Comparison of focal cryoballoon ablation with 10- and 8-second doses for treatment of Barrett's esophagus–related neoplasia: results from a prospective European multicenter study (with video) CME

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Background and Aims: Focal cryoballoon ablation (FCBA) is currently being investigated for the treatment of Barrett's esophagus (BE)-related neoplasia in a European multicenter study (Euro-Coldplay study). After inclusion of 28 of 107 patients, the initial dose of 10 seconds was lowered to 8 seconds. The current study aimed to compare the efficacy and safety of a single FCBA treatment session with 10 seconds versus 8 seconds.

Methods: Treatments were performed at 7 European BE referral centers. All 28 patients treated with 10 seconds were compared with 28 consecutive patients treated with 8 seconds. The gastroesophageal junction was ablated circumferentially followed by all visible BE. To assess efficacy and safety, 3 expert adjudicators, blinded to physician and dose, compared pre- and post-treatment images. Primary outcomes were median BE surface regression and stricture rate after single-session FCBA.

Results: We included 56 patients (10-second cohort, n = 28; 8-second cohort, n = 28) with a median BE length of C0M2 (Prague classification). Baseline characteristics did not significantly differ between the cohorts. The median BE surface regression after a single FCBA session was comparable for 10 seconds and 8 seconds (80% [95% confidence interval {CI}, 75-90] and 80% [95% CI, 66-90], respectively; $P = .65$). Strictures requiring dilation were seen in 19% (95% CI, 4-33) and 15% (95% CI, 4-30) of the 10-second and 8-second groups, respectively ($P = 1.00$). Two patients in the 10-second group developed a severe stricture requiring >3 dilations.

Conclusions: In patients with limited BE, single-session FCBA with 8 seconds showed similar BE surface regression as compared with 10 seconds and may theoretically result in fewer and less severe strictures. Therefore, we suggest using 8 seconds as the standard dose for FCBA. (Clinical trial registration number: NL7253.) (Gastrointest Endosc 2022;96:743-51.)

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Cryoballoon ablation (CBA) is a relatively new endoscopic ablation technique developed for the eradication of Barrett's esophagus (BE)–related neoplasia[1] and holds several potential advantages compared with radiofrequency ablation (RFA), the current standard of care.[2-4] CBA is believed to maintain the architecture of the extracellular matrix and therefore potentially allows deeper tissue ablation with lower stricture rates.[5] Moreover, CBA might be associated with improved patient tolerance.[6]

Initially, focal CBA (FCBA) was introduced to treat small surface areas, with each ablation covering approximately 2 cm^2. Previous studies have demonstrated that FCBA, mostly performed with ablations of 10 seconds, is feasible, effective, and safe for the treatment of BE with a relatively small surface extent containing flat-type early neoplasia, with complete eradication of intestinal metaplasia in 88% to 100% of cases.[6-9] Because these studies included a limited number of patients with short follow-up, the efficacy and safety of FCBA is currently being investigated in a large, prospective, European, multicenter study (Euro-Coldplay study; Netherlands Trial Registry NL7253).

After including 28 of the planned 107 patients, the Euro-Coldplay study was temporarily paused because of an unexpected high stricture rate when compared with the literature. Aiming at improving safety while preserving efficacy, the initial dose of 10 seconds was lowered to 8 seconds, and 28 patients were subsequently treated with the lower dose. For the current study, we compared the efficacy and safety of a single FCBA treatment with 10 seconds versus 8 seconds in the 56 patients with limited BE who were consecutively enrolled in the Euro-Coldplay study. This comparison formed the basis for the formal decision of whether or not continuation of the study was justified after the dose reduction.

METHODS

Study setting and patient selection

We performed a retrospective analysis of prospectively collected data from the Euro-Coldplay study. In this prospective, multicenter, single-arm study, patients from 7 European tertiary BE referral centers were included. Patients (age $\geq$18 years) with short BE segments (C $\leq$2 cm and M $\leq$5 cm according to the Prague classification) and an indication for ablation therapy were eligible for study participation. Ablation therapy was indicated for patients with flat BE with either confirmed low-grade dysplasia or high-grade dysplasia or residual BE after endoscopic resection of a visible lesion containing any degree of dysplasia or low-risk early esophageal adenocarcinoma (ie, invasion depth of <500 μm, good/moderate differentiation grade, absence of lymphovascular invasion, and negative deep resection margins). Exclusion criteria were prior extensive endoscopic resection (>2 cm in length and/or >50% of esophageal circumference), prior endoscopic ablation therapy, esophageal stricture preventing advancement of a therapeutic endoscope, active esophagitis (higher than Los Angeles grade A), or esophageal varices. For the current study, we included all 28 patients treated with the initial dose of 10 seconds and the first 28 patients treated with the lowered dose of 8 seconds (Fig. 1).

Focal C2 Cryoballoon Ablation system

The C2 Cryoballoon Ablation system (Pentax Medical, Redwood City, Calif, USA) consists of a handheld controller, foot pedal, balloon catheter, and disposable cartridges containing liquid nitrous oxide (Supplementary Fig. 1, available online at www.giejournal.org). The system is compatible with therapeutic endoscopes with an accessory channel of at least 3.7 mm. The compliant balloon automatically adjusts to the size of the esophagus and contains a rotatable spray diffuser in the center. Using the foot pedal, the user can position the spray diffuser, and a continuous flow of nitrous oxide can be emitted to the balloon at approximately –80°C. Depending on the type of balloon catheter, different surface areas can be treated. For the Euro-Coldplay study, we used the focal cryoballoon catheter that covers approximately 2 cm^2 of the esophagus per ablation (Fig. 2).

Treatment

All patients were treated by experienced endoscopists (A.R., J.J.G.H.M.B., R.E.P., R.B., R.J.H., T.B., H.N., and B.L.A.M.W.) who were specifically trained in FCBA and had a minimum of 5 lead-in cases before enrolling patients. An endoscopy system from Pentax Medical with high-resolution white-light endoscopy and i-SCAN Optical Enhancement imaging were used for all study procedures. The BE segment was carefully inspected with documentation of the C&M classification and the location of the most proximal islands. Still images were acquired of every 1 cm of the entire BE segment, and videos were recorded at the discretion of the physician. Electrocoagulation markings were optionally placed at the gastroesophageal junction to guide optimal positioning of the balloon. All study procedures began with circumferential ablation of the gastroesophageal junction followed by ablation of all visible BE (including BE islands) using side-by-side ablations with either 10-second or 8-second applications and without restriction of the total number of ablations (Video 1, available online at www.giejournal.org). The dose was lowered to 8 seconds or 6 seconds for, respectively, the 10-second and 8-second cohort in case of severe scarring (eg, because of prior endoscopic resection) or to prevent overlapping ablations in case of a small remaining area of untreated Barrett's mucosa.

All procedures were performed on an inpatient or outpatient basis according to the site's standard of care for anesthesia and sedation. A study representative from the coordinating center (C.N.F. and/or A.O.) attended all procedures on-site to ensure protocol compliance and to collect study data. The duration of the endoscopy was defined as the time between introduction and removal of the endoscope, and ablation time was defined as the time between insertion and removal of the FCBA catheter.

Follow-up

All patients received high-dose proton pump inhibitors (equivalent to esomeprazole 40 mg twice daily) after treatment. Additional acid-inhibiting medication was prescribed at the discretion of the physician (eg, H2 receptor antagonist and/or sucralfate suspension). After treatment, patients were asked to register retrosternal pain, dysphagia, and analgesic use in a symptom diary daily for 14 days (Supplementary Fig. 2, available online at www.giejournal.org). Retrosternal pain was scored at rest and during meals on a numeric rating scale from 0 (no pain) to 10 (worst pain ever experienced). Dysphagia was scored on a validated scale from 0 (no dysphagia) to 4 (no passage even for liquids).[10] In addition, patients were contacted on day 7 (±2 days) to

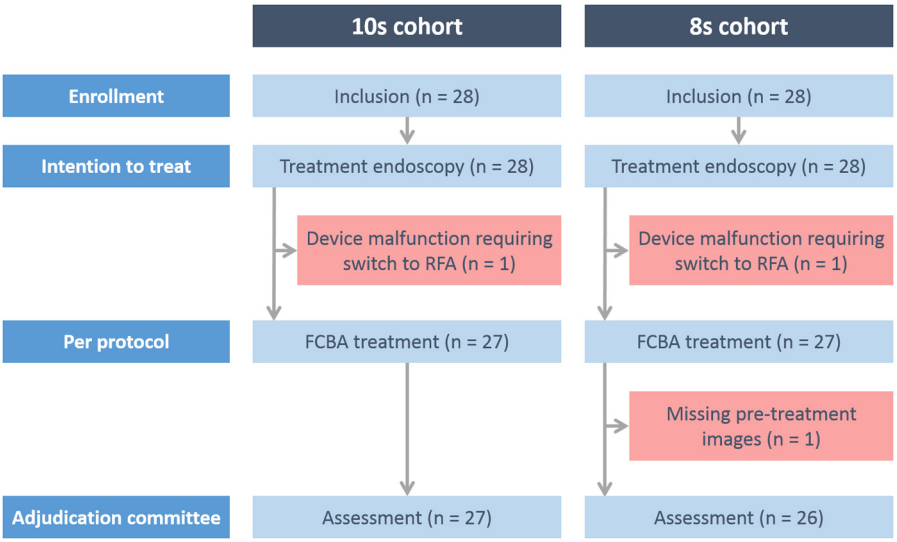

Figure 1. Flowchart of patient inclusion, treatment, and adjudication committee assessment. *FCBA*, Focal cryoballoon ablation; *10s*, 10-second; *8s*, 8-second; *RFA*, radiofrequency ablation.

evaluate retrosternal pain, dysphagia, analgesic use, and adverse events.

A subsequent FCBA session was scheduled after 12 weeks (±4), during which images (and optional videos) were recorded of every 1 cm of the original BE segment. In case of active esophagitis or inflammation, the second FCBA treatment was postponed and the images from the next follow-up endoscopy (ie, after complete healing of the esophagus) were used for the adjudicator evaluation.

Adjudicator assessment

Efficacy and safety were evaluated by the adjudication committee, consisting of 3 BE expert endoscopists (L.A.H., A.A., and B.E.S.) not involved in the Euro-Coldplay study. Each adjudicator compared pre- and post-treatment images and videos in a systematic manner to determine the BE surface regression percentage and esophageal scarring after single-session FCBA. All images and videos were provided in a random order with the adjudicator blinded to treating physician and dosages. Esophageal scarring was scored as none, mild (ie, scarring without retraction), moderate (ie, scarring with retraction but no significant narrowing of the esophageal lumen), or severe (ie, scarring with reduction of luminal diameter; Supplementary Fig. 3, available online at www.giejournal.org). The grade of esophageal scarring was determined by majority vote, but for discrepancies among all 3 readings a consensus meeting was held with the 3 committee members to establish the final score. For BE surface regression, the median of the 3 readings was used.

Outcomes

The primary outcomes were efficacy and safety. Efficacy was defined as the median BE surface regression percentage after a single FCBA treatment as evaluated by the adjudication committee. Safety was defined as the esophageal stricture rate after a single FCBA treatment. Secondary outcomes were esophageal scarring as evaluated by the adjudication committee, feasibility, incidence of (serious) adverse events (Supplementary Table 1, available online at www.giejournal.org), and tolerability. To determine feasibility, we evaluated technical success (ie, FCBA treatment of all visible BE as intended), device malfunctions (ie, technical failure of FCBA with the need for device replacement or switch to RFA), and procedure and ablation times. Tolerability was assessed through composite pain scores (ie, maximum value of 2 questions in the symptom diary regarding retrosternal pain at rest and when eating), presence of major pain (ie, composite pain score ≥4), dysphagia (score dichotomized to present or absent), and analgesic use (yes or no).

Statistical analysis

No formal sample size was calculated, because it was determined by the number of patients treated with the initial dose of 10 seconds (n = 28) who were compared with an equal number of patients treated with the lowered dose of 8 seconds (n = 28). Statistical analysis was performed using the Statistical Software Package SPSS version 27.0 for Windows (IBM Corp, Armonk, NY, USA). For baseline descriptive statistics, mean with standard deviation was used for variables with parametric distribution, and median with 25th and 75th percentiles was used for nonparametric distribution. Outcome variables were reported as medians with adjusted 95% confidence intervals (CIs) obtained with simple bootstrapping with 1000 samples. Mann-Whitney U test, χ^2 test, and Fisher exact test were used to compare groups where appropriate. Tolerability analyses were

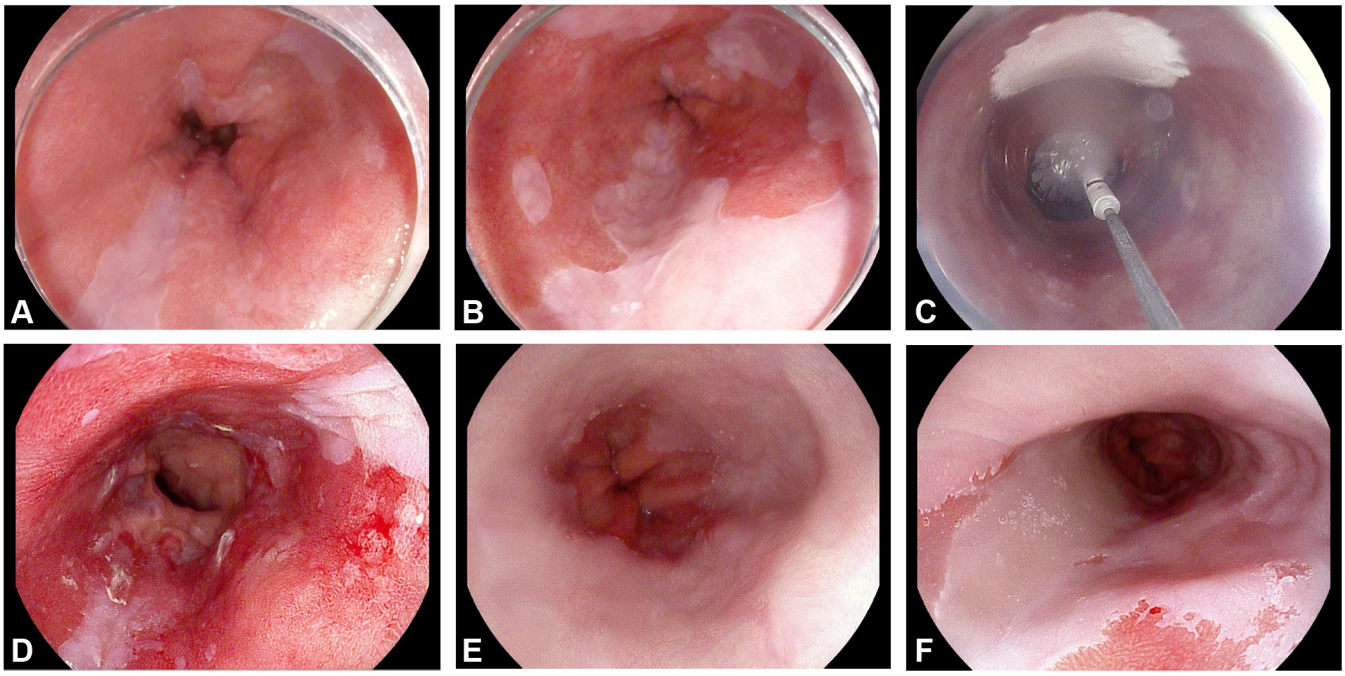

Figure 2. Focal cryoballoon ablation treatment. **A** and **B,** Flat-type C0M5 Barrett's esophagus (BE) with high-grade dysplasia. **C,** The first application of focal cryoballoon ablation with 8-second dose created an ice patch. **D,** The entire BE segment was treated with 12 ablations of 8 seconds after which a distinctive red mucosal color was visible. **E** and **F,** Follow-up endoscopy at 12 weeks showed C0M0 BE (E) with some remaining Barrett islands at the 4, 6, and 8 o'clock position (F), resulting in a median BE surface regression score of 85% without esophageal scarring.

performed in R version 4.0.3 for Mac (R Foundation for Statistical Computing, Vienna, Austria) with mixed model linear (composite pain score) and logistic (major pain, dysphagia, and painkiller use) regression analysis. Restricted cubic splines with 5 knots were considered to evaluate the effects for continuous covariates (age and BE segment length) and were included if they improved the model fit (lowering of the Akaike information criterion >2).

Ethics

The study protocol and subsequent amendments of the Euro-Coldplay study were reviewed and approved by the Medical Research Ethics Committees United. Written informed consent was obtained from all patients participating in the study, and all patients included before amending the protocol were notified of lowering the initial dose. A Data Safety Monitoring Board was established to monitor patient safety. The study is registered at www.trialregister.nl (Netherlands Trial Register NL7253).

RESULTS

Study population

We included 56 patients (10-second cohort, n = 28; 8-second cohort, n = 28) who were consecutively treated in the Euro-Coldplay study between April 2019 and October 2020. Baseline characteristics, summarized in Table 1, did not significantly differ between the 2 cohorts.

Feasibility

In both cohorts, 1 patient (1/28, 4%) could not be treated with FCBA because of a device malfunction requiring a switch to RFA. All results hereafter are reported per protocol (Fig. 1; n=27 per cohort). Device malfunctions with the need for device replacement occurred more often in the 10-second cohort (7/27, 26%) than the 8-second cohort (1/27, 4%; $P = .05$). Most device malfunctions occurred during the procedure (10 seconds, 4/7; 8 seconds, 1/1), whereas others occurred during setup (10 seconds, 3/7). After replacement of a FCBA component, all procedures were successfully completed. The technical success rate was comparable for both groups (10 seconds vs 8 seconds: 96% vs 100%; $P = 1.00$). The median ablation time was 9 minutes (95% CI, 7-12), and the median total procedure time was 21 minutes (95% CI, 18-32) for the 10-second cohort, which did not differ significantly from the 8-second cohort (median ablation time, 10 minutes [95% CI, 7-12; $P = .85$]; median total procedure time, 19 minutes [95% CI, 17-23; $P = .21$). In patients treated with 10 seconds, the number of ablations was significantly lower compared with the 8-second group (7 [95% CI, 5-8] vs 9 [95% CI, 7-12], respectively; $P = .02$).

Efficacy

In 1 patient from the 8-second cohort, BE surface regression was not assessable because of missing pretreatment images (Fig. 1). Based on the adjudication committee evaluation (Table 2), the median BE surface

regression after a single FCBA treatment was not significantly different for 10 seconds versus 8 seconds (80% [95% CI, 75-90] and 80% [95% CI, 66-90], respectively; $P = .65$). Eight patients (10-second cohort, n = 3; 8-second cohort, n = 5) had a median BE surface regression below 50%. In 2 of these patients (8-second cohort), inflammation and/or ulcerations were seen at the first follow-up endoscopy, and a second FCBA treatment was postponed. Overall, the correlation between the adjudicators was high, with a difference of <30% between the lowest and highest BE regression score in most cases (35/53, 66%).

Safety

In the 10-second cohort, 5 of 27 patients (19%; 95% CI, 4-33) developed a stricture requiring dilation as compared with 4 of 27 patients (15%; 95% CI, 4-30; $P = 1.00$) in the 8-second cohort (Table 2). The median number of dilations was comparable between the 2 groups (10-second cohort, median of 1 dilation; 8-second cohort, median of 2 dilations; $P = .78$). However, 2 patients (7%) in the 10-second cohort had a severe stricture with the need for more than 3 dilations (total of 5 and 8 dilations, respectively). In addition, strictures in the 10-second group seemed to develop after a lower number of ablations. All strictures in the 10-second cohort were seen after <10 ablations versus 1 of 4 strictures in the 8-second group (Supplementary Table 2, available online at www.giejournal.org).

The rate of esophageal scarring as evaluated by the adjudication committee was similar between the 2 groups (10 seconds vs 8 seconds: 59% [95% CI, 41-78] vs 54% [95% CI, 35-73]; $P = .69$). Although the proportion of patients with severe scarring was higher in the 10-second group (22% [95% CI, 7-37] vs 12% [95% CI, 0-27] for the 8-second group), this difference was not statistically significant ($P = .47$).

Overall, 2 serious adverse events occurred that were both unrelated to FCBA treatment. One patient had a long-term hospitalization (>10 days) after a planned surgery (10-second cohort), and 1 patient suffered a fracture requiring surgical intervention (8-second cohort).

Tolerability

Four symptom diaries (10-second cohort, 1/27; 8-second cohort, 3/27) were missing. Based on all available symptom diaries, postprocedural pain, major pain, dysphagia, and painkiller use were not significantly different for the 2 doses (Fig. 3). Forty-one percent of patients reported adjusting their daily activities after treatment with no significant differences for the 2 doses (10 patients treated with 10 seconds vs 12 patients treated with 8 seconds, $P = .49$). The median duration until all normal daily activities were resumed was short and did not differ significantly for the 2 doses (10 seconds vs 8 seconds: 2 days [95% CI, 1-4] vs 2 days [95% CI, 1-3]; $P = .57$).

DISCUSSION

This is the first study comparing 2 doses for FCBA showing that a lower dose of 8 seconds is equally effective as 10 seconds. Overall, the stricture rate did not significantly differ between both doses, although severe strictures requiring >3 dilations were solely seen in the 10-second group.

The starting dose of the Euro-Coldplay study was based on previous studies that established 10 seconds as the standard dose for FCBA.[6-9,11] However, these studies were performed with the first-generation device, whereas for the Euro-Coldplay study a next generation became available. This next-generation system was improved by adding a foot pedal to enable repositioning of the spray diffuser within the balloon and abate the need for a second operator to perform ablations and larger cartridges to reduce the number of cartridge exchanges. Considering the similarities of both systems, the energy delivery, which emanates from the conversion of nitrous oxide from liquid to gas, was taken to be equivalent. Nonetheless, after enrollment of the first 28 patients, the stricture rate was higher than expected based on previous results. While the study was temporarily on hold, a thorough technical analysis was performed to compare energy delivery and ice formation between the 2 systems. During simulated use, a dose of 10 seconds with the next-generation device resulted in more energy delivery and ice formation. Possible explanations for the higher energy delivery with the next-generation system are the addition of the foot pedal that increases the ease of use and may shorten the time between ablations, the continuous inflation of the cryoballoon during repositioning of the spray catheter and cartridge exchanges, and the potential influence of larger cartridges on the cryogen flow. After additional testing showed that a dose of 8 seconds for the next-generation device was comparable with a dose of 10 seconds with the first-generation device, the study was amended to continue with a dose of 8 seconds.

For both doses, single-session FCBA resulted in a median BE surface regression of 80%, which is comparable with single-session RFA with reported regression percentages of 78% to 90%.[12-14] Only 8 of 56 patients (14%) had a BE surface regression of <50%, which is also comparable with RFA (5%-13%).[12,15] It must be emphasized that the percentage of BE regression after a single treatment session is a surrogate endpoint. The most common clinical outcome is complete eradication of intestinal metaplasia, which is generally achieved by combining multiple treatment modalities in subsequent treatment sessions. However, for this study we were only interested in the outcomes of each FCBA dose after a single treatment session. The histologic outcomes of repetitive FCBA treatments will be evaluated in the final report on the ongoing Euro-Coldplay study.

TABLE 1. Baseline characteristics of 56 patients with Barrett's esophagus who underwent focal cryoballoon ablation treatment with either 10-second or 8-second dose

	10-second dose (n = 28)	8-second dose (n = 28)	*P* value*
Male sex	26 (93)	23 (82)	.42
Age, y	68 (58-73)	67 (59-72)	.93
Body mass index, kg/m^2	27 (25-30)	28 (24-30)	.97
ASA classification			.41
I	3 (11)	1 (4)	
II	19 (68)	23 (82)	
III	6 (21)	4 (14)	
Prior fundoplication	0 (0)	1 (4)	1.00
Reflux esophagitis	1 (4)	1 (4)	1.00
Hiatal hernia	28 (100)	26 (93)	.49
Hiatal hernia length, cm	2 (2-3)	3 (2-4)	.16
Prior endoscopic resection	17 (61)	19 (68)	.58
Worst pretreatment histology			.82
Low-grade dysplasia	8 (29)	8 (29)	
High-grade dysplasia	8 (29)	10 (36)	
Esophageal adenocarcinoma	12 (43)	10 (36)	
Preablation Barrett's esophagus length, cm			
Circumferential	0 (0-0)	0 (0-1)	.30
Maximum	2 (1-3)	3 (1-3)	.99

Values are n (%) or median (25th to 75th percentile).
*For Mann-Whitney U test, χ^2 test, or Fisher exact test.

TABLE 2. Overview of feasibility outcomes, adjudicator committee assessments, and stricture rate for both cohorts

	10-second cohort (n = 27)	8-second cohort (n = 27)	*P* value*
Feasibility			
Device malfunction	7 (26)	1 (4)	.05
Total procedure time, min	21 (17-33)	19 (16-26)	.21
Ablation time, min	9 (6-16)	10 (6-13)	.85
No. of ablations	7 (5-9)	9 (6-15)	.02
Technical success	26 (96)	27 (100)	1.00
Adjudication committee assessment†			
Barrett's esophagus surface regression, %	80 (75-92)	80 (59-92)	.65
Esophageal scarring‡			
None	11 (41)	12 (46)	.69
Mild	6 (22)	7 (27)	.69
Moderate	4 (15)	4 (15)	1.00
Severe	6 (22)	3 (12)	.47
Stricture rate			
Stricture requiring dilation	5 (19)	4 (15)	1.00
Severe stricture requiring >3 dilations	2 (7)	0 (0)	.44
No. of dilations	1 (1-8)	2 (1-3)	.78

Values are n (%), median (25th to 75th percentile), or median with range (number of dilations).
*For Mann-Whitney U test, χ^2 test, or Fisher exact test.
†Not assessable in 1 patient (8-second cohort) because of missing pretreatment images.
‡For 3 patients (10-second cohort, n = 1; 8-second cohort, n = 2) the final score was determined through consensus.

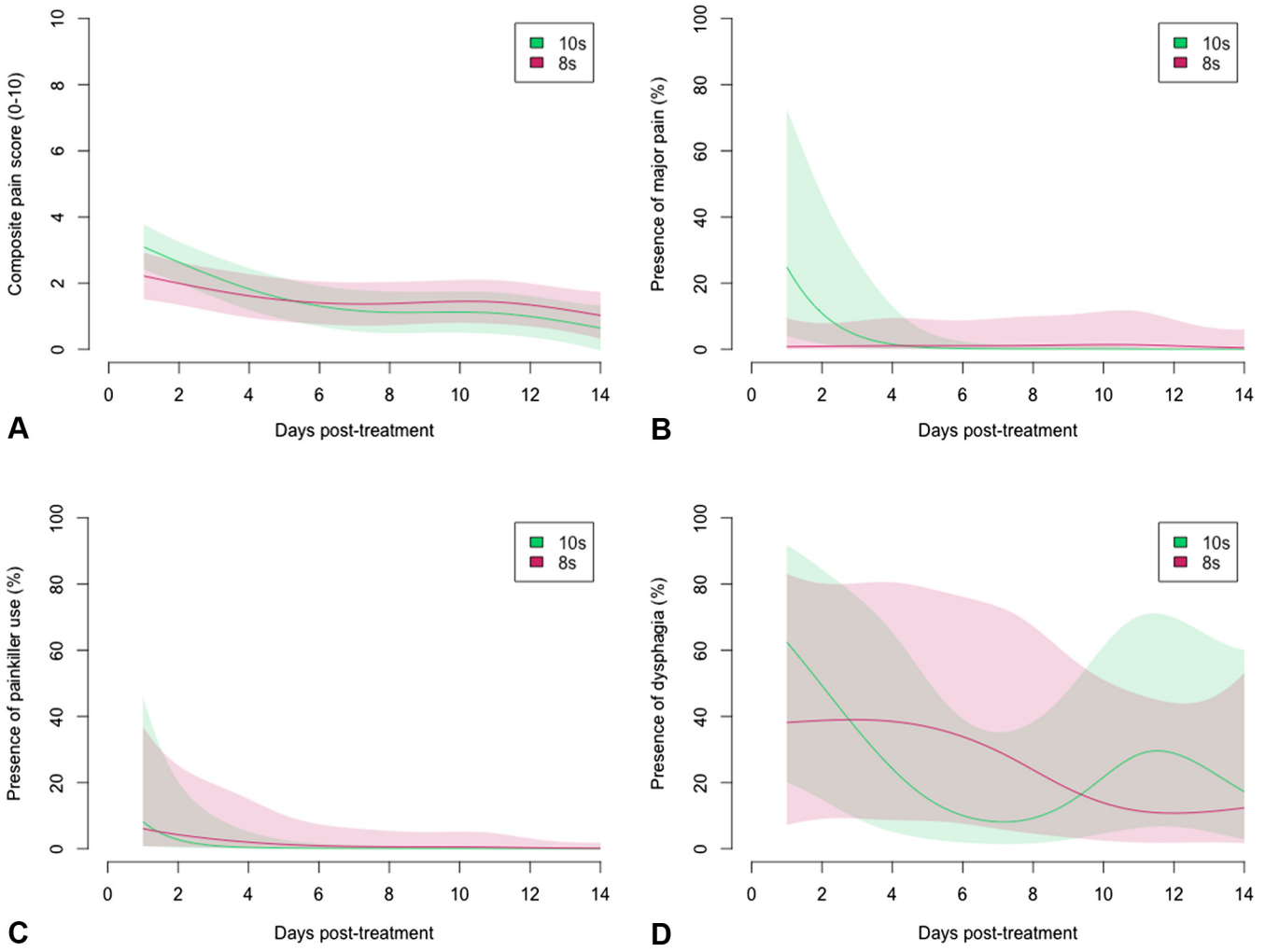

Figure 3. Postprocedural pain, major pain, dysphagia, and analgesic use after focal cryoballoon ablation treatment with either 10-second (10s; *green*) or 8-second (8s; *red*) ablations. Course of (**A**) the mean composite pain score, (**B**) presence of major pain, (**C**) painkiller use, and (**D**) presence of dysphagia per treatment dose over time with 95% confidence intervals. The composite pain score was defined as the maximum value of 2 questions in the symptom diary regarding pain at rest and pain when eating (scale 0-10, with 0 indicating no pain and 10 worst pain ever experienced). Major pain was defined as a composite pain score of 4 or higher. The course of pain was calculated with mixed-model linear regression and the presence of major pain, dysphagia, and painkiller use with mixed-model logistic regression, adjusted for the covariates age, sex, Barrett's esophagus segment length, and prior endoscopic resection. Although major pain was observed more frequently in the first days after treatment for the 10s dose, overall, pain ($P = .92$), major pain ($P = .95$), dysphagia ($P = .84$), and painkiller use ($P = .36$) were not significantly different for the 2 doses, also reflected by the continuous overlap in confidence intervals.

Although the stricture rate was statistically not different between the 10-second and 8-second group (19% [95% CI, 4-33] and 15% [95% CI, 4-30], respectively), these percentages should be interpreted with caution given the small sample size and large CIs. Strictures in the 10-second cohort seemed to occur after a lower number of ablations than for the 8-second cohort. In the 8-second cohort, 3 of 4 patients with a stricture received >10 ablations versus 0 of 5 patients in the 10-second group (Supplementary Table 2). Additionally, 36 of 58 patients (64%) underwent a prior endoscopic resection. This rate is higher than other studies on CBA reporting endoscopic resection rates of 34% to 46%[9,11] but comparable with our daily clinical practice.[16] Still, this relatively high number of prior endoscopic resections may have negatively impacted the stricture rate in both cohorts, especially because almost all stricture soccurred in patients with a prior endoscopic resection (10 seconds vs 8 seconds: 4/5 vs 4/4) (Supplementary Table 2). In addition to factors related to endoscopic treatment, patient-specific characteristics may also have contributed to the risk of stricture formation, such as severity of acid reflux and genetic factors. Moreover, it is important to note that the stricture rates for single-session FCBA cannot be directly compared with the stricture rates reported for FCBA or RFA consisting of repetitive treatment sessions.[9,11,17-19]

The feasibility of FCBA is reflected by the high technical success rate and short procedure and ablation times in both cohorts. Device malfunctions occurred in a significant proportion of patients (8/54) but were less frequently seen in the 8-second cohort, which demonstrates the maturation of the technique. In addition, FCBA was well tolerated, which is in accordance with other studies showing good patient tolerability for cryoablation therapy.[6,20]

Our comparative study evolved after the first 28 patients treated with 10 seconds in the Euro-Coldplay study showed a high rate of stenosis. The study was placed on hold until the results of 8 seconds could be evaluated, and continuation of the study at 8 seconds was considered to be justified by the Data Safety Monitoring Board. This sequence of events resulted in the first study comparing 2 FCBA doses, which may have valuable implications for daily clinical practice. Another important strength of this study is the multicenter setting in BE expert centers. Moreover, all FCBA treatments were solely performed by specifically trained endoscopists and directly monitored on-site by an attending study representative. In addition, outcomes were evaluated by 3 highly experienced expert endoscopists based on all available images and videos. Although the assessments partially depended on the quality of the images and the evaluation of BE surface regression can be challenging, especially in smaller Barrett segments, there was a high correlation between the readings of the experts.

This study also has several limitations that need to be addressed. First, the study had a small sample size, which was restricted by the number of patients treated with the initial dose of 10 seconds. Furthermore, we were only able to compare both doses after a single FCBA treatment, because the 10-second cohort was consecutively treated with 8 seconds after the dose reduction. However, multiple treatment sessions may theoretically increase the stricture risk because of a cumulative effect of ablation therapy.

Ultimately, the results from the ongoing Euro-Coldplay study (Netherlands Trial Registry NL7253), during which patients undergo a maximum of 5 repetitive FCBA treatments, will provide us with more definite data on the efficacy and safety of FCBA in BE patients. In addition, subsequent studies should also evaluate a CBA device that enables treatment of larger surface areas.[21] The combination of initial treatment by a large-area device followed by FCBA is an essential prerequisite to implement CBA in future clinical practice.

In conclusion, our data suggest that a single FCBA session with 8 seconds results in a comparable surface regression of BE as compared with 10 seconds. Considering that a dose of 8 seconds may theoretically result in fewer and less severe strictures, we suggest using 8 seconds as the standard dose to ensure the safety of FCBA while maintaining efficacy.

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Abbreviations: BE, Barrett's esophagus; CBA, cryoballoon ablation; FCBA, focal cryoballoon ablation; RFA, radiofrequency ablation.

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Supplementary Figure 1. The C2 Cryoballoon Ablation System (Pentax Medical, Redwood City, Calif, USA) consisting of a controller with nitrous oxide cartridges stored under the black cap, foot pedal, and balloon catheter.

Day 1

The first two questions refer to PAIN after the treatment.

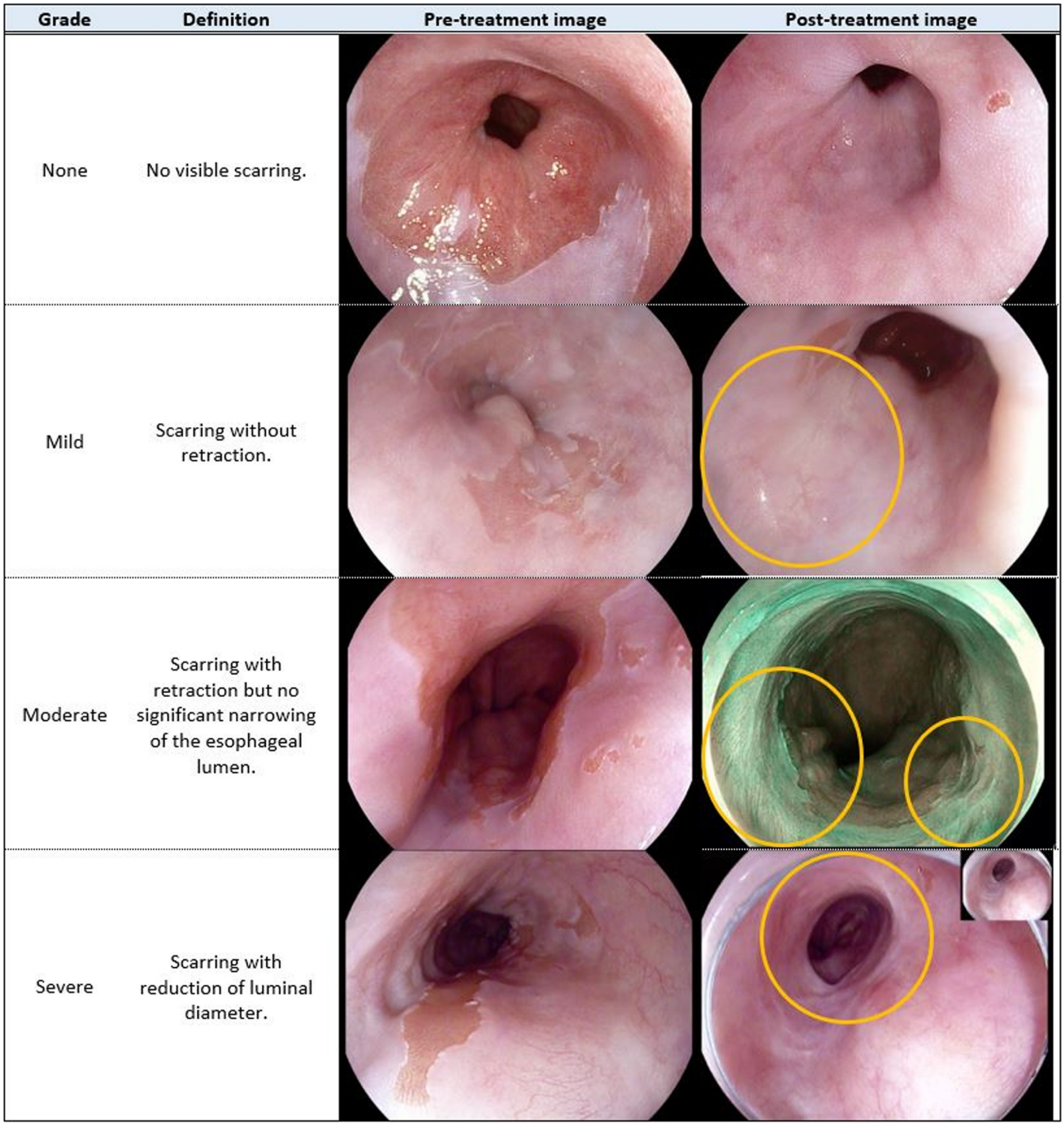
Please give a number between 0 and 10 which states the severity of pain experienced. A score of 0 indicates no pain at all. A score of 10 indicates the most severe pain you can imagine.

1. When you eat or drink, do you experience pain behind the breastbone? Note: You may only give one answer.	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	0 1 2 3 4 5 6 7 8 9 10	no pain at all severe and extreme pain
2. When you DO NOT eat or drink, do you experience pain behind the breastbone? Note: You may only give one answer.	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	0 1 2 3 4 5 6 7 8 9 10	no pain at all severe and extreme pain
3. Have you taken painkillers today? Note: you may give more than one answer.	□ □ □ □		No Yes, Paracetamol Yes, Ibuprofen, Brufen, Diclofenac or Voltaren Yes, another painkiller

The next question refers to how food and drinks pass down behind the breastbone.

4. How do you experience eating and drinking? Does it pass down easily? Note: you may only choose one answer. Choose the answer that best describes your symptoms.	○ ○ ○ ○ ○		No problem, I can eat and drink normally Some discomfort, but I can eat some solids Definite discomfort, I have to crush and puree all food A lot of discomfort, I can only drink, but not eat solids I cannot eat or drink

Supplementary Figure 2. Symptom diary to register retrosternal pain (both at rest and during meals), dysphagia, and analgesic use daily for 14 days after focal cryoballoon ablation treatment.



Supplementary Figure 3. Examples of the different grades of esophageal scarring after a single focal cryoballoon ablation treatment as scored by the adjudication committee.

SUPPLEMENTARY TABLE 1. Definition of adverse events classified according to the severity and onset time

Adverse event	Severity	Definition
Any type of adverse event	Mild	Unplanned hospital admission and/or <3 days of hospitalization
	Moderate	4-10 days of hospitalization
	Severe	>10 days of hospitalization, ICU admission, and/or need for surgery
Bleeding with the need for intervention	Mild	<3 days of hospitalization, hemoglobin drop <3 mmol/L, and/or no transfusion
	Moderate	4-10 days of hospitalization, <4 units of blood transfused, repeat endoscopic intervention, and/or radiologic intervention
	Severe	>10 days of hospitalization, ICU admission, >4 units of blood transfused, and/or need for surgery
Stricture with the need for intervention	Severe	Stenosis requiring >3 dilations, stent placement, or incision therapy
Onset time	Acute	During focal cryoballoon ablation procedure
	Early	0-48 h after the procedure
	Late	>48 h after the procedure

ICU, Intensive care unit.

SUPPLEMENTARY TABLE 2. Details of 9 patients who developed a stricture requiring dilation after single-session focal cryoballoon ablation treatment

Patient no.	Preablation Barrett's esophagus length (cm)	Prior endoscopic resection	Axial length endoscopic resection (cm)	Circumferential extent endoscopic resection (%)	No. of ablation	No. of dilations
10 seconds (n = 5)						
1	C0 M0 E.5	EMR-MBM	1	40	4	1
2	C0 M3 E3	EMR-MBM	2	50	6	8
3	C0 M1 E4	EMR-MBM	2	30	9	1
4	C2 M4 E4	—	—	—	9*	1
5	C0 M3 E3	EMR-MBM	2	30	9	5
8 seconds (n = 4)						
1	C2 M3 E3	EMR-MBM	1	20	11	3
2	C1 M2 E2	EMR with captivator	2	30	20	2
3	C1 M4 E4	Endoscopic submucosal dissection	2	50	15†	1
4	C0 M1 E1	EMR-MBM	1	42	7	1

C, Circumferential; *E*, most proximal Barrett extent including islands; *EMR-MBM*, EMR with multiband mucosectomy; *M*, maximum.
*Eight ablations of 10 seconds and 1 ablation of 8 seconds to prevent overlapping ablation areas.
†Twelve ablations of 8 seconds and 3 ablations of 6 seconds to prevent overlapping ablation areas.