University of Dundee

Evaluation of coronary artery disease as a risk factor for reticular pseudodrusen

McCarter, Rachel V.; McKay, Gareth J.; Quinn, Nicola B.; Chakravarthy, Usha; MacGillivray, Tom J.; Robertson, Gavin; Pellegrini, Enrico; Trucco, Emanuele; Williams, Michelle C.; Peto, Tunde; Dhillon, Baljean; van Beek, Edwin Jr; Newby, David E.; Kee, Frank; Young, Ian S.; Hogg, Ruth E.

Link to publication in Discovery Research Portal

1 **Evaluation of Coronary Artery Disease as a Risk Factor for**

2 **Reticular Pseudodrusen.**

3

4 *McCarter RV,[1] McKay GJ,[1] Quinn NB,[1] Chakravarthy U,[1] MacGillivray*

5 *TJ,[2] Robertson G,[2] Pellegrini E,[2] Trucco E,[3] Williams MC,[4] Peto T,[1]*

6 *Dhillon B,[2] van Beek EJR,[5] Newby DE,[4] Kee F,[1*] Young IS,[1*] Hogg RE.[1a]*

7

8 *[1]Center for Public Health, Queen's University Belfast. [2]VAMPIRE project,*

9 *Center for Clinical Brain Sciences, The University of Edinburgh.*

10 *[3]VAMPIRE project, Computing, School of Science and Engineering,*

11 *University of Dundee. [4]Center of Cardiovascular Science, University of*

12 *Edinburgh. [5]Clinical Research Imaging Center, University of Edinburgh.*

13 * NICOLA Study Principal Investigator and Study Originator

14

15 *[a]Corresponding author: Dr Ruth E. Hogg

16 Center for Public Health, Queen's University Belfast, Institute of Clinical Science

17 Block A, Royal Hospital, Grosvenor Road, Belfast, Northern Ireland, BT12 6BA.

18 Email: r.e.hogg@qub.ac.uk

19 Word count: 3143

20

ABSTRACT

Purpose: Reticular pseudodrusen (RPD) is a risk factor for late age-related macular degeneration (AMD). Associations between RPD and coronary artery disease (CAD) have been reported from small case-control studies. This study investigated the association of RPD within a predominantly CAD cohort.

Methods: A subgroup of subjects from a multicenter randomized controlled trial of computed tomography coronary angiography (CTCA) underwent ultra-widefield (UWF) retinal imaging CAD determined by CTCA was categorized as normal, non-obstructive or obstructive Specific AMD features in UWF images were graded Standardized grids were used to record the spatial location of AMD features, including RPD. Multivariate confounder adjusted regression models assessed the association between RPD and CAD.

Results: The 534 participants were aged from 27-75 years (mean 58 ±9 years; 425 (80%) ≥50 years) with a male preponderance (56%). Within the study sample, 178 (33%) had no CAD, 351 (66%) had CAD, 182 (34%) had hypertension and 42 (24%) had neither CAD nor hypertension. RPD was detected in 30 participants (5.6%) and bilaterally in 23. Most participants with bilateral RPD had drusen >125 μm (early AMD). After adjustment for potential confounders (age, sex, drusen >125 μm, smoking status), multivariate analysis found no significant association between CAD and RPD (odds ratio [OR] 1.31; 95% Confidence Interval [CI] (0.57-3.01); p=0.52). A significant association was identified between RPD and drusen >125 μm (OR 3.18; 95% CI (1.61-6.27); p= 0.001).

44   **Conclusion:** We found no evidence to support an association between CAD

45   and RPD. RPD was strongly associated with early AMD features, when

46   present.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of permanent blindness in the developed world with the most sight loss occurring in the late stages, namely geographic atrophy (GA) and choroidal neovascularization (CNV).[1] Risk factors for progression from early to late AMD include advancing age,[2] cardiovascular disease (CVD),[3-5] obesity,[6] cigarette smoking,[7] ethnicity,[8] hypertension,[3] high cholesterol,[9] genetic variants such as apolipoprotein E (*ApoE*) gene,[10] age-related maculopathy susceptibility 2 (*ARMS2*) gene,[11] complement factor H (*CFH*)[12] and inflammatory markers such as C-reactive protein (*CRP*).[13] Recently, reticular pseudodrusen (RPD) have been shown to be an important independent risk factor for progression to both GA[14,15] and CNV.[14,16] In addition, various risk factors have been reported to be associated with RPD including advancing age, female gender, smoking, *ARMS2*, *C3, VEGFA* and *CFH* genetic variants.[17-19]

The prevalence of RPD reported in the literature has varied depending on the study design, the extent to which confounding variables are accounted for, and the imaging modality used in its detection. Initial reports of the association came from data collected on AMD cohorts recruited in hospital eye clinics and reported high prevalences ranging from 29 - 52%. [17, 20-22] Data from population based studies are limited and show large variation, such as 0.4% from the Melbourne Collaborative Cohort study to 4.9% in the Rotterdam study and 13% in the Alienor study.[18,19,23] Such varying estimates might be attributed to the different imaging and grading protocols used.

72 The strong association between RPD and a thin choroid has prompted a spate of

73 small studies that have sought associations between RPD and cardivasccular

74 disease.[24-28] Cymerman et al reported in a small prospective cohort of patients with

75 no known retinal disease recruited from a cardiovascular clinic; 23 participants with

76 coronary artery disease (CAD) had a higher frequency of RPD compared to 15 who

77 did not have CAD.[24] A literature review by Rastogi and Smith[25] on the association

78 between AMD, RPD with CVD highlighted studies reporting an association between

79 RPD and hypertension and angina.[26-29] Smith and colleagues hypothesized that the

80 increased mortality from systemic-vascular disease that affects males more severely

81 compared to females, may account for the higher proportion of women with RPD that

82 has been observed in various population-based studies.[29] Notably this review

83 highlighted the potential importance of large prospective cohort studies sampling

84 participants >45 years with and without CAD to identify RPD development and

85 potential associations.[25]

86

87 A sub-study of the SCOT-HEART (SH) trial that incorporated ultrawide field (UWF)

88 retinal imaging offered a unique opportunity to explore the relationship between CAD

89 and RPD. The use of widefield technology to evaluate the retinal fundus offered an

90 additional advantage as RPD is commonly located in the retinal arcades and beyond

91 [26] and to date there is only one study that has estimated RPD prevalence that has

92 included central and peripheral retinal locations.[30] However the sensitivity of UWF to

93 detect RPD has not been established. We therefore first validated the methodology

94 using images from a population based epidemiological study (the Northern Ireland

95 Cohort of Longitudinal Ageing [NICOLA]) which captured both UWF, CFP, OCT,

96 infra-red and autofluorescence (AF) images of the retina and subsequently used the

97 SH trial sub-study UWF images to explore the relationship between RPD and CAD.

98

MATERIALS AND METHODS

99

100 **Validation of detection of RPD by UWF imaging**

101 Nine hundred consecutive participants were selected from the NICOLA Study. CFP

102 was performed on the Canon CX-1 Digital Fundus Camera (Canon U.S.A., Inc.,

103 Melville, NY, U.S.A.). Stereoscopic pairs centered on the optic disc and macula were

104 captured. CFP images were viewed and graded using the Oculab program (Digital

105 Healthcare Oculab, V3.7.98.0, Emis Health, Leeds, UK). UWF retinal imaging was

106 performed on the Optos Tx200 Scanning Laser Ophthalmoscope (Optos PLC,

107 Dunfermline, UK) using both color and AF acquisition modes. Images were viewed

108 and graded using the Optos V^2 Vantage Pro software (version 2.9.4.2). OCT images

109 were captured using the Heidelberg Spectralis SD-OCT/SLO (Heidelberg

110 Engineering, Heidelberg, Germany). Images were reviewed using the Heidelberg

111 eye explorer, HEYEX software version 1.9.10.0. Multimodal grading was undertaken

112 with display of the multicolor enface retinal image (includes infrared reflectance,

113 green reflectance and blue reflectance) centered on the fovea. The grading

114 distinguished the reticulated pattern visible on the en face images which were

115 classified as RPD from subretinal drusenoid deposits (SDD) which are the OCT

116 correlate seen on the high resolution OCT B scans. This distinction was made as

117 mild and subtle features of SDD can be present before RPD are seen on the en face

118 imaging modalities.

119 UWF images were graded for the presence or absence of RPD by a trained single

120 grader who was not involved in any other grading procedures with quality assurance

6

121 and review by a retina specialist (UC). Multimodal (CFP, MultiColor, AF and OCT

122 images) grading was undertaken by trained graders in the network of UK Reading

123 Center's (NetwORC UK) for the presence or absence of RPD. Detection of RPD on

124 any modality was taken as evidence of presence of this feature. Sensitivity and

125 specificity of the UWF imaging in detecting RPD compared to the RPD detected from

126 the NICOLA cohort's *en face* images was computed.

127

128 **The SCOT-HEART (SH) Study and Sample**

129 The SH trial (ClinicalTrials.gov, number NCT01149590) was a multicenter

130 randomized controlled trial undertaken in Scotland (2010-2014) on 4,146

131 participants, aged 18-75 years, drawn from 12 cardiology clinics across Scotland.[31]

132 The main aim of the study was to determine the role of multidetector computed

133 tomorraphy in the diagnosis and management of patients attending rapid access

134 chest pain clinics. Participants were randomly assigned to either standard care

135 (control intervention) or standard care and the computed tomography coronary

136 angiography (CTCA) and calcium scores (intervention). CAD was categorized in the

137 SH study as: (i) obstructive CAD, atherosclerotic plaque encompassing a luminal

138 cross-sectional area of ≥70% in at least one major epicardial vessel; (ii) non-

139 obstructive CAD, either atherosclerotic plaque encompassing a luminal cross-

140 sectional area of <70% but >10% in at least one major epicardial vessel, or a

141 calcium score >400 AU (Agatston units) or >90th percentile for age and sex; or (iii)

142 minimal or no CAD. Non-obstructive disease was further sub-divided into mild (10-

143 50% luminal cross-sectional area) or moderate (50-70% luminal cross-sectional

144 area) stenosis. At two sites (Edinburgh and Dundee), consecutive patients were

145   approached to undergo UWF imaging immediately before or after undergoing CTCA.

146   We assessed 534 participants from a sub-study of SH who had UWF imaging

147   captured using two Optos P200C Scanning Laser Ophthalmoscopes (Optos PLC,

148   Dunfermline, UK) in addition to the normal study procedures at two sites (the Clinical

149   Research Imaging Center in Edinburgh and the Clinical Research Center Dundee).[32]

150

151   **Image Grading in SH**

152   Specific features of AMD in UWF images were graded for AMD characteristics

153   (increased pigment, decreased pigment, drusen, maximum drusen size, reticular

154   pseudodrusen, GA and CNV) and other peripheral abnormalities using the 'Study-

155   specific Grading Procedures for OPERA Study,' guidelines (November 2013).[33] The

156   Optos software utilised a modified Studies of Ocular Complications of AIDS (SOCA)

157   optos peripheral retina AMD study (OPERA) grid (Figure 1) which was divided into

158   three zones: Zone 1 (posterior pole), Zone 2 (extends from Z1 to a circle through the

159   ampullae of the vortex veins) and Zone 3 (extends from Z2 to the outer periphery).

160   The Manchester grid was superimposed on the SOCA grid to estimate the

161   ungradable areas (Figure 2). In accordance with the OPERA guidelines, at least 50%

162   of the subfield should be visible to grade; if < 50% of the subfield was visible, it was

163   graded as "Cannot Grade." If AMD characteristics and other pathologies were

164   present in a Cannot Grade subfield, and if the grader was ≥ 90% certain the lesion

165   was present, then grading was ascribed. Drusen presence was graded as follows:

166   absent; questionable; 1-5 drusen; 6-20 drusen; >20 drusen or cannot grade. The

167   maximum drusen size was graded as follows: < 125µm; ≥ 125µm, < 250µm distinct;

168   ≥ 125µm, < 250µm indistinct; ≥ 250µm distinct; ≥ 250µm indistinct or cannot grade.

169   RPD was graded as follows: absent; questionable; < 25% of subfield; 25-49% of

170 subfield; 50-74% of subfield; ≥ 75% of subfield or cannot grade. RPD were defined

171 as yellow interlacing networks ranging from 125 µm to 250 µm in width or lesions

172 that occurred in regular well-defined domains (Figure 3). Images in which RPD were

173 questionable were arbitrated by a retinal specialist (UC).

174

175 **Statistical Analysis**

176 Statistical analyses were performed using IBM SPSS Statistics version 20

177 (Portsmouth, UK). Intraobserver agreement was calculated after 1 in 20 of the

178 images were randomly regraded for RPD and drusen using kappa (k) statistics,

179 which express the extent of agreement beyond chance. The interpretation of the k

180 statistic was as follows: 0, no agreement; 0 to 0.2, slight agreement; 0.21 to 0.40, fair

181 agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.8, substantial agreement;

182 and >0.81, almost perfect agreement.[34]

183

184 Univariate analysis (Chi-squared test or fisher's exact test for categorical variables

185 and independent t-test for continuous variables) was used to examine differences in

186 the demographic characteristics of participants according to presence or absence of

187 RPD. General estimating equations (GEE) which enabled data from both eyes to be

188 included were used to examine the association between RPD and CAD while

189 accounting for other factors identified as significant from the univariate analysis.

190

191 **RESULTS**

192 **Validation study**

193   UWF imaging detected 8 participants with reticular drusen (2 unilateral and 6

194   bilateral; 100% sensitivity).. Multimodal imaging (color, multicolor, infra-red and

195   autofluorescence) detected reticular drusen in 7 of those which were seen on *en*

196   *face* images The specificity of the UWF imaging was 99.9%. In one case, the UWF

197   imaging detected RPD beyond the field of view captured by the combination of

198   retinal imaging (Figure 4). The positive predictive value (PPV) was calculated at

199   87.5% and the negative predictive value (NPV) was 100%.

200

201   **Participant Characteristics in SH study**

202   Table 1 summarizes SH study participant characteristics. In total 534

203   individuals had UWF retinal images captured. Two participants [4 eyes] proved

204   difficult to scan and images were not obtained. This left 532 pairs of eyes for

205   grading. The mean age was 58 years (range=27-75, SD 9.5) with 425 (80%)

206   aged over 50 years. There were 299 males (56%). 178 (33%) had no CAD, 351

207   (66%) had CAD present, whilst 182 (34%) had hypertension and 42 (24%) had

208   no CAD or hypertension.

209

210   **Intragrader agreement in SH study**

211   The intragrader agreement illustrated in Table 2 gives the kappa range for the AMD

212   features, the presence of RPD ranged from: 0.62-0.76, drusen: 0.58-0.64, maximum

213   drusen size: 0.55-0.62, increased pigment: 0.54-0.61, decreased pigment: 0.55-0.62,

214   GA: 0.62-0.76, neovascular AMD: 0.57-0.66 and peripheral abnormality: 0.55-0.59

215   within zones 1-3. For the lesions which were absent in the cohort the discordance in

216   the grading originated from a change of grade of feature absent to ungradeable

217   between the two gradings.

218

Prevalence of RPD and AMD features in the SH study

219 RPD was present in one or both eyes of 30 participants (5.6%) and bilateral in 23

220

221 participants (4.3%). Drusen >125µm were present in 201 participants (38%).

222 Participants with RPD ranged in age from 33-75 years (mean 59) and there were

223 equal numbers of males and females. The other AMD features graded as present in

224 the participants were as follows: 352 (66%) had hyperpigmentation, 55 (10%) had

225 hypopigmentation, 2 (0.4%) had unilateral GA, none of the participant was classified

226 as having neovascular AMD and 183 (34%) showed other non-AMD peripheral

227 abnormalities.

228

Association of CAD with RPD

229

230 CAD was present in 20 participants and absent in 10 participants with RPD,

231 however, no statistically significant association between RPD and CAD was found on

232 either the unadjusted or adjusted generalized estimating equations (GEE) model

233 ($p>0.05$, Table 3). With respect to associations between RPD and other early AMD

234 features a strong association was noted with drusen >125µm in the fully adjusted

235 model. Eighteen participants had both RPD and drusen >125µm, while 11

236 participants had RPD alone without evidence of soft drusen.

237

DISCUSSION

238

239 This is the first study to report the prevalence of RPD from a cohort drawn from a

240 cardiovascular clinical setting which had also captured UWF retinal images thus

241 allowing an examination of potential associations . Contrary to previous reports, we

242 failed to find a significant association between RPD and the presence of

243   anatomically defined CAD.[24-27,29]   Our findings are in accordance with population

244   based studies and some of the clinical cohorts that did not report significant

245   associations between RPD and CAD or hypertension.[17-19,21-23]   In fact, the

246   prevalence of RPD observed in the current study (30 out of 534 participants - 5.6%)

247   is similar to that reported by the population based Rotterdam study (4.9%),[18]

248   providing additional support for the view that CAD is not associated with an

249   increased prevalence of RPD.

250

251   While 80% of participants were aged over 50, a common age restriction for many

252   AMD studies, interestingly 8 participants with RPD were aged under 50, the

253   youngest aged 33. Of these 4 (50%) also had evidence of drusen >125µm whereas

254   the rest had no other features of AMD present. In the overall sample, 7 participants

255   had RPD without any other AMD features similar to previous observations,[18] which

256   may reflect a different phenotype given that RPD have been reported in other retinal

257   diseases such as Sorsby fundus dystrophy, pseudoxanthoma elasticum and

258   acquired vitelliform lesions.[35-37] Given the rarity of these participants, it is likely that

259   studies of large sample size or pooled analyses across studies will be required to

260   improve our understanding of the relevance of these isolated RPD.

261

262   This is also the second study, to our knowledge, that used UWF imaging for the

263   evaluation of RPD.[30] The validation protocols implemented using NICOLA image

264   data confirmed the reliability of this approach to detect the reticular pattern that has

265   been observed when using other *en face* modalities such as IR or AF imaging.

266   Nonetheless we are of the view that as with other en face modalities color UWF also

267   underestimates the prevalence because the earliest stages of this phenotype of SDD

268 is best appreciated on high resolution SD OCT.[38] Stage one SDD is defined by the

269 dispersed nature of the deposits of granular hyperreflective material that is present

270 in the outer retina in the region of the photoreceptors' inner and outer segments (the

271 IS/OS boundary) and the retinal pigment epithelium, prior to the characteristic

272 reticulated pattern that accompanies stages 2 and 3, which have been attributed to

273 focal deposits that cause marked alterations to the IS/OS boundary and thus

274 become detectable by en face imaging.[38] Currently it is accepted that detection of

275 RPD is best when a multimodal approach, combining infra-red reflectance, AF and

276 SD-OCT are used.[23,39] We were however reassured by the validation study which

277 demonstrated the benefit of the increased field of view provided by UWF imaging

278 and that RPD was evident in at least one participant in the retinal fundus in an area

279 that is typically not evaluated in AMD studies using CFP (35° or 45°), raising the

280 possibility of under ascertainment when the evaluated images are restricted to the

281 central fundus.

282

283 A potential limitation of this study is the choice of controls and the few RPD cases,

284 as all recruits were attending the cardiology clinic for suspected angina. However the

285 trial participants were recruited from a Chest pain clinic, and they were subsequently

286 classified as having no CAD on the basis of clinical examination, computed

287 tomography coronary angiography and calcium scores. Whether this cohort is

288 representative of what may be observed in a random population based sample is

289 unclear. Even though we adjusted for age, sex and the presence of smoking, given

290 the focus of the SH trial, some of the traditional AMD risk factors, such as diet and

291 known genetic risk variants, were not available and therefore residual confounding

292 may be present.

293

294   In conclusion, our study does not support previously reported associations with CAD,

295   yet the strong association observed with other AMD features in this non-AMD cohort

296   highlights the necessity for improved understanding of the mechanisms and

297   ethiology of this intriguing phenotype. To do so, more data from large and well

298   characterized longitudinal population based studies with multimodal imaging will be

299   required. addition, pooled analyses of multiple studies to improve statistical power

300   may help untangle the complexity of the risk factors and sub-phenotypes involved.

301

316

317

References

319   1. Klaver CC, Wolfs RC, Vingerling JR, Hofman A, de Jong PT. Age-specific

320   prevalence and causes of blindness and visual impairment in an older population:

321   The Rotterdam study. *Arch Ophthalmol.* 1998;116:653-658.

322   2. Smith W, Assink J, Klein R, et al. Risk factors for age-related macular

323   degeneration: Pooled findings from three continents. *Ophthalmology.* 2001;108:697-

324   704.

325   3. Hogg RE, Woodside JV, Gilchrist SE, et al. Cardiovascular disease and

326   hypertension are strong risk factors for choroidal neovascularization. *Ophthalmology.*

327   2008;115:1046-1052. e2.

328   4. Wu J, Uchino M, Sastry SM, Schaumberg DA. Age-related macular degeneration

329   and the incidence of cardiovascular disease: A systematic review and meta-analysis.

330   *PLoS ONE.* 2014;9:e102216.

331   5. Wieberdink RG, Ho L, Ikram MK, et al. Age-related macular degeneration and the

332   risk of stroke: The Rotterdam study. *Stroke.* 2011;42:2138-2142.

333   6. Seddon JM, Cote J, Davis N, Rosner B. Progression of age-related macular

334   degeneration: Association with body mass index, waist circumference, and waist-hip

335   ratio. *Arch Ophthalmol.* 2003;121:785-792.

336   7. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of

337   cigarette smoking and age-related macular degeneration in women. *JAMA.*

338   1996;276:1141-1146.

339   8. Klein R, Klein BE, Tomany SC, Meuer SM, Huang G. Ten-year incidence and

340   progression of age-related maculopathy: The Beaver Dam eye study.

341   *Ophthalmology.* 2002;109:1767-1779.

342   9. Curcio CA, Millican CL, Bailey T, Kruth HS. Accumulation of cholesterol with age

343   in human bruch's membrane. *Invest Ophthalmol Vis Sci.* 2001;42:265-274.

344   10. Klaver CC, Kliffen M, van Duijn CM, et al. Genetic association of apolipoprotein E

345   with age-related macular degeneration. *The American Journal of Human Genetics.*

346   1998;63:200-206.

347   11. Smailhodzic D, Klaver CC, Klevering BJ, et al. Risk alleles in CFH and ARMS2

348   are independently associated with systemic complement activation in age-related

349   macular degeneration. *Ophthalmology.* 2012;119:339-346.

350   12. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-

351   related macular degeneration. *Science.* 2005; 308:385-389.

352   13. Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-

353   reactive protein and age-related macular degeneration. *JAMA.* 2004;291:704-710.

354   14. Finger RP, Wu Z, Luu CD, et al. Reticular pseudodrusen: A risk factor for

355   geographic atrophy in fellow eyes of individuals with unilateral choroidal

356   neovascularization. *Ophthalmology.* 2014;121:1252-1256.

357   15. Marsiglia M, Boddu S, Bearelly S, et al. Association between geographic atrophy

358   progression and reticular pseudodrusen in eyes with dry age-related macular

359   degeneration. *Invest Ophthalmol Vis Sci.* 2013;54:7362-7369.

16

360   16. Cohen SY, Dubois L, Tadayoni R, Delahaye-Mazza C, Debibie C, Quentel G.

361   Prevalence of reticular pseudodrusen in age-related macular degeneration with

362   newly diagnosed choroidal neovascularisation. *Br J Ophthalmol.* 2007;91:354-359.

363   17. Wu Z, Ayton LN, Luu CD, Baird PN, Guymer RH. Reticular pseudodrusen in

364   intermediate age-related macular degeneration: Prevalence, detection, clinical,

365   environmental, and genetic associations. *Invest Ophthalmol Vis Sci.* 2016;57:1310-

366   1316.

367   18. Buitendijk GH, Hooghart AJ, Brussee C, et al. Epidemiology of reticular

368   pseudodrusen in age-related macular degeneration: The Rotterdam study. *Invest*

369   *Ophthalmol Vis Sci.* 2016;57:5593-5601.

370   19. Finger RP, Chong E, McGuinness MB, et al. Reticular pseudodrusen and their

371   association with age-related macular degeneration: The Melbourne collaborative

372   cohort study. *Ophthalmology.* 2016;123:599-608.

373   20. Hogg RE, Silva R, Staurenghi G, et al. Clinical characteristics of reticular

374   pseudodrusen in the fellow eye of patients with unilateral neovascular age-related

375   macular degeneration. *Ophthalmology.* 2014;121:1748-1755.

376   21. Zarubina AV, Neely DC, Clark ME, et al. Prevalence of subretinal drusenoid

377   deposits in older persons with and without age-related macular degeneration, by

378   multimodal imaging. *Ophthalmology.* 2016;123:1090-1100.

379   22. Huisingh C, McGwin G, Neely D, et al. The association between subretinal

380   drusenoid deposits in older adults in normal macular health and incident age-related

381   macular degeneration. *Invest Ophthalmol Vis Sci.* 2016;57:739-745.

382   23. Chan H, Cougnard-Grégoire A, Delyfer M, et al. Multimodal imaging of reticular

383   pseudodrusen in a population-based setting: The Alienor study. *Invest Ophthalmol*

384   *Vis Sci.* 2016;57:3058-3065.

385   24. Cymerman RM, Skolnick AH, Cole WJ, Nabati C, Curcio CA, Smith RT.

386   Coronary artery disease and reticular macular disease, a subphenotype of early age-

387   related macular degeneration. *Curr Eye Res.* 2016;1:1482-1488.

388   25. Rastogi N, Smith RT. Association of age-related macular degeneration and

389   reticular macular disease with cardiovascular disease. *Surv Ophthalmol.* 2015;

390   61:422-433.

391   26. Klein R, Meuer SM, Knudtson MD, Iyengar SK, Klein BE. The epidemiology of

392   retinal reticular drusen. *Am J Ophthalmol.* 2008;145(2):317-326. e1.

393   27. Boddu S, Lee MD, Marsiglia M, Marmor M, Freund KB, Smith RT. Risk factors

394   associated with reticular pseudodrusen versus large soft drusen. *Am J Ophthalmol.*

395   2014;157:985-993. e2.

396   28. Smith RT, Merriam JE, Sohrab MA, et al. Complement factor H 402H variant and

397   reticular macular disease. *Arch Ophthalmol.* 2011;129:1061-1066.

398   29. Smith RT, Sohrab MA, Busuioc M, Barile G. Reticular macular disease. *Am J*

399   *Ophthalmol.* 2009;148:733-743. e2.

400   30. Domalpally A, Clemons TE, Danis RP, et al. Peripheral retinal changes

401   associated with age-related macular degeneration in the age-related eye disease

402   study 2: Age-related eye disease study 2 report number 12 by the age-related eye

403 disease study 2 optos peripheral retina (OPERA) study research group.

404 *Ophthalmology.* 2017;S0161-6420:31491-31499.

405 31. Newby DE, Williams MC, Hunter A, et al. CT coronary angiography in patients

406 with suspected angina due to coronary heart disease (SCOT-HEART): an open-

407 label, parallel group, multicentre trial. *Lancet.* 2015;385:2383-2391.

408 32. Pellegrini E, Robertson G, Trucco E, et al. Blood vessel segmentation and width

409 estimation in ultra-wide field scanning laser ophthalmoscopy. *Biomed Opt Express.*

410 2014; 5:4329-4337.

411 33. University of Wisconsin Fundus Photograph Reading Center. Study-specific

412 grading procedures for OPERA study. 2013.

413 34. Landis JR, Koch GG. The measurement of observer agreement for categorical

414 data. *Biometrics.* 1977;33(1):159-174.

415 35. Gliem M, Hendig D, Finger RP, Holz FG, Issa PC. Reticular pseudodrusen

416 associated with a diseased bruch membrane in pseudoxanthoma elasticum. *JAMA*

417 *Ophthalmology.* 2015;133:581-588.

418 36. Gliem M, Müller PL, Mangold E, et al. Reticular pseudodrusen in sorsby fundus

419 dystrophy. *Ophthalmology.* 2015;122:1555-1562.

420 37. Freund KB, Laud K, Lima LH, Spaide RF, Zweifel S, Yannuzzi LA. Acquired

421 vitelliform lesions: Correlation of clinical findings and multiple imaging analyses.

422 *Retina.* 2011;31:13-25.

423   38. Zweifel SA, Spaide RF, Curcio CA, Malek G, Imamura Y. Reticular

424   pseudodrusen are subretinal drusenoid deposits. *Ophthalmology.* 2010;117:303-

425   312.e1.

426   39. Schaal KB, Legarreta AD, Feuer WJ, et al. Comparison between widefield en

427   face swept-source OCT and conventional multimodal imaging for the detection of

428   reticular pseudodrusen. *Ophthalmology.* 2016.

429

430
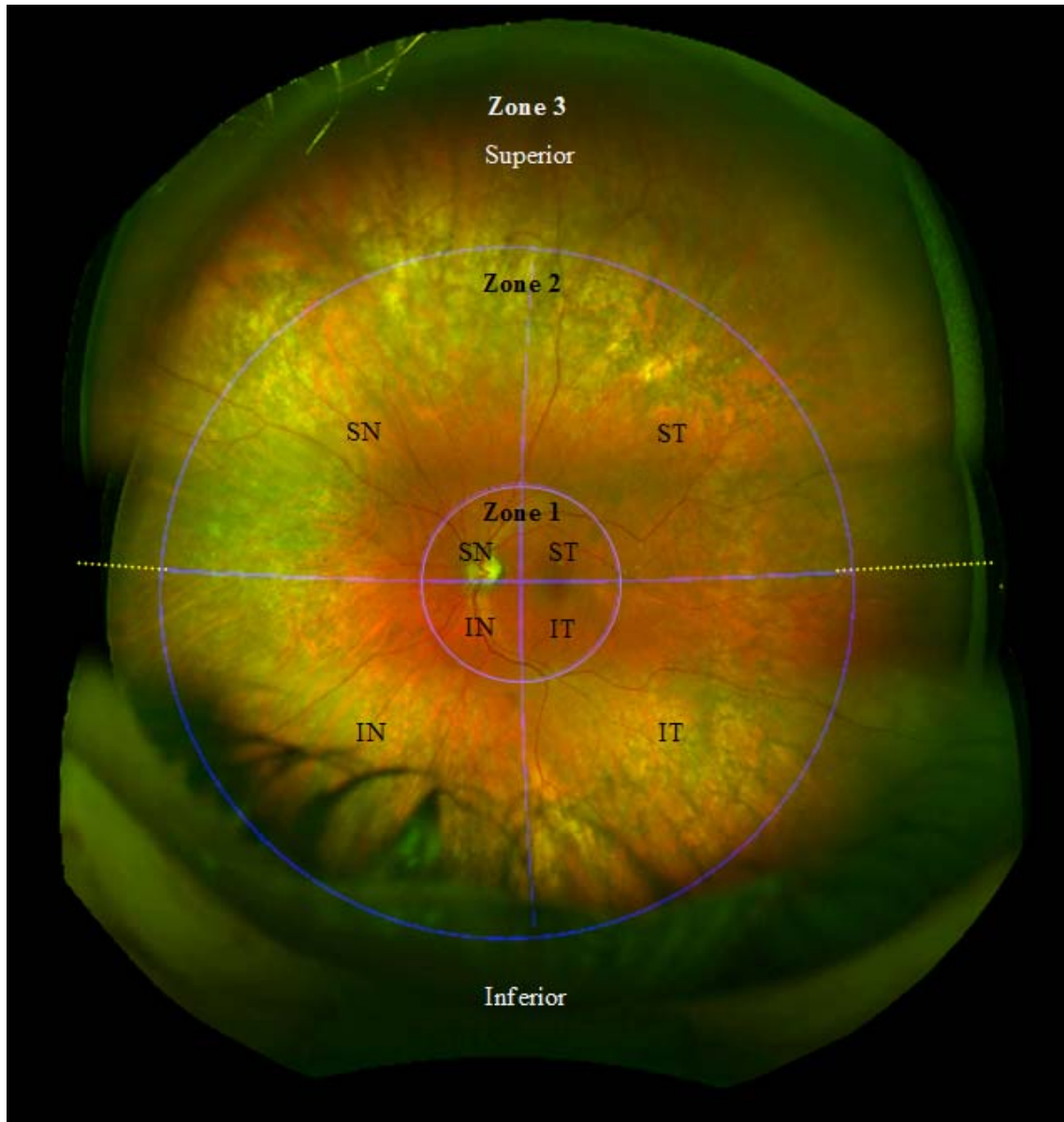
Figure 1: The Modified SOCA Grid utilized on the Optos Software.

Z1 and Z2 are each divided into four quadrants: superonasal (SN), superotemporal (ST), inferotemporal (IT), and inferonasal (IN). Z3 is divided into two hemispheres (superior, inferior) using a visual extension of the horizontal cross line (yellow dashed lines). Taken from the Study-Specific Grading Procedures for OPERA, University of Wisconsin (2013).[33]

437
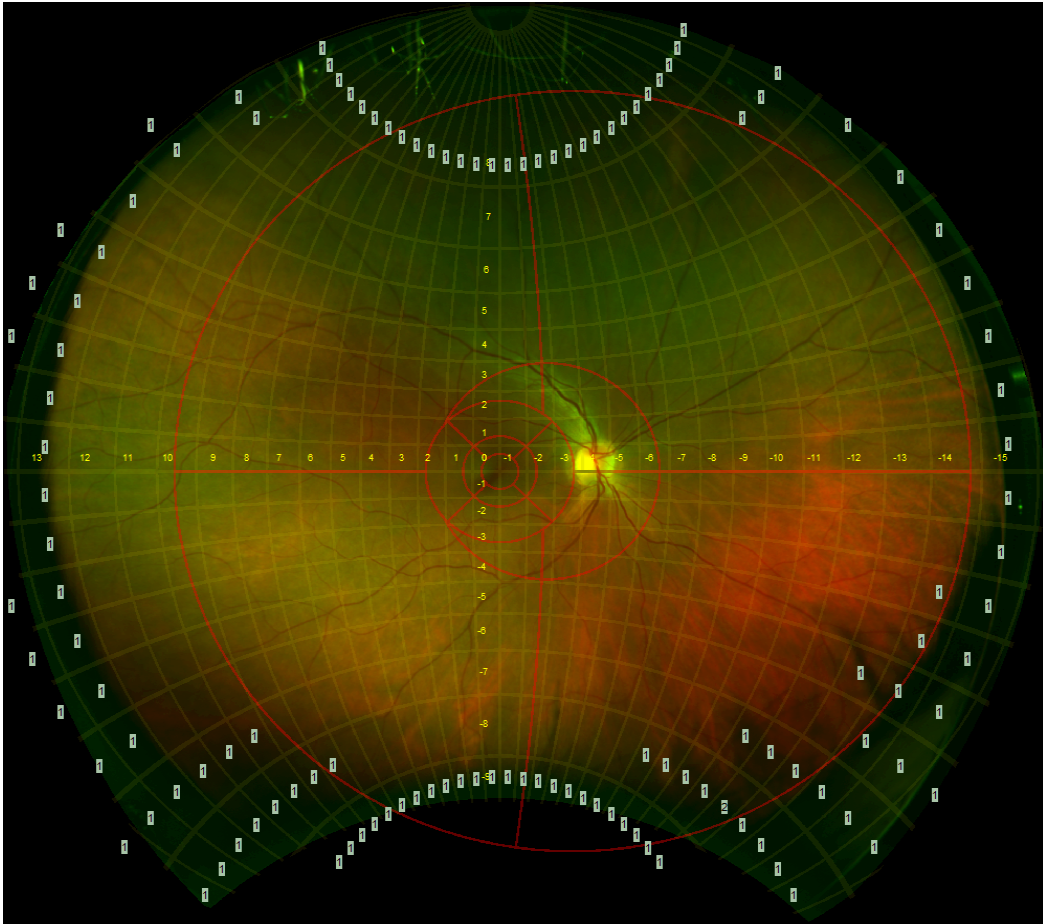
Figure 2: Optos ultra-widefield retinal image grading grids for specific AMD characteristics.

The SOCA grid is divided into three zones: Zone 1 (posterior pole), Zone 2 (extends from Z1 to a circle through the ampullae of the vortex veins) and Zone 3 (extends from Z2 to the outer periphery). The Manchester grid was superimposed onto the SOCA grid to assess the ungradable areas.
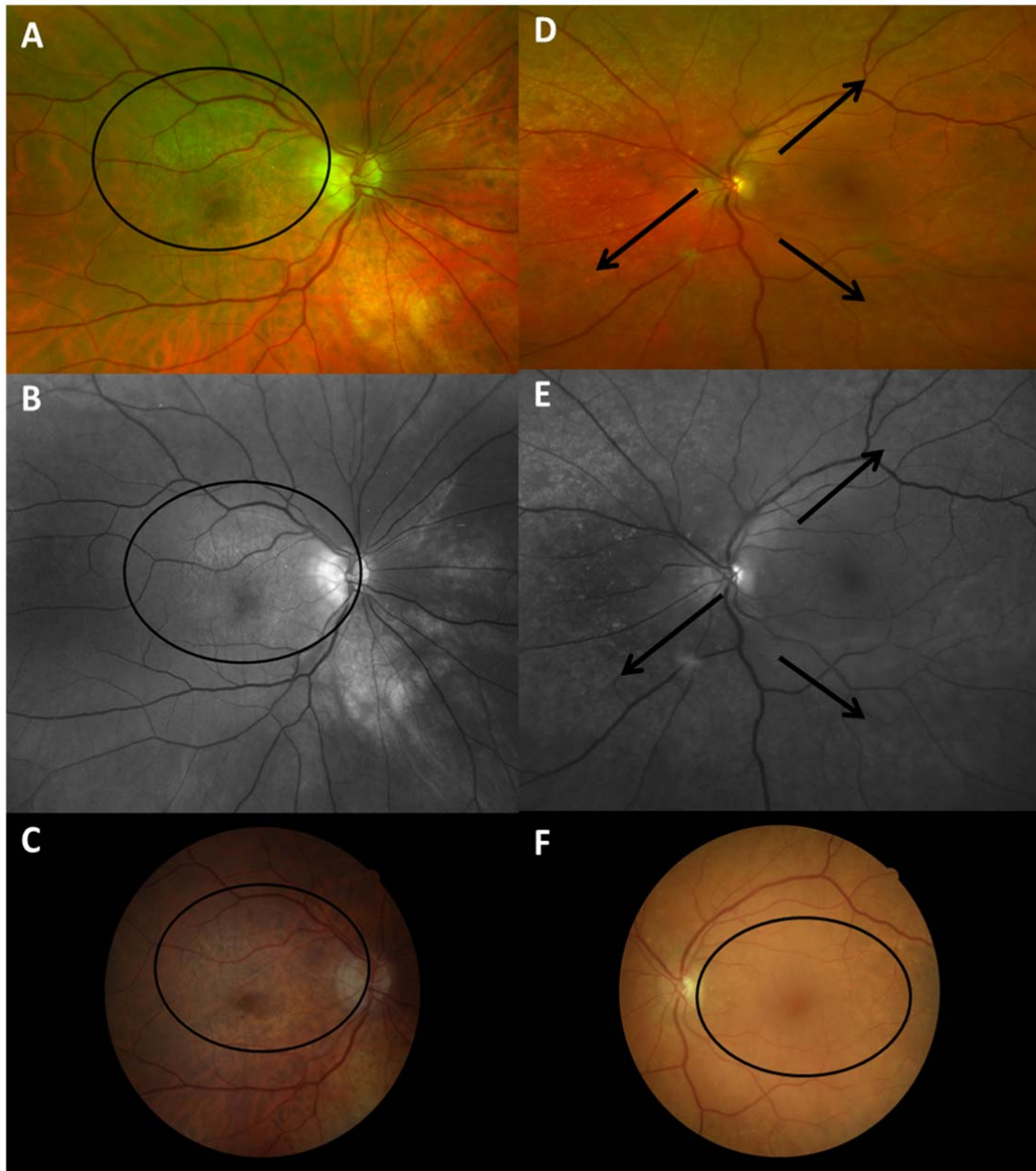
445

446
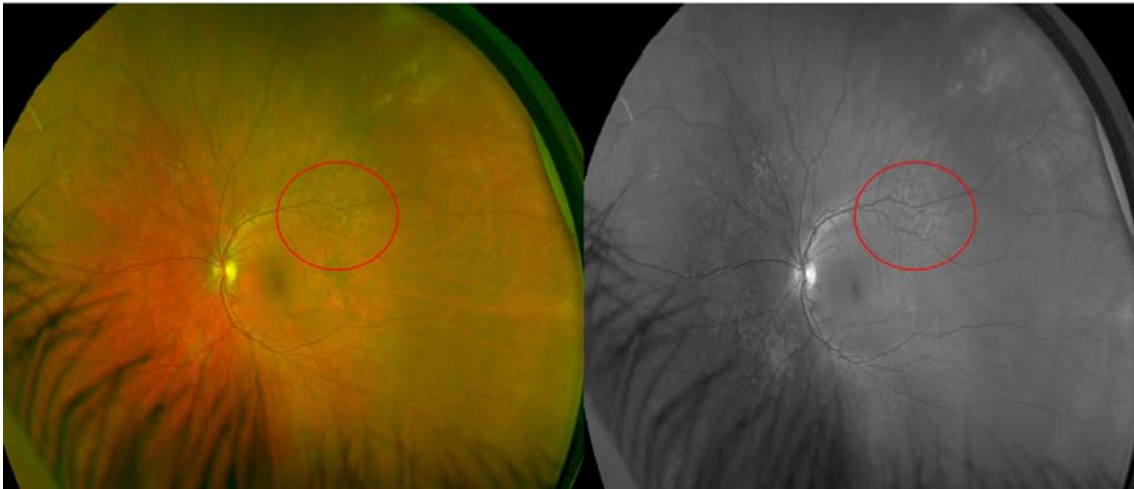
Figure 3: Optos ultra-widefield retinal image illustrating RPD.

RPD is a subtype of AMD associated with subretinal drusenoid deposits located between the retinal pigment epithelium and the inner ellipsoid zone.

450

Figure 4 shows the RPD interlacing pattern on both the UWF and fundus camera image. **A.** UWF pseudo color image showing RPD (black circle). **B.** UWF green laser imaging with RPD visible within the black circle. **C.** Fundus camera image with RPD within the black circle. **D.** UWF pseudo color image with arrows pointing to areas of RPD. **E.** UWF green laser imaging with arrows annotating areas of RPD. In this case RPD was detected beyond the field of view of color fundus photography. **F.**

458   Corresponding fundus camera image with no readily visible RPD within the black

459   circle.

460 **Table 1.** Summary statistics for study participants.
461

| | | Reticular Pseudodrusen (1 or both eyes) | | |
	All participants N=534	Absent N=504	Present N=30	P
Age Mean (SD)	58 (10)	58 (9)	59 (12)	0.76
Sex (%) Male Female	299 (56) 235 (44)	284 (56) 220 (44)	15 (50) 15 (50)	0.57
BMI Mean (SD)	30 (7)	30 (7)	28 (6)	0.19
CAD diagnosis (%) None Non-Obstructive-Mild Non-Obstructive-Moderate Obstructive CAD Missing	178 (33) 114 (21) 87 (16) 150 (28) 5 (1)	168 (33) 105 (21) 84 (17) 142 (28) 5(1)	10 (33) 9 (30) 3 (10) 8 (27) 0 (0)	0.71
CAD (%) Absent Present Missing	178 (33) 351 (66) 5 (1)	168 (33) 331 (66) 5 (1)	10 (33) 20 (67) 0 (0)	0.99
Assign Score Mean (SD)	18 (12)	18 (12)	17 (11)	0.56
Coronary Artery Calcium Score Mean (SD)	314 (805)	310 (814)	376 (634)	0.67
Hypertension (%) No Yes Missing	346 (65) 182 (34) 6 (1)	327 (65) 171 (34) 6 (1)	19 (63) 11 (37) 0 (0)	0.84
Diabetes (Type1 or 2) (%) No Yes	483 (90) 51 (10)	455 (90) 49 (10)	28 (93) 2 (7)	0.76
Drusen >125μm (%) Absent Present Missing	330 (62) 201 (38) 3 (1)	319 (63) 183 (36) 2 (1)	11 (37) 18 (60) 1 (3)	0.01
Smoking History (%) Never Ex-smoker Current Smoker	256 (48) 193 (36) 85 (16)	244 (48) 183 (36) 77 (15)	12 (40) 10 (33) 8 (27)	0.25

462

463

464 **Table 2.** Intragrader agreement for the individual age-related macular

465 degeneration phenotypes.

AMD Characteristic	Kappa Range		
	Zone 1	Zone 2	Zone 3
Neovascular AMD	0.66	0.57	0.61
Increased Pigment	0.59	0.54	0.61
Decreased Pigment	0.66	0.55	0.62
Geographic Atrophy	0.66	0.76	0.62
Drusen	0.59	0.64	0.58
Maximum Drusen Size	0.60	0.62	0.55
Reticular Pseudodrusen	0.67	0.76	0.62
Peripheral Abnormality	N/A	0.59	0.55
Presence of other Pathology (All zones)	0.62		

466

467

468 **Table 3 –** Investigation of coronary artery disease as a risk factor for reticular

469 pseudodrusen using generalized estimating equations.

470

	Unadjusted model			Age and Sex adjusted			Multivariate adjusted*		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
CAD	1.30	0.58-2.92	0.52	1.33	0.57-3.11	0.52	1.31	0.57-3.01	0.52
Age				1.01	0.95-1.07	0.78	1.00	0.95-1.06	0.92
Sex				1.51	0.67-3.40	0.32	1.40	0.62-3.14	0.42
Drusen >125 µm							3.18	1.61-6.27	**0.001**

471

472 *Multivariate model was adjusted for age, sex and smoking status.

473