the MACUSTAR study, a longitudinal study validating various functional, structural and patient-reported outcome measures in a large cohort of intermediate AMD patients which is still ongoing [43, 44].

Curcio et al. [45] described the use of various outcomes (obtained from rod-mediated dark adaptation, 2-color dark-adapted microperimetry, light-adapted perimetry, photopic acuity, mesopic acuity, photopic contrast sensitivity, mesopic contrast sensitivity, color fundus photography, near-infrared reflectance, optical coherence tomography angiography, quantitative autofluorescence, low luminance questionnaire, Vision in Low Luminance questionnaire and other assessments) in the Alabama Study on Early Age-Related Macular Degeneration 2 (ALSTAR2) which is also ongoing.

Sensitivity of Composite End Points

None of the articles compared sensitivities of single end points for reaching accepted outcomes to sensitivities of composite end points.

Discussion

Several variations of combined outcome measures and composite end points have been used in clinical studies of early and intermediate AMD. The most frequent combinations were those of various structural end points, followed by combinations of structural and functional end points. However, no structural clinical trial end point except the relatively rare event of progression to advanced neovascular or atrophic AMD is currently accepted by regulatory authorities and health technology assessment bodies [43]. Due to increasing numbers of patients with AMD, new therapies are urgently required and for this, validated end points are a prerequisite to enable future therapeutic developments [4].

In the 2017 National Eye Institute/United States Food and Drug Administration end point workshop on AMD, the potential benefit of using surrogate end points as predictors of a clinically meaningful outcome (such as photoreceptor loss) was highlighted [7]. We have identified several combined AMD outcome measures used as surrogates for the loss of photoreceptors reported in the literature. The majority are simple binary outcome measures indicating that a catalogue of single yes- or no-type

end points are combined [20, 21]. Usually, the overall end point is reached when at least one of the single end points is reached (Boolean OR operator). An example used by many of the studies identified in our review is conversion to late AMD which includes the single end points "conversion to neovascular AMD" and "conversion to geographic atrophy" [25–27, 29, 39, 46]. This composite end point reflects the strong association between vision loss and the presence of any advanced disease stage [1, 3] and is an accepted end point by regulatory authorities [43]. However, due to the relatively slow progression of AMD (on average 5–20 events per 100 person-years) and the need for shorter trial durations for novel future therapeutics [43, 47], it is unsuitable for studies of early or intermediate AMD. Thus, end points associated with earlier AMD disease stages and with a high sensitivity for progression are required. Progression of classic structural parameters such as drusen size or hyperpigmentation (and their correlates on optical coherence tomography) do not show strong enough associations with vision loss to be acceptable to regulators [48]. The composite end point nascent geographic atrophy appears to be a promising predictor of atrophy development, yet it is not associated with neovascular AMD and does not include a functional dimension, as desired by regulatory agencies [7, 17]. With respect to functional end points, BCVA has been shown to be insensitive to the deficit specific to early AMD stages and seems to be inappropriate both as a single end point and as part of an intermediate AMD-targeted composite end point from what is currently known [6, 7]. Other functional variables like LLVA, microperimetry and dark adaptometry appear more promising but lack data over the long term [6, 11, 13, 15]. In summary, we have found different approaches of using binary outcome measures in the literature but none seems to be ready for use in prospective large-scale clinical trials.

Another potential composite end point category is continuous end points which use scores calculated from the single end points of different levels of measurement. Composite scores have been sparsely used in AMD studies to date. However, continuous composite end points have a high potential because they allow integration of different outcome categories and thus can lead to an increase in statistical power within treatment studies when carefully validated [49]. Sensitivity testing and a validation of different composite end points in AMD research have yet to be performed which is why the MACUSTAR and ALSTAR2 studies as well as the AMD Ryan Initiative Study (ARIS) are currently being conducted [43–45, 50].

Similarly to composite end points, a variety of single outcomes have been associated with progression to late-stage disease [3, 36, 51–64]. Schaal et al. [65] have published a comprehensive review of anatomical end points in nonexudative AMD. Overall, many different composite end points are available in the literature, but broader consensus definitions of AMD outcome measures are required [7].

The use of composite end points is also met with interest in other areas of ophthalmology. Due to the absence of a gold standard of determining physiological changes versus disease progression, glaucoma researchers use surrogate end points regularly including intraocular pressure and certain visual field indices [66]. These single surrogate end points can be combined to composite scores. Such composite end points in glaucoma have been demonstrated to increase accuracy of prediction of progression, reduce measurement variability and require smaller sample sizes than single end points derived from, for example, perimetry [22, 67]. Similarly, the role of surrogate end points as well as composite end points in clinical studies of dry eye disease is growing [68, 69]. Specifically, various clinical scores are used as end points, enabling the development of continuous composite end points [68].

Beyond ophthalmology, composite end points have been met with considerable interest in the context of Alzheimer's disease where combined cognitive and functional outcome measures have gained in importance over the last few years [70]. An analysis of 2 expedited pharmaceutics approval pathways of the European Medicines Agency across specialities between 2011 and 2018 showed that the majority of authorizations was based on surrogate end points, and a relevant number of authorizations included composite end points [71]. Thus, reliable and valid composite end points are required to enable future therapeutic developments in intermediate AMD, which represent a huge unmet need.

The strengths of our work include the systematic review of the available literature as well as the data synthesis and categorization into different types of composite end points. The focused search of only one data base (PubMed) may limit generalizability of results and reduce completeness. However, a high number of relevant studies can generally be expected to be published in journals indexed in PubMed.

In conclusion, the use of composite end points and combined outcome measures in longitudinal and interventional studies of early and intermediate AMD is increasing. Various composite measures have been used but there is a lack of standardization and validation. To date no agreement on the best approach to implement combined end points in clinical trials of early stages of AMD exists.

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Acknowledgments

We are very grateful for the continuous support provided by Nathalie Seigneuret at the IMI Office in Brussels. We also gratefully acknowledge the work put into this project by consortium members who have since moved on to work elsewhere.

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Conflict of Interest Statement

J.H.T.: Heidelberg Engineering, Optos, Zeiss Meditec, CenterVue. S.S.-V.: Acucela/Kubota Vision Apellis, Novartis, Allergan, Bayer, Bioeq/Formycon, Carl Zeiss Meditec, CenterVue, Galimedix, Roche; Heidelberg Engineering, Katairo, Optos, Oxurion, Roche/Genentech. D.P.C.: Allergan, Roche, Santen, Centervue. H.D.: Boehringer-Ingelheim. U.F.O.L.: employee of F. Hoffmann-La Roche Ltd. C.B.: none. M.S.: Pixum Vision. R.S.: Allergan, Allimera Sciences, Bayer, Novo Nordisk, Novartis, Thea, Roche. J.C.-V.: Aerpio Therapeutics, Alimera Sciences, Allergan, Bayer, Boehringer-Ingelheim, Novartis, Zeiss Meditec, Oxular Ltd. A.T.: none. G.W.: employee of Novartis Pharma AG. S.L.: employee of Bayer AG. F.G.H.: Acucela, Allergan, Apellis, Bayer, Boehringer-Ingelheim, Bioeq/Formycon, CenterVue, Ellex, Roche/Genentech, Geuder, Grayburg Vision, Heidelberg Engineering, Kanghong, LinBioscience, NightStarX, Novartis, Optos, Pixium, Vision, Oxurion, Stealth BioTherapeutics, Zeiss. R.P.F.: Novartis, Bayer, Allergan, Alimera, Roche/Genentech, Santhera, Opthea, Inositec, Ellex, CentreVue, Zeiss, Heidelberg Engineering.

Funding Sources

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking 439 under grant agreement No. 116076. This Joint Undertaking receives support from the 440 European Union's Horizon 2020 research and innovation programme and EFPIA.

Author Contributions

F.G.H., R.P.F., S.S.-V., M.S., U.F.O.L., D.P.C., H.D., A.T., J.C.-V. and R.S. designed the study. J.H.T. compiled the data set. J.H.T, R.P.F., S.S.-V., C.B., D.P.C., S.L. and M.S. wrote the manuscript. All authors contributed substantially to the conception or design of the study, data acquisition, data analysis or data interpretation as well as to drafting the manuscript or critically revising it. They approved the final version to be published.

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