

Surgical management of subfoveal choroidal neovascular membranes in age-related macular degeneration by macular relocation: experiences of an early-stopped randomised clinical trial (MARAN Study)

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Abstract

Rationale The MARAN (Macular Relocation in Age-related Neovascular disease) trial was planned to assess the effectiveness of full macular relocation (MR) in patients with neovascular age-related macular degeneration (AMD).

Design Randomised, prospective, controlled clinical trial.

Methods Patients suffering from visual loss because of AMD were randomised to either surgery or a control group receiving standard treatment (observation or photodynamic therapy (PDT)). The primary end point was the change of visual acuity (VA) (ETDRS) 52 weeks after randomisation compared with initial VA, and secondary end points included reading performance, contrast sensitivity, stability of fixation, eye-specific quality of life, and the absolute number of letters read correctly at 52 weeks compared with initial examination.

Results Owing to early determination, only 28 patients were included in the study. The study did not show a difference between the two groups with respect to the final visual result or any of the secondary outcomes measured. The study was limited by the low recruitment that was, at least in part, attributed to the inherent risks for those patients

randomised to the surgical arm of the study as well as to the emerging new treatments for AMD.

Conclusion The results of the MARAN trial failed to recruit a sufficient number of patients and a superiority of surgery over observation or PDT in patients with exudative AMD was not shown. There was a trend that the reading function was superior after surgery. In the light of the new pharmacological treatments, surgical options such as MR will be an option for only selected cases.

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Keywords: age-related macular degeneration; macular relocation; randomised clinical trial

Introduction

Before the introduction of anti-VEGF therapies, there was a paucity of treatment options for patients presenting with exudative complications of age-related macular degeneration (AMD) and there was little quality evidence to support macular relocation (MR) surgery vs the standard therapy available at that time, namely observation or photodynamic therapy (PDT). Against this background, a clinical randomised trial was set up to

determine the efficacy of macular location in patients with clinical signs and symptoms of exudative AMD. Information about the MARAN trial (Macular Relocation in Age-related Neovascular disease) is available on The National Research Register <http://www.nrr.nhs.uk/ViewDocument.asp?ID=N0207150031>. The trial was stopped because of low recruitment and the availability of efficient pharmacological approaches. This report evaluates the experiences and results from the MARAN trial.

Materials and methods

Study design

The study was designed as a multicentre, prospective, randomised (1:1) clinical trial investigating the outcome of surgical course. Patients were randomised into two groups: a treatment group (MR group) (in these patients, the MR surgery was carried out)^{1,2} and a control group (ST group) that received Standard Treatment, meaning observation in most cases and PDT in patients with classic membranes.

On the basis of earlier studies, a standard deviation of four lines on the ETDRS charts for the sample size calculation was assumed. A mean change of visual acuity (VA) over 1 year of 1.5 lines on the ETDRS chart was judged as clinically relevant. A sequential testing procedure according to O'Brien and Fleming³ should be used to adopt the significance level resulting in $\alpha_{\text{final}} = 0.048$ for the final analysis. For a global significance level $\alpha = 0.05$, a power of 90% requires 155 patients per group, that is, a total of 310 patients for the whole trial. Control examinations took place 12, 26, 38 and 52 weeks after randomisation, the final examination took place 104 weeks after randomisation (see Figure 1).

Primary and secondary end points

The primary end point was the change in the VA (according to ETDRS (modified protocol)⁴) in the study eye, measured at 52 weeks after randomisation compared with the VA at the entry examination. The VA was defined as number of lines with at least four letters read on the ETDRS charts and expressed as LogMAR.

The following criteria were regarded as secondary end points (each measured at 52 weeks after randomisation compared with the entry examination):

- (1) *Reading performance of the study eye.* The reading performance is evaluated using the Radner Reading charts for a testing distance of 25 cm.⁵ Reading acuity was expressed as in logRAD. The MNREAD acuity chart were used in the trial site, Liverpool, the testing distance was 40 cm. For data analysis, these logMAR values were corrected to a testing distance of 25 cm according to Radner *et al.*⁵
- (2) *Contrast sensitivity of the study eye.* The contrast sensitivity was defined as the lowest contrast level, at which two of the three letters on the Pelly–Robsen charts were read correctly.^{6,7}
- (3) *Eye-specific quality of life.* In the MARAN trial, the NEI-VFQ questionnaire was used in the respective native language version.^{8,9}
- (4) *Absolute number of letters read correctly in the study eye.* The absolute number of letters read correctly on the ETDRS charts was evaluated as a further secondary end point.

Statistical methods

The statistical analyses were carried out using SAS, version 9.1 (SAS, Cary, NY, USA). The Mann–Whitney-*U*-test was used because of the non-normality of the data.

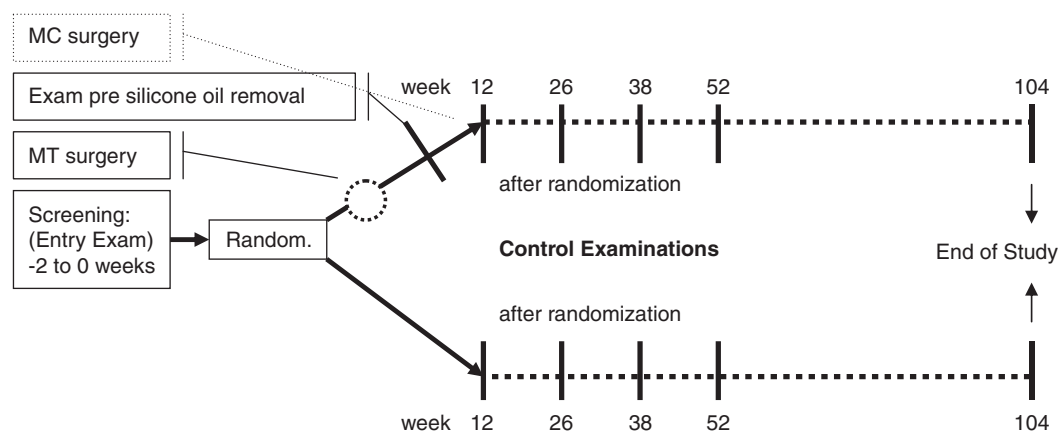


Figure 1 Overview and time course of the MARAN trial. Exam, examination; Random, randomisation; MT surgery, macular relocation surgery; MC surgery, muscular counter-rotation surgery.

All other analyses are regarded as explorative (hypothesis generating). No interim analysis was carried out because of the low recruitment rate and recruitment was stopped after the randomisation of 28 patients. Therefore, a significance level of $\alpha = 0.05$ was used for the final analysis.

Results

Patients

A total of 28 patients were randomised between October 2002 and June 2004. Owing to low recruitment, the trial was discontinued in July 2004. The result of the randomisation was an assignment of 13 patients to the MR group and 15 patients to the ST group. None of the patients in the ST received PDT as a ST. One of the patients (patient no. 25) withdrew from the study immediately after the randomisation. Another patient withdrew after the control examination after 38 weeks (patient no. 22, randomised to the MR group) owing to poor health. One patient (no. 11) was randomised to the control group, but she requested MR and this was carried out 6 weeks after randomisation. Three patients withdrew their consent to MR surgery after being randomised to the surgery group (patient no. 12, 15, 22). One patient randomised to the ST group died 4 weeks after the control examination in week 52 (patient no. 9). An overview of all patients in the MARAN trial is shown on the flow chart (Figure 2).

For analysis of the primary end point, data from 26 patients were used: two patients (patient no. 22 randomised to the MR group, patient no. 25 randomised to the ST group) were excluded from the calculations, as only measurements from the entry examination were available.

Baseline characteristics

Patients were aged 71.9 ± 6.5 years at time of entry examination. The gender was equally distributed between the two groups. A total of 15 right and 13 left eyes were included.

A total of 22 eyes with occult and six mixed (<50% classic) membranes were included. Five patients presented with an RPE detachment, eight with subretinal extrafoveal haemorrhage were equally distributed in both treatment and control group. With respect to the lens status, the two groups show no difference in phakic and pseudophakic status ($P = 0.63$). There was no other functional or morphological difference between the two groups. VA at study entry was 0.7 ± 0.2 logMAR. Loss of vision was on average 9.7 ± 4.9 weeks.

Surgical interventions

In 3 of the 13 patients randomised to the MR group, no MR surgery was carried out (patient No. 12, 15, 22). Nine of the patients undergoing MR surgery had silicone oil removal and counter-rotation of the muscles as a secondary procedure. In the ST group, two eyes underwent cataract surgery and one patient received PDT. In the MR group, nine patients had silicone oil removal and counter-rotation of the muscles was carried out as a secondary intervention.

Evaluation of efficacy: analysis of the primary end point

There was no difference between the MR and the ST groups at 52 weeks after entry (MR: 0.4 ± 0.5 , $n = 13$, ST: 0.4 ± 0.4 , $n = 15$; $P = 0.80$, Mann-Whitney-U-test). The median difference between the MR and ST group at 12 months was -0.05 logMAR (confidence interval of -0.5 to $+3.0$) indicating that the MR group had slightly better vision. The median change in VA in each group was $+0.4$ logMAR in the MR group and $+0.5$ logMAR in the ST group (Figure 3).

Analysis of the secondary end points

- (1) *Reading performance*: There was no significant difference between the two groups with respect to reading performance.
- (2) *Contrast sensitivity*: The data show no difference between the MR group and the ST group.
- (3) *Eye-specific quality of life*: The data show no difference between the treatment group and the control group in any of the 12 subscales.
- (4) *Number of letters read correctly*: The median changes show deterioration in the number of letters read correctly in the study eye for both groups. There was no significant difference between the groups.
- (5) *Long-term development of VA*: The data show no difference between the two groups.
- (6) *Time course of VA*: The results show no influence on the VA in the three fixed effects that were investigated.

Discussion

The MARAN trial aimed to assess the efficacy of a new surgical approach in AMD and was designed as a multicentre, prospective, randomised (1:1) clinical trial. The surgery is difficult and complications, such as proliferative vitreoretinopathy and double vision, need to be considered. The trial planned to recruit 310 patients. In spite of the widening of the inclusion criteria, the recruitment rate was slow and the trial was stopped after

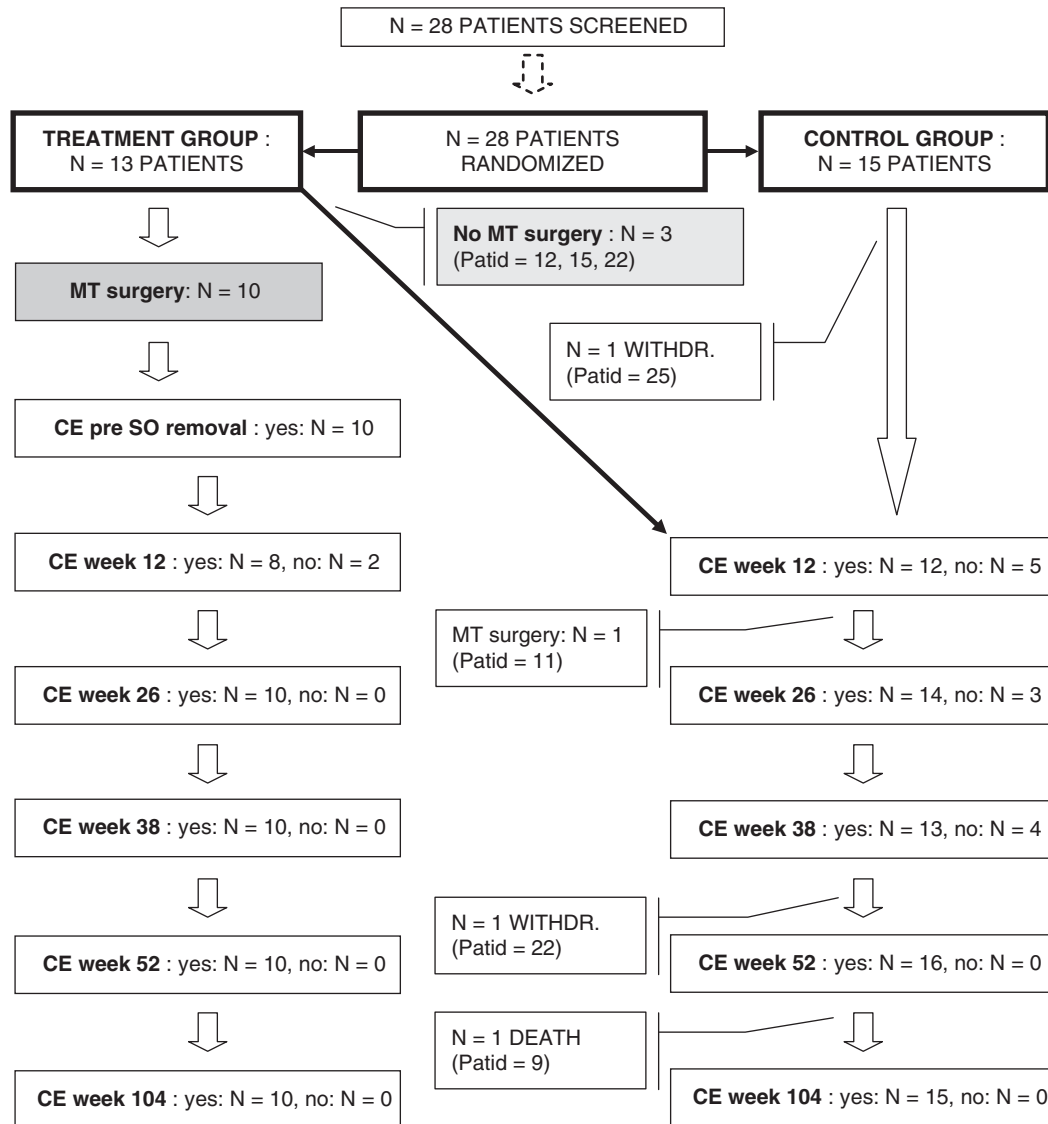


Figure 2 Patient's flow chart. CE, control examination; MT surgery, macular relocation surgery; SO, silicone oil.

28 patients. Therefore, MARAN trial was unable to confirm the clinical observation that MR ameliorates the loss of reading ability or influences the quality of life¹⁰⁻¹³ in patients with neovascular AMD.

Overall, the external validity of the study is limited: only a tenth of the calculated number of patients was enrolled. This might account for the difference in our finding when compared with other non-randomised studies and one randomised study reporting a benefit of MR.^{10,11,14,15}

When the trial was first conceived, there was no viable alternative treatment for minimally classic and occult CNV. By the time the trial was started, PDT was fast becoming part of ST. VEGF inhibitors were being tested in clinical trials and combinatory treatments of steroids and PDT were being investigated.¹⁶⁻¹⁸ It was therefore

difficult to recruit patients to a study when other less-invasive treatments were being developed.

It was not possible to reject the null hypothesis, as no statistical difference was found between the MR and ST groups for either the primary or the secondary end points. We did find deterioration in the level of visual function for all parameters evaluated in both groups.

In conclusion, the MARAN trial was unable to show the efficacy of MR surgery. This is in accordance to a recently published meta-analysis,¹⁹ showing that, after MR an improvement of VA of two or more lines was found in 31% and a deterioration of two or more lines in 27%. Only for patients with subretinal haemorrhages, estimates were significantly different (improvement of VA 62%, deterioration of VA 13%). The recruitment criteria excluded those patients with predominantly

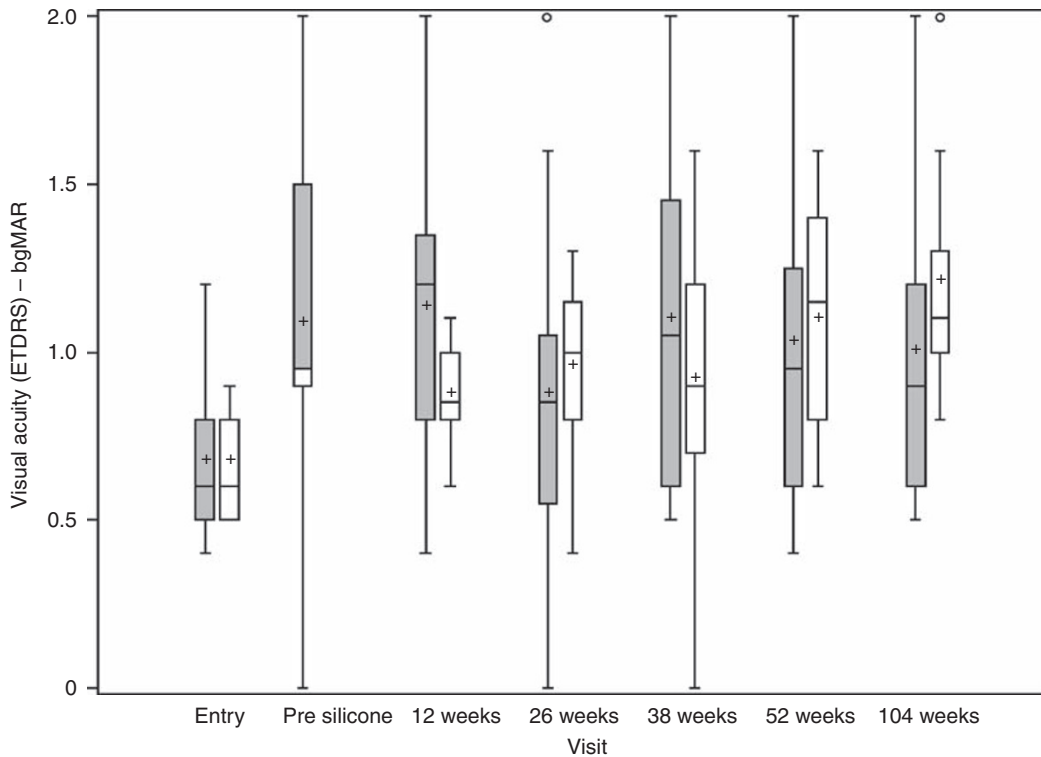


Figure 3 Time course of the visual acuity on the study eye for both groups. Macular relocation (grey) and standard treatment group (white).

classic and pure classic CNV. It may be that in this subgroup of patients, superior outcome can be achieved with surgery as opposed to PDT.¹⁰ The onset of visual deterioration is often earlier and the deterioration more rapid with classic CNV. By selecting patients with minimally classic and occult membrane, we may be selecting patients with insidious disease such that there would be extensive photoreceptor and neuroretinal damage that could not be rescued by MR.

With the MARAN trial, the advent of pharmacological treatments has effectively called time on the study. However, despite the effectiveness of anti-VEGF therapies in most patients with AMD, there may still remain indications for MR surgery in some, such as in patients with large subretinal haemorrhages²⁰ or in Anti-VEGF non-responders.²¹ In this respect, the results of the MARAN study will help to refine patient selection and expectations from MR surgery.

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Dreyhaupt J, Bauer C, Munzinger J, Unnebrink K, Freiberger A, Seibert-Grafe M, and Victor N were involved in the statistical evaluation, monitoring and writing of the paper.

References

- 1 Aisenbrey S, Lafaut BA, Szurman P, Grisanti S, Luke C, Krott R *et al*. Macular relocation with 360 degrees retinotomy for exudative age-related macular degeneration. *Arch Ophthalmol* 2002; **120**: 451–459.
- 2 Wolf S, Lappas A, Weinberger A, Kirchhof B. Macular relocation for surgical management of subfoveal choroidal neovascularizations in patients with AMD: first results. *Graefes Arch Clin Exp Ophthalmol* 1999; **237**: 51–57.
- 3 O' Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35**: 549–556.
- 4 Jousen AM, Heussen FM, Joeres S, Llacer H, Prinz B, Rohrschneider K *et al*. Autologous relocation of the choroid and retinal pigment epithelium in age-related macular degeneration. *Am J Ophthalmol* 2006; **142**: 17–30.
- 5 Radner W, Willinger U, Obermayer W, Mudrich C, Velikay-Parel M, Eisenwort B. Eine neue Lesetafel zur gleichzeitigen Bestimmung von Lesevisus und Lesegeschwindigkeit. *Klin Monatsbl Augenheilkd* 1998; **213**: 174–181.
- 6 Holz FG, Unnebrink K, Engenhardt-Cabilic R, Bellmann C, Pritsch M, Voelcker HE, for the RAD-Study Group. Results of a prospective randomised controlled double-blind multicenter clinical trial on external beam radiation therapy

- for subfoveal choroidal neovascularization secondary to AMD (RAD-Study). *Ophthalmology* 1999; **106**: 2239–2247.
- 7 Bellmann C, Unnebrink K, Rubin GS, Miller D, Holz FG. Visual acuity and contrast sensitivity in patients with neovascular age-related macular degeneration. Results from the Radiation Therapy for Age-Related Macular Degeneration (RAD) Study. *Graefes Arch Clin Exp Ophthalmol* 2003; **241**: 968–974.
 - 8 Franke GH, Esser J, Voigtländer A, Mähner N. Erste Ergebnisse zur psychometrischen Prüfung des NEI-VFQ (National Eye Institute Visual Function Questionnaire), eines psychodiagnostischen Verfahrens zur Erfassung der Lebensqualität bei Sehbeeinträchtigten. *Z Med Psychol* 1998; **7**: 178–184.
 - 9 Mangione CM. The National Eye Institute 25-item Visual Function, Questionnaire (VFQ-25)—Scoring algorithm. 2000; 1–15.
 - 10 Toth CA, Lapolice DJ, Banks AD, Stinnett SS. Improvement in near visual function after macular relocation surgery with 360-degree peripheral retinectomy. *Graefes Arch Clin Exp Ophthalmol* 2004; **242**: 541–548.
 - 11 Gelisken F, Voelker M, Schwabe R, Besch D, Aisenbrey S, Szurman P et al. Full macular relocation vs photodynamic therapy with verteporfin in the treatment of neovascular age-related macular degeneration: 1-year results of a prospective, controlled, randomised pilot trial (FMT-PDT). *Graefes Arch Clin Exp Ophthalmol* 2007; **245**: 1085–1095.
 - 12 Luke M, Ziemssen F, Bartz-Schmidt KU, Gelisken F. Quality of life in a prospective, randomised pilot-trial of photodynamic therapy vs full macular relocation in treatment of neovascular age-related macular degeneration—a report of 1 year results. *Graefes Arch Clin Exp Ophthalmol* 2007; **245**: 1831–1836.
 - 13 Cahill MT, Banks AD, Stinnett SS, Toth CA. Vision-related quality of life in patients with bilateral severe age-related macular degeneration. *Ophthalmology* 2005; **112**: 152–158.
 - 14 Park CH, Toth CA. Macular relocation surgery with 360-degree peripheral retinectomy following ocular photodynamic therapy of choroidal neovascularization. *Am J Ophthalmol* 2003; **136**: 830–835.
 - 15 Mruthyunjaya P, Stinnett SS, Toth CA. Change in visual function after macular relocation with 360 degrees retinectomy for neovascular age-related macular degeneration. *Ophthalmology* 2004; **111**: 1715–1724.
 - 16 Gragoudas ES, Adamis AP, Cunningham Jr ET, Feinsod M, Guyer DR, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004; **351**: 2805–2816.
 - 17 Heier JS, Boyer DS, Ciulla TA, Ferrone PJ, Jumper JM, Gentile RC, et al., FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol* 2006; **124**: 1532–1542.
 - 18 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al., MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1419–1431.
 - 19 Falkner CI, Leitich H, Frommlet F, Bauer P, Binder S. The end of submacular surgery for age-related macular degeneration? A meta-analysis. *Graefes Arch Clin Exp Ophthalmol* 2007; **245**: 490–501.
 - 20 Wong D, Durnian JM. Surgical treatment of age-related macular degeneration: will there be a role in the future? *Clin Experiment Ophthalmol* 2007; **35**: 167–173.
 - 21 Lux A, Llacer H, Heussen FM, Joussem AM. ‘Non-responders’ to Bevacizumab (Avastin) therapy of choroidal neovascular lesions. *Br J Ophthalmol* 2007; **91**: 1318–1322.

Appendix

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