Prevention of Retinal Detachment in Stickler Syndrome

The Cambridge Prophylactic Cryotherapy Protocol

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Purpose: The Stickler syndromes are the most common causes of inherited and childhood retinal detachment; however, no consensus exists regarding the effectiveness of prophylactic intervention. We evaluate the long-term safety and efficacy of the Cambridge prophylactic cryotherapy protocol, a standardized retinal prophylactic treatment developed to prevent retinal detachment arising from giant retinal tears in type 1 Stickler syndrome.

Design: Retrospective comparative case series.

Participants: Four hundred eighty-seven patients with type 1 Stickler syndrome.

Methods: Time to retinal detachment was compared between patients who received bilateral prophylaxis and untreated controls, with and without individual patient matching. Patients receiving unilateral prophylaxis (after fellow eye retinal detachment) were similarly compared with an appropriate control subgroup. Individual patient matching ensured equal age and follow-up between groups and that an appropriate control (who had not suffered a retinal detachment before the age at which their individually matched treatment patient underwent prophylactic treatment) was selected. Matching was blinded to outcome events. Individual patient matching protocols purposely weighted bias against the effectiveness of treatment. All treatment side effects are reported.

Main Outcome Measures: Time to retinal detachment and side effects occurring after prophylactic treatment.

Results: The bilateral control group (n = 194) had a 7.4-fold increased risk of retinal detachment compared to the bilateral prophylaxis group (n = 229) (hazard ratio [HR], 7.40; 95% confidence interval [CI], 4.53–12.08; P < 0.001); the matched bilateral control group (n = 165) had a 5.0-fold increased risk compared to the matched bilateral prophylaxis group (n = 165) (HR, 4.97; 95% CI, 2.82–8.78; P < 0.001). The unilateral control group (n = 104) had a 10.3-fold increased risk of retinal detachment compared to the unilateral prophylaxis group (n = 64) (HR, 10.29; 95% CI, 4.96–21.36; P < 0.001); the matched unilateral control group (n = 39) had a 8.4-fold increased risk compared to the matched unilateral prophylaxis group (n = 39) (HR, 8.36; 95% CI, 3.24–21.57; P < 0.001). No significant long-term side effects occurred.

Conclusions: In the largest global cohort of type 1 Stickler syndrome patients published, all analyses indicate that the Cambridge prophylactic cryotherapy protocol is safe and markedly reduces the risk of retinal detachment. Ophthalmology 2014;121:1588-1597 © 2014 by the American Academy of Ophthalmology.

Supplemental video is available at www.aaojournal.org.
pars plana \(^5\) and this predisposition offers the unique opportunity for a specific prophylactic strategy to prevent such tears from progressing to retinal detachment.

The Cambridge prophylactic cryotherapy protocol was developed with the specific rationale of preventing retinal detachment arising from giant retinal tears. For over 37 years, prophylaxis has been offered to all type 1 Stickler syndrome patients and deployed in a standardized, uniform manner. \(^20\) We report results on the largest global cohort of type 1 Stickler syndrome patients with regard to the efficacy and safety of this standardized protocol in reducing the risk of retinal detachment and blindness.

**Methods**

**Patients and Study Design**

Patients with type 1 Stickler syndrome (Online Mendelian Inheritance in Man no. 108300) were retrospectively identified from the Vitreoretinal Research Unit database, clinical records, and research pedigree files, the diagnosis being made according to published clinical criteria. \(^1\) All patients who received any form of nonstandardized prophylaxis (including any previous focal laser or cryotherapy to identified retinal breaks or areas of lattice degeneration, previous 360° prophylactic laser retinopexy, previous prophylactic scleral buckling, or previous 360° prophylactic cryotherapy undertaken in other eye units, but completed posterior to the oral retina [equatorially]) were excluded. Only patients with both eyes available for study were included.

Mutation analysis was confirmed in the majority of cases and in every case where vitreous phenotyping was not possible due to previous bilateral vitrectomy.

Patients were divided into 4 groups for analysis. (1) The bilateral prophylaxis group comprised patients who had suffered no previous retinal detachment and had undergone the Cambridge prophylactic cryotherapy protocol to both eyes. (2) The bilateral control group comprised patients who had not undergone the prophylactic protocol (patients may have suffered unilateral, bilateral, or no previous retinal detachment). (3) The unilateral prophylaxis group comprised patients who had undergone the prophylactic protocol after retinal detachment in their fellow eye. (4) The unilateral control group comprised patients who had not undergone the prophylactic protocol but suffered previous unilateral or bilateral retinal detachment (control subgroup).

**Primary Outcome Measures**

We measured (1) time to retinal detachment (this also included any case requiring further retinopexy after prophylactic cryotherapy but without formal retinal detachment repair) and (2) side effects resulting from prophylactic treatment.

Outcomes between groups receiving the Cambridge prophylactic cryotheraphy protocol and their respective controls were retrospectively compared. To account for differences in age and follow-up duration, individual patient matching was undertaken between the bilateral prophylaxis and bilateral control groups, and the unilateral prophylaxis and unilateral control groups (see matching protocols below). To facilitate equal age at last review between matched pairs, a control group follow-up “cropping” step was implemented; any retinal detachment that occurred during this “cropped” period was discarded because it did not occur during the matched follow-up time. Matching created comparison groups exactly equal in number, age, and follow-up duration, and in which patients receiving prophylaxis did so before any potential retinal detachment event in their individually matched control.

**Matching Protocol 1: Bilateral Prophylaxis versus Bilateral Control Group**

1. All bilateral prophylaxis group patients with both eyes available for analysis were included for matching.
2. Observers were blinded to prophylactic cryotherapy failure status.
3. All bilateral prophylaxis group patients were arranged in descending order of length of follow-up after prophylactic cryotherapy. Those patients with less than 1 year of follow-up after prophylactic cryotherapy were excluded from further analysis.
4. The bilateral prophylaxis group patient with the longest follow-up after prophylactic cryotherapy was selected for matching. The age at which this patient underwent prophylactic cryotherapy and their age at last review were noted for subsequent control matching.
5. All bilateral control group patients with both eyes available for analysis were included for matching.
6. From the bilateral control group, all patients who had their first retinal detachment at an age equal to or less than the age at which the selected bilateral prophylaxis group patient had their prophylactic cryotherapy were excluded from the current round of matching (but returned to the bilateral control group for subsequent rounds of matching).
7. Observers were blinded to the retinal detachment status in this selected subgroup of bilateral control group patients available for the current round of matching.
8. From this subgroup, the patient with an equal or next closest (but older) age at last review was selected to be matched to the selected bilateral prophylaxis group patient (if no control group patient had an equal or older age at last review, the selected prophylaxis group patient was considered unmatched and excluded from further matching analysis; analysis would then restart from step 4).
9. Once matched, these patients were removed from their respective bilateral prophylaxis and bilateral control groups and made unavailable for further matching.
10. Steps 4 through 9 were repeated, using the bilateral prophylaxis group patient with the next longest post-prophylactic cryotherapy follow-up as the next selected case for matching.
11. Matching continued until all bilateral prophylaxis group patients had been matched to an appropriate bilateral control or were excluded from matching.
12. The matched bilateral prophylaxis and bilateral control group patients were unmasked with regard to prophylactic cryotherapy failure and retinal detachment status, respectively.
13. Individual patient ages at last review in the matched bilateral control group (purposely selected to be equal in age or older) were compared with the individual patient ages at last review in the corresponding matched bilateral prophylaxis group and “cropped” accordingly to equal the age at last review of their match. Any retinal detachment events that occurred in the matched bilateral control group patients during this “cropped” period were excluded from further analysis.
14. Prevalence of retinal detachment was then compared between the matched bilateral prophylaxis and “cropped” matched bilateral control groups.

**Matching Protocol 2: Unilateral Prophylaxis versus Unilateral Control Group**

1. All unilateral prophylaxis group patients with both eyes available for analysis were included for matching.
Steps 4 through 10 were repeated using the unilateral prophylaxis group patients were arranged in descending order of length of follow-up after prophylactic cryotherapy. Those patients with less than 1 year of follow-up after prophylactic cryotherapy were excluded from further analysis.

The unilateral prophylaxis group patient with the longest follow-up after prophylactic cryotherapy was selected for further matching. The age at which this patient suffered their first retinal detachment (untreated eye), the age at which they underwent prophylactic cryotherapy (treated eye), and their age at last review were noted for subsequent control matching.

All unilateral control group patients with both eyes available for analysis were included for matching.

Observers were blinded to retinal detachment status in the second eye.

The unilateral control group patient with an age of first retinal detachment closest to that of the selected unilateral prophylaxis group patient’s age of first retinal detachment was selected for further matching (if there was a difference of greater than 3 years, the selected unilateral prophylaxis group patient was considered unmatched and excluded from further matching; analysis would then restart from step 4). If the selected unilateral control group patient’s age at last review was equal to or older than the selected unilateral prophylaxis group patient’s age at last review, they were considered for the final matching step (if the age at final review was less than the selected unilateral prophylaxis group patient’s age at last review, the matching process returned to step 7, selecting the unilateral control group patient with the next closest age of first retinal detachment).

The final matching step involved unmasking the selected unilateral control group patient’s retinal detachment status in their second eye. If the selected unilateral control group patient did not have a second retinal detachment event or the age at which they had their second retinal detachment was older than the age at which the selected unilateral prophylaxis group patient had their prophylactic cryotherapy, they were considered an appropriate match (if the selected unilateral control group patient’s age at second retinal detachment was the same or younger than the age at which the selected unilateral prophylaxis group patient had their cryotherapy, the match was considered inappropriate and the matching process returned to step 7, selecting the unilateral control group patient with the next closest age of first retinal detachment).

Once matched, these patients were removed from their respective unilateral prophylaxis and unilateral control groups and made unavailable for further matching.

Steps 4 through 10 were repeated using the unilateral prophylaxis group patient with the next longest follow-up after prophylactic cryotherapy as the next selected case for matching.

Matching continued until all unilateral prophylaxis group patients had been matched to an appropriate control or were excluded from matching.

The matched unilateral prophylaxis group patients were unmasked with regard to prophylactic cryotherapy failure. Individual patient ages at last review in the matched unilateral control group (purposely selected to be equal in age or older) were compared with the individual patient ages at last review in the corresponding matched unilateral prophylaxis group and “cropped” accordingly to equal the age at last review of their match. Any retinal detachment event that occurred in the matched unilateral control group patients during this “cropped” period were excluded from further analysis.

The prevalence of retinal detachment was then compared between the matched unilateral prophylaxis and “cropped” matched unilateral control groups.

The Cambridge Prophylactic Cryotherapy Protocol

Informed, written consent was obtained from all patients electing to undergo prophylactic treatment. Under general anesthesia, carefully monitored 360° transconjunctival prophylactic cryotherapy was applied in a contiguous ribbon at the junction of the postoral retina with the pars plana (Fig 1; procedure Video available at www.aaojournal.org).

Side Effects

The occurrence of the following prophylaxis side effects was assessed: change in pre- and postoperative visual acuity, lid and conjunctival inflammation, accommodation insufficiency, discomfort, photophobia, macular pucker, and any perioperative surgical complication. Anesthetic recovery records were reviewed for episodes of nausea or vomiting.

Statistical Analysis

Kaplan—Meier survival curves and log-rank tests were used to compare time-to-event outcomes between patients. For the bilateral prophylaxis versus bilateral control group, the primary outcome was time from birth to first retinal detachment. However, for the matched bilateral prophylaxis versus matched bilateral control group, it was time from cryotherapy (or the corresponding time in the individually matched control) to first retinal detachment. For the unilateral prophylaxis versus unilateral control group, the primary outcome was time from first retinal detachment to second retinal detachment. However, for the matched unilateral prophylaxis versus matched unilateral control group, it was time from cryotherapy (or the corresponding time in the individually matched control) to second retinal detachment. Sex-adjusted hazard ratios for treatment effect and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. All statistical tests were 2-sided and used a 5% significance level. Analyses were completed using SPSS software 21.0 (IBM Corp., Armonk, NY).

Results

Four hundred eighty-seven patients with type 1 Stickler syndrome from 239 family pedigrees met the inclusion criteria; 229 underwent bilateral prophylaxis, 64 underwent unilateral prophylaxis, and 194 received no prophylactic intervention (104 of whom qualified for the unilateral control subgroup). Of these, 426 patients (87.5%) were tested for COL2A1 mutations; the mutation detection rate using the Cambridge 2-stage diagnostic screening strategy was 96.9% at the time of study completion. Demographic details are given in Table 1.

Bilateral Prophylaxis versus Bilateral Control Group

The prevalence of retinal detachment in the bilateral prophylaxis group was 8.3% (19/229), of which 7.9% (18/229) were unilateral...
and 0.4% (1/229) bilateral. The prevalence of retinal detachment in the bilateral control group was 53.6% (104/194), of which 10.3% (20/194) were unilateral and 43.3% (84/194) bilateral (Fig 2). Of the 20 retinal detachment events occurring after prophylaxis, 12 required surgical repair and 8 were managed with additional retinopexy alone; all 188 control group retinal detachments required formal surgical repair.

The median time to first retinal detachment was 18.28 years (95% CI, 14.92–21.63) in the bilateral control group; a median time was not reached in the bilateral prophylaxis group (Fig 3A). The hazard ratio of having a retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 7.40 (95% CI, 4.53–12.08; P<0.001) (Table 2).

Matched Bilateral Prophylaxis versus Matched Bilateral Control Group

The individual matching protocol resulted in 165 patients with equal age at last review and follow-up duration being paired for comparison. The prevalence of retinal detachment in the matched bilateral prophylaxis group was 9.1% (15/165), of which 8.5% (14/165) were unilateral and 0.6% (1/165) bilateral. The prevalence of retinal detachment in the matched bilateral control group was 37.0% (61/165), of which 16.4% (27/165) were unilateral and 20.6% (34/165) bilateral (Fig 2). Of the 16 retinal detachment events occurring after prophylaxis, 2 were managed with additional retinopexy alone; all 95 matched control group retinal detachments required formal surgical repair. Before “cropping,” the prevalence of retinal detachment in the matched bilateral control group was 61.8% (102/165); 89 retinal detachment events were “cropped” and omitted from analysis.

The median time to retinal detachment was 16.41 years (95% CI, 5.31–27.51) in the matched bilateral control group; a median time was not reached in the matched bilateral prophylaxis group (Fig 3B). The hazard ratio of having a retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 4.97 (95% CI, 2.82–8.78; P<0.001) (Table 2).

Unilateral Prophylaxis versus Unilateral Control Group

The prevalence of second eye retinal detachment in the unilateral prophylaxis group was 12.5% (8/64) compared with 80.8% (84/104) in the unilateral control group (Fig 2). Of the 8 retinal detachment events occurring after prophylaxis, 6 required surgical repair and 2 were managed with additional retinopexy alone; all 84 second eye retinal detachments in the control group required formal surgical repair.

The median time to second eye retinal detachment was 4.00 years (95% CI, 2.17–5.83) in the unilateral control group compared with 51.60 years (95% CI, 13.29–88.83) in the unilateral prophylaxis group (Fig 3C). The hazard ratio of having a second eye retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 10.29 (95% CI, 4.96–21.36; P<0.001) (Table 2).

Matched Unilateral Prophylaxis versus Matched Unilateral Control Group

The individual matching protocol resulted in 39 patients with equal age at last review and follow-up duration being paired for comparison. The prevalence of second eye retinal detachment in the matched unilateral prophylaxis group was 15.4% (6/39) compared
with 69.2% (27/39) in the matched unilateral control group (Fig 2). Of the 6 retinal detachment events occurring after prophylaxis, 5 required surgical repair and 1 was managed with additional retinopexy alone; all 27 matched control group second eye retinal detachments required formal surgical repair. Before “cropping,” the incidence of second eye retinal detachment in the matched unilateral control group was 87.2% (34/39); 7 second eye retinal detachments were “cropped” and omitted from analysis.

The median time to second eye retinal detachment was 5.93 years (95% CI, 0.00—13.66) in the matched unilateral control group; a median time was not reached in the matched unilateral prophylaxis group (Fig 3D). The hazard ratio of having a second eye retinal detachment without prophylaxis, based on treatment effect adjusted for sex, was 8.36 (95% CI, 3.24—21.57; P < 0.001) (Table 2).

**Prophylaxis Failure**

Failure of retinal cryotherapy prophylaxis occurred in 9.0% (27/299) of patients receiving treatment. The average age at the time of the cryotherapy procedure in the failed cases was 21.5 years (range, 2.4—59.6 years; standard deviation, 19.2 years) and the average time from treatment to prophylaxis failure was 5.6 years (range, 0.1—22.4 years; standard deviation, 7.2 years).

Eighteen eyes required formal surgical retinal detachment repair. Six of these cases were due to retinal breaks identified posteriorly and 5 cases were attributed to treated anterior breaks being lifted off or extending through the cryotherapy treatment barrier. There was a single case treated for a break that developed at the junction of the posterior edge of the cryotherapy treatment and untreated retina. No data were available for 6 cases requiring surgical retinal detachment repair, 2 of which presented with associated proliferative vitreoretinopathy owing to delayed presentation after retinal detachment.

Of the 10 cases of prophylaxis classed as “failure” but managed with additional retinopexy alone, 7 cases were for retinal breaks occurring posteriorly (3 of which had associated subretinal fluid); 2 cases were for localized retinal detachments that were being held by the cryotherapy treatment (but a further retinopexy barrier was applied for additional security), and 1 case was for a suspected break at the junction of the posterior edge of the cryotherapy-treated and untreated retina.

All failure cases were unilateral except one bilateral case, which developed in a 4-year-old child with a coexisting diagnosis of Down syndrome; the operation record documented concerns regarding the appearance of the peripheral retina at the time of cryotherapy. Bilateral prophyllactic cryotherapy failure was diagnosed 51 days after treatment; the right retinal detachment had
associated proliferative vitreoretinopathy and the left retinal detachment was secondary to an inferior horseshoe tear located posteriorly to the treatment barrier.

**Side Effects**

The Cambridge prophylactic cryotherapy protocol caused no reported significant long-term side effects in any of the 293 patients who underwent treatment. In particular, no cases of choroidal hemorrhage, macular pucker, or unexplained visual loss occurred. The mean logarithm of the minimum angle of resolution visual acuity before and after prophylaxis, recorded in 414 eyes (182 bilateral prophylactic and 50 unilateral prophylactic group patients), was 0.29 (range, -0.18 to 1.80; standard deviation, 0.29) and 0.25 (range, -0.18 to 1.30; standard deviation, 0.24), respectively. At review, visual acuity was the same or better than preoperative acuity readings in all patients, except for a single 38.4-year-old patient with a previously diagnosed Foster Fuch’s spot and progressive macular atrophy, who did not regain unilateral preoperative vision. Table 3 summarizes all reported side effects.

**Discussion**

The risk of retinal detachment in patients with type 1 Stickler syndrome is very high.13–23 The oldest patient in the current series to suffer their first retinal detachment was 78.5 years. The median survival time to first retinal detachment in the bilateral control group was 18.3 years, and the median survival time from first to second retinal detachment in the unilateral control group was 4.0 years. The most disturbing cases, however, are the late presentations of preverbal children with inoperable bilateral retinal detachments. Severe visual loss, compounded by the hearing, speech, and mobility problems associated with this disorder, results in a significant, life-long impact on the future of these young people.

Recent development and provision of 2-stage diagnostic screening7 means that type 1 Stickler syndrome can now be accurately identified and confirmed in over 90% of cases.15 Further refinement with specialized minigene and multiplex ligation-dependent probe amplification analysis has resulted in a mutation detection rate of 96.9% at the time of completion of this study (Department of Health National Specialist Commissioning Team [NSCT], Stickler Diagnostic Service, unpublished data, June 2011).

Our current practice algorithm for managing patients with Stickler syndrome commences with multidisciplinary team phenotyping to direct which collagen gene is to be sequenced. Identification of a COL2A1 mutation confirms the clinical diagnosis of type 1 Stickler syndrome and patients are offered genetic counseling. The risk of retinal detachment versus the risks of retinal prophylaxis is discussed with patients and families. Should prophylactic intervention be sought, patients are routinely wait-listed for surgery.

Type 1 Stickler syndrome carries a life-long risk of retinal detachment and prophylaxis is offered to patients of any age. Historically, prophylaxis was only given after the age of 5, when children were considered cooperative enough to accurately phenotype the vitreous on slit-lamp biomicroscopic examination. Currently, predictive molecular
testing in family pedigrees with known mutations allows confirmation of the subtype of the Stickler syndrome at any age, facilitating earlier prophylaxis. Early, accurate diagnosis is essential if prophylaxis is to be offered before retinal detachment occurs. Although rare before 1.5 years of age, the youngest child seen with bilateral retinal detachments was 6 weeks of age; the youngest patient to receive prophylaxis in our series was 10.8 months.

The rationale of the Cambridge prophylactic cryotherapy protocol is to prevent retinal detachment secondary to giant retinal tears; prevention of “conventional” posterior breaks would not be expected or intended. This limitation needs to be clarified to patients consenting to treatment, explaining that the expectation is to substantially reduce (but not eliminate) the risk of retinal detachment.

Cryotherapy rather than prophylactic laser retinopexy was used for every treated patient in this series as past experience has shown it to be safe when deployed according to this specific protocol and to avoid introducing a further confounding variable of a different treatment modality. The results provide the first benchmark against which future treatment modalities or strategies could be compared.

It is accepted that the results of any form of retrospective analysis should be interpreted with caution because they may be more prone to bias; previous studies of prophylaxis in Stickler syndrome are no exception. Although patients and

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Figure 3. Kaplan–Meier survival curves and log-rank test outcomes for matched and unmatched prophylactic and control groups. A, Time from birth to first retinal detachment for the bilateral prophylaxis versus bilateral control group. B, Time from cryotherapy (or the corresponding time in the individually matched control) to first retinal detachment for the matched bilateral prophylaxis versus matched bilateral control group. C, Time from first retinal detachment to second retinal detachment for the unilateral prophylaxis versus unilateral control group. D, Time from cryotherapy (or the corresponding time in the individually matched control) to second retinal detachment for the matched unilateral prophylaxis versus matched unilateral control group.
First, let's analyze the document's content and format. It appears to be a scientific paper discussing the efficacy of prophylactic cryotherapy in Stickler syndrome. The text is divided into sections discussing the design of the study, the results, and implications. The document includes tables and statistical analyses.

### Table 2. Unadjusted and Sex-adjusted Hazard Ratios with 95% Confidence Intervals for Matched and Unmatched Prophylactic and Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral control vs bilateral prophylaxis</td>
<td>7.27*</td>
<td>4.47–11.87</td>
</tr>
<tr>
<td>(unadjusted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral control vs bilateral prophylaxis</td>
<td>7.40*</td>
<td>4.53–12.08</td>
</tr>
<tr>
<td>(sex adjusted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched bilateral control vs matched bilateral prophylaxis (unadjusted)</td>
<td>4.77*</td>
<td>2.71–8.40</td>
</tr>
<tr>
<td>Matched bilateral control vs matched bilateral prophylaxis (sex adjusted)</td>
<td>4.97*</td>
<td>2.82–8.78</td>
</tr>
<tr>
<td>Unilateral control vs unilateral prophylaxis (unadjusted)</td>
<td>10.06*</td>
<td>4.86–20.84</td>
</tr>
<tr>
<td>Unilateral control vs unilateral prophylaxis (sex adjusted)</td>
<td>10.29*</td>
<td>4.96–21.36</td>
</tr>
<tr>
<td>Matched unilateral control vs matched unilateral prophylaxis (unadjusted)</td>
<td>6.85*</td>
<td>2.80–16.75</td>
</tr>
<tr>
<td>Matched unilateral control vs matched unilateral prophylaxis (sex adjusted)</td>
<td>8.36*</td>
<td>3.24–21.57</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*P<0.001.

Table 2 shows the hazard ratios and 95% confidence intervals for matched and unmatched prophylactic and control groups for bilateral and unilateral control versus prophylaxis. The hazard ratios are significantly increased, indicating a protective effect of prophylactic cryotherapy.

### Table 3. Recorded and Reported Side Effects occurring after Prophylactic Cryotherapy

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Affected, n/N (%)</th>
<th>Mean (SD) Age (yrs)</th>
<th>Mean (SD) Time to Resolution (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lid/conjunctival inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>75/293 (25.6)</td>
<td>10.7 (9.9)</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Moderate</td>
<td>40/293 (13.7)</td>
<td>17.4 (18.3)</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Marked</td>
<td>20/293 (6.8)</td>
<td>14.8 (16.0)</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>35/293 (11.9)</td>
<td>15.8 (12.5)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Accommodation insufficiency</td>
<td>28/293 (9.6)</td>
<td>25.8 (14.2)</td>
<td>5.3 (2.5)</td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td>7/293 (2.4)</td>
<td>21.2 (18)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anisocoria/mydriasis</td>
<td>6/293 (2.0)</td>
<td>30.2 (23.1)</td>
<td>6.8 (2.9)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>3/293 (1.0)</td>
<td>25.1 (24.6)</td>
<td>2.7 (1.2)</td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>2/293 (0.7)</td>
<td>9.2 (2.5)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>New floater</td>
<td>1/293 (0.3)</td>
<td>18.3</td>
<td>6</td>
</tr>
</tbody>
</table>

SD = standard deviation.

The side effects are listed with the number of occurrences and percentages, along with the mean age and time to resolution. For example, mild lid/conjunctival inflammation affects 25.6% of patients, with a mean age of 10.7 years and a resolution time of less than 4 weeks.

In summary, the study demonstrates the efficacy of prophylactic cryotherapy in reducing the risk of retinal detachment in Stickler syndrome, with a clear benefit shown for matched bilateral controls versus bilateral prophylaxis. The results are supported by the statistical analyses in Table 2 and the detailed reporting of side effects in Table 3.
up) with 194 untreated control patients. The results definitively demonstrate that the Cambridge prophylactic cryotherapy protocol is safe and significantly reduces the risk of retinal detachment in type 1 Stickler syndrome.

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References

Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
CI = confidence interval; HR = hazard ratio; RD = retinal detachment.

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