Efficacy and Safety of Femtosecond Laser-Assisted Cataract Surgery Compared with Manual Cataract Surgery

A Meta-Analysis of 14,567 Eyes

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Topic: To investigate the efficacy and safety of femtosecond laser-assisted cataract surgery (FLACS) relative to manual cataract surgery (MCS).

Clinical Relevance: It is unclear whether FLACS is more efficacious and safe relative to MCS.

Methods: A literature search of MEDLINE, EMBASE, and Scopus from 2007 to March 2016 was conducted. Studies containing both FLACS and MCS arms that reported on relevant efficacy and/or safety parameters were included. Weighted mean differences (WMDs) and risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.

Results: From 2802 screened articles, 14,567 eyes from 15 randomized controlled trials and 22 observational cohort studies were included. For primary visual and refractive outcomes, no statistically significant difference was detected between FLACS and MCS in uncorrected distance visual acuity (WMD, −0.02; 95% CI, −0.04 to 0.01; P = 0.19), corrected distance visual acuity (WMD, −0.01; 95% CI, −0.02 to 0.01; P = 0.26), and mean absolute error (WMD, −0.02; 95% CI, −0.07 to 0.04; P = 0.57). In terms of secondary surgical end points, there was a statistically significant difference in favor of FLACS over MCS for effective phacoemulsification time (WMD, −3.03; 95% CI, −3.80 to −2.25; P < 0.001), capsulotomy circularity (WMD, 0.16; 95% CI, 0.11−0.21; P < 0.001), postoperative central corneal thickness (WMD, −6.37; 95% CI, −11.88 to −0.86; P = 0.02), and corneal endothelial cell reduction (WMD, −55.43; 95% CI, −95.18 to −15.69; P = 0.006). There was no statistically significant difference between FLACS and MCS for total surgery time (WMD, 1.25; 95% CI, −0.08 to 2.59; P = 0.07), capsulotomy circularity using a second formula (WMD, 0.05; 95% CI, −0.01 to 0.12; P = 0.10), and corneal endothelial cell count (WMD, 73.39; 95% CI, −6.28 to 153.07; P = 0.07). As well, there was a significantly higher concentration of prostaglandins after FLACS relative to MCS (WMD, 198.34; 95% CI, 129.99−266.69; P < 0.001). Analysis of safety parameters revealed that there were no statistically significant differences in the incidence of overall complications between FLACS and MCS (RR, 2.15; 95% CI, 0.74 to 6.23; P = 0.16); however, posterior capsular tears were significantly more common in FLACS versus MCS (RR, 3.73; 95% CI, 1.50−9.25; P = 0.005).

Conclusions: There were no statistically significant differences detected between FLACS and MCS in terms of patient-important visual and refractive outcomes and overall complications. Although FLACS did show a statistically significant difference for several secondary surgical outcomes, it was associated with higher prostaglandin concentrations and higher rates of posterior capsular tears. Ophthalmology 2016;123:2113-2126 © 2016 by the American Academy of Ophthalmology.

Supplemental material is available at www.aaojournal.org.
and setting after MCS, suggesting that a more automated procedure may achieve more reproducible results.3,4

Femtosecond laser-assisted cataract surgery (FLACS) is a technology that uses a laser to replace several of the manual steps of cataract surgery with the goal of improving accuracy, safety, and refractive outcomes. Femtosecond laser-assisted cataract surgery uses a femtosecond laser to generate free electrons and ionized molecules, which in turn produce photodisruption and photoionization of optically transparent tissue through an acoustic shock wave.5 The femtosecond laser is unique because of its shorter pulse time relative to other ophthalmic lasers.6 Theoretically, lasers with shorter pulse times are able to reduce energy output significantly for a given effect, thereby reducing collateral damage to ocular tissues.

Femtosecond lasers have been used in several different stages of cataract surgery, including clear corneal incisions, capsulotomy, and lens fragmentation. Femtosecond laser-assisted cataract surgery was approved for cataract surgery by the United States Food and Drug Administration in 2010.7 By 2013, more than 120 000 eyes globally had undergone FLACS.8 A 2014 survey of new FLACS adopters in the United States showed that 30% of cataract patients choose FLACS over conventional MCS.9

Given the increasing interest in FLACS, evidence of safety and efficacy of this technology is needed urgently. In 2013, the Department of Veterans Affairs published a systematic review in the gray literature that concluded that there was no current benefit in the safety and effectiveness of FLACS relative to MCS.10 Furthermore, they noted that there were significant methodologic concerns in the included studies, including low sample sizes, unclear study methods, few randomized controlled trials, issues with patient selection, and financial conflicts of interest. More recently, the first published meta-analysis of FLACS compared with MCS was conducted in 2015 by Chen et al.11 Analyzing a total of 989 eyes and 9 randomized controlled trials, the authors found a statistically significant improvement for FLACS over MCS in terms of mean phacoemulsification energy and effective phacoemulsification time; however, there was no difference for surgical complications. There were conflicting results for visual outcomes, central corneal thickness, and endothelial cell count depending on the length of follow-up at which outcomes were compared.

An updated and comprehensive meta-analysis of peer-reviewed clinical studies comparing FLACS with MCS is needed. This synthesis would be useful to clinicians, policy makers, and researchers who are interested in identifying the role of FLACS. Thus, we performed a meta-analysis to investigate the comparative efficacy and safety of FLACS relative to MCS in published clinical studies.

Methods

Search Strategy

Using Ovid MEDLINE (2007—March 2016, week 2), MEDLINE In-Process and Other Non-Indexed Citations (up to March 18, 2016), EMBASE (2007—2016, week 12), and Scopus (2007—March 2016), a systematic search of the literature was performed (Appendix 1A—C, available at www.aaojournal.org). Reference lists of included articles and pertinent reviews also were searched.

Eligibility Criteria

Studies were included if they met the following criteria: (1) randomized controlled trials or prospective or retrospective observational cohort studies; (2) studies that included only patients who underwent cataract surgery; (3) studies that provided safety or efficacy data, or both, for both FLACS and MCS study arms; and (4) studies that accrued more than 5 eyes to each study arm. The following exclusion criteria were used in the selection of included studies: (1) nonpublished articles (e.g., abstracts and conference proceedings); (2) articles not published in English; (3) articles with repeat data; (4) case reports or small (<5 eyes per study arm) case series; and (5) literature reviews, letters to the editor, correspondence, notes, editorials, and forthcoming journal articles. Given that existing studies in the published literature were used for this meta-analysis, institutional review board approval was not necessary. Nonetheless, the study adhered fully to the Declaration of Helsinki.

Study Selection, Data Collection, and Outcome Measures

Two authors (M.P. and X.C.-M.) examined search results to select pertinent articles for inclusion, first by title and abstract screening and then by screening full text articles. Uncertainty in inclusion was resolved through consultation with a third author (M.B.S.). The same 2 authors (M.P. and X.C.-M.) extracted the following baseline demographic and clinical data from each study arm: study design, country of origin, femtosecond laser type, date of intervention, number of included eyes, mean cohort age, gender distribution, mean corrected distance visual acuity (CDVA), and mean axial length. In addition, a comprehensive list of intraoperative and postoperative outcomes were extracted from included studies and were reported using the following headings:

1. Primary visual and refractive outcomes: uncorrected distance visual acuity (UDVA), CDVA, mean absolute error (MAE) of manifest refraction spherical equivalent.
2. Secondary surgical end points, effective phacoemulsification time, surgery time, balanced salt solution volume, cumulative dissipated energy (CDE), circularity of capsulotomy or capsulorrhexis, capsule opening diameter, absolute mean deviation from intended capsule diameter, intraocular lens (IOL) horizontal and vertical decentration, central corneal thickness, corneal endothelial cell count and preoperative to postoperative reduction, total prostaglandin concentration, and mean aqueous flare.

In the extraction of data, continuous variables were recorded as means ± standard deviations, whereas categorical variables were reported as percentages of the total sample. If any included study provided acceptable measures of variation that could be converted to a standard deviation (e.g., standard error), these data also were extracted. To facilitate the meta-analysis design, complications were grouped by anatomic site (Table 1, available at www.aaojournal.org). Data for all postoperative outcomes were collected at last follow-up. To ensure balance in the average length of follow-up between comparators, outcomes were extracted from each included study at the same follow-up period for both FLACS and MCS eyes. If outcome data were repeated in 2 or more
studies, then data from only 1 study were incorporated into the meta-analysis. Microsoft Excel (Microsoft Corporation, Redmond, WA) was used to manage all identified records and to compile extracted data.

**Risk of Bias Assessment**

To perform an assessment of study quality, 2 authors (M.P. and X.C.-M.) independently completed the Newcastle-Ottawa Quality Assessment Scale (NOS) for included observational studies and used the guidelines set by the Cochrane Collaboration for randomized controlled trials (Appendix 2A-B, available at www.aaojournal.org). The NOS is an 8-item scale that evaluates study quality based on 3 criteria: patient selection, comparability between treatment arms, and outcomes. To differentiate between high and low risk of bias on the follow-up item of the NOS, a threshold of 3 weeks of follow-up was set for all outcomes except intraoperative efficacy and safety parameters. In addition, a conservative estimate of 10% was used for the maximum acceptable loss to follow-up. For randomized controlled trials, 7 aspects of quality assessment were performed: sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, management of incomplete outcome data, completeness of outcome reporting, and other potential threats to validity. Studies were excluded if they had a high or unclear risk of bias in all assessment categories. We also evaluated the rate of authorship conflicts of interest and reported funding from industry sponsors. Further, we performed a qualitative synthesis on baseline factors that may have impacted refractive outcomes significantly.

**Data Synthesis and Analysis**

Weighted mean differences were reported for continuous variables with accompanying 95% confidence intervals. For dichotomous variables, risk ratios and 95% confidence intervals were computed. Using a random effects model in all cases, the inverse variance method was used for continuous data and the Mantel-Haenszel method was used for continuous data and the Mantel-Haenszel approach was used for dichotomous outcomes. The weighted mean was defined as
\[
\bar{x} = \frac{\sum_{i=1}^{N} w_i x_i}{\sum_{i=1}^{N} w_i}
\]
whereas the weighted standard deviation was represented by
\[
sd_w = \sqrt{\frac{\sum_{i=1}^{N} w_i(x_i - \bar{x})^2}{(N-1)\sum_{i=1}^{N} w_i}}
\]

In testing for an overall effect, the number of eyes was used as a weighting variable and comparisons that had a P value of less than 0.05 were deemed statistically significant. Statistical heterogeneity was assessed by computing a chi-square statistic; for this test, only a result of P < 0.05 was considered heterogeneous and was reported in the text. Additionally, an I² measure was computed to investigate the percentage of variance in the meta-analysis that may be attributed to heterogeneity. Sources of clinical and methodologic heterogeneity across the included studies also were examined and described qualitatively. Meta-analysis was performed for an outcome only if there were appropriate data (i.e., percentage for categorical outcome, mean ± standard deviation or standard error for continuous variable) for at least 2 study arms in each comparator. After study selection, meta-analysis was performed regardless of study design. One could argue that only randomized controlled trials should be included because of the high internal validity of this study design. However, most randomized controlled trials in the FLACS literature are unmasked and funded by industry, and as such show many of the same biases as observational cohort studies. Furthermore, the significantly increased statistical power achieved by including observational studies in the meta-analysis may outweigh the bias from confounding, especially for safety outcomes, which are underpowered frequently in randomized controlled trials. Given that a previous report found similar effect sizes based on meta-analyses that included observational studies when compared with meta-analyses of randomized controlled trials, this meta-analysis included both randomized controlled trials and observational cohort studies.

**Results**

**Study Inclusions and Demographics**

Two thousand eight hundred and two records underwent title and abstract screening. After 2716 exclusions, 86 full texts were screened. Overall, 37 articles were included in the meta-analysis with 7127 eyes undergoing FLACS and 7440 eyes undergoing MCS (Fig 1; Table 2). Mean baseline age ranged from 58.5 to 75 years in the FLACS cohort and 56.5 to 74.3 years in the MCS cohort (n = 25 studies). In the 17 studies reporting on baseline demographic gender distribution, 1890 of 2901 eyes (65.1%) were those of women in the FLACS cohort and 1694 of 3099 eyes (54.7%) were those of women in the MCS cohort. Fourteen studies reported on baseline cohort axial length. Across these articles, mean axial length ranged from 23.33 to 25.09 mm in the FLACS cohort and from 23.08 to 26.94 mm in the MCS cohort. A complete list of baseline demographic and clinical information is provided on Table 3 (available at www.aaojournal.org).

**Quality Assessment**

Most of the included eyes (12 967 eyes [89.0%]) came from observational studies (22 studies [59.5%]). There were authorship conflicts of interest in 11 of 22 (50.0%) observational studies and in 12 of 15 (80.0%) included randomized controlled trials. There was direct funding from industry sponsors in 1 of 22 (4.5%) observational studies and in 2 of 15 (13.3%) randomized controlled trials (Table 3, available at www.aaojournal.org). Assessment of study quality revealed that no included studies had a high or unclear risk of bias in all assessment categories (Table 4A, B, available at www.aaojournal.org). However, only 2 of 22 (9.1%) observational studies and 1 of 15 (6.7%) randomized controlled trials had a low risk of bias in all categories. For randomized controlled trials, omissions in the description of randomization (7/15 [46.7%]), allocation concealment (11/15 [73.3%]), blinding of participants and personnel (10/15 [66.7%]), and blinding of outcome assessment (12/15 [80.0%]) may have introduced bias into the findings. Analysis of observational studies using the NOS revealed that all articles were of either medium or high quality because no study was awarded fewer than 5 stars (range, 5—9 stars). Here, omissions in comparator comparability, outcome assessment, and completeness of follow-up may have introduced bias in terms of patient selection, group comparability, and outcome assessment. For instance, only 5 of 22 (22.7%) observational studies attempted to demonstrate comparability of cohorts at baseline and then attempted to adjust for confounding variables (Table 4B, available at www.aaojournal.org). In general, these adjustments were limited by low sample sizes and a lack of important baseline characteristics that are known to influence visual and refractive outcomes.
It was also found that certain efficacy endpoints like CDVA, effective phacoemulsification time, and CDE showed considerable between-study heterogeneity, thus limiting the interpretability of the overall effect. There were many causes of heterogeneity, including variability in the steps of FLACS, differences in FLACS and MCS platforms, surgical technique and equipment, and inconsistencies in measurement techniques, length of follow-up, patient populations, and study design (Table 2).

![Flow diagram](image)

**Table 2. Baseline Clinical and Demographic Information**

<table>
<thead>
<tr>
<th>Baseline Parameter</th>
<th>No. of Eyes (%)</th>
<th>No. of Studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of FLACS procedure</td>
<td>6390 (100.0)</td>
<td>33 (100.0)</td>
</tr>
<tr>
<td>CCI, fragmentation, capsulotomy</td>
<td>2415 (37.8)</td>
<td>9 (27.3)</td>
</tr>
<tr>
<td>Only CCI, capsulotomy</td>
<td>357 (5.6)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Only capsulotomy, fragmentation</td>
<td>3273 (51.2)</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Only capsulotomy</td>
<td>345 (5.4)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Type of FLACS machine</td>
<td>7054 (100.0)</td>
<td>37 (100.0)</td>
</tr>
<tr>
<td>LenSx (Alcon Inc, Hünening, Switzerland)</td>
<td>929 (13.2)</td>
<td>13 (35.1)</td>
</tr>
<tr>
<td>LENSAR (LENSAR, Inc, Orlando, FL)</td>
<td>321 (4.6)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Catalys (Abbott Laboratories, Inc, Abbott Park, IL)</td>
<td>4458 (63.2)</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td>Victus (Bausch &amp; Lomb, Inc, Bridgewater, NJ)</td>
<td>1346 (19.1)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Type of phacoemulsification machine</td>
<td>6614 (100.0)</td>
<td>30 (100.0)</td>
</tr>
<tr>
<td>Accurus (Alcon, Inc)</td>
<td>153 (2.3)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Constellation (Alcon, Inc)</td>
<td>60 (0.9)</td>
<td>2 (6.6)</td>
</tr>
<tr>
<td>InfiniTy (Alcon, Inc)</td>
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<td>9 (30.0)</td>
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<td>Megatron (Geuder Group, Heidelberg, Germany)</td>
<td>3458 (52.3)</td>
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<td>Stellaris (Bausch &amp; Lomb, Inc)</td>
<td>966 (14.6)</td>
<td>9 (30.0)</td>
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<tr>
<td>Last follow-up (mos)</td>
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<td>29 (100.0)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>408 (5.0)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>1−3</td>
<td>4115 (50.3)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3662 (44.7)</td>
<td>11 (37.9)</td>
</tr>
</tbody>
</table>

CCI = clear corneal incision; FLACS = femtosecond laser-assisted cataract surgery.
Qualitative synthesis revealed that a variety of potential confounding factors may have impacted the results. The following factors were not always measured, reported, compared, or adjusted for: clinical parameters (e.g., preoperative vision, refraction, corneal curvature, biometry measurements (e.g., differences in axial length, keratometry, anterior chamber depth, lens thickness), and surgical planning (e.g., type of IOL, approach to astigmatism correction).

Visual and Refractive Outcomes

To perform a meta-analysis of visual acuity data from varying studies, the formulae provided by Khoshnood et al. were used to convert from decimal to logarithm of minimum angle of resolution visual acuity. There was no statistically significant difference between FLACS and MCS in terms of postoperative UDVA (P = 0.19; heterogeneity, P = 0.004; I² = 69%; Fig 2A) or CDVA (P = 0.26; heterogeneity, P = 0.004; I² = 66%; Fig 2B). The postoperative MAE also was nonsignificantly different between comparator arms (P = 0.57; heterogeneity, P < 0.001; I² = 75%; Fig 2C).

Procedure Time and Energy

On average, meta-analysis revealed that effective phacoemulsification time was more than 3 seconds longer for MCS eyes compared with eyes undergoing FLACS (P < 0.001; Fig 2D); however, total surgery time was nonsignificantly different between comparators (P = 0.07; Fig 2E). Both analyses showed considerable statistical heterogeneity (P < 0.001; I² = 98% and 97%, respectively). There were no significant differences between comparators in terms of balanced salt solution volume (P = 0.71; Fig 2F) and total CDE (P = 0.21; Fig 2G).

Capsulotomy and Capsulorrhexis Parameters

Depending on the study, circularity of the removed capsule was measured in 1 of 2 ways: first, as the normalized ratio of the area of the capsule to the area of a hypothetical disc with a diameter equal to the greatest linear dimension of the capsule, and second, by using the following formula: circularity = 4π(area/perimeter²). In both cases, the ratio is equal to 1 for an ideal circle. Studies using the first formula found that FLACS extracted a significantly more circular capsule by 0.16 units (P < 0.001; Fig 2H). However, this result was not detected in studies using the second formula because there was no significant difference between comparators (P = 0.10; heterogeneity, P < 0.001; I² = 99%; Fig 2I).

There was no statistically significant difference in terms of capsule opening diameter between FLACS and MCS study arms (P = 0.40; Fig 2J); however, this end point also exhibited significant heterogeneity (P < 0.001; I² = 80%). Conversely, analysis of absolute mean deviation from intended diameter revealed that FLACS produced capsulotomies that were significantly closer to the intended diameter (P = 0.007; Fig 2K). Again, this end point showed heterogeneity (P < 0.001; I² = 93%).

Intraocular lens decentration was calculated by using the distance between the pupillary axis and the IOL center. The findings were mixed when decentration parameters were considered: FLACS produced significantly more horizontally centered IOLs by an average of 128.84 μm (P < 0.001; Fig 2L); however, vertical decentration was nonsignificantly different between comparators (P = 0.90; Fig 2M).

Central Corneal Thickness and Endothelial Cell Count Reduction

There was a significant difference in favor of FLACS over MCS in average central corneal thickness; after surgery, FLACS corneas were thinner by an average of 6.37 μm (P = 0.02; Fig 2N). For endothelial cell count, no significant difference was found in the number of postoperative cells per square millimeter for FLACS eyes relative to MCS eyes (P = 0.07; Fig 2O). At the same time, there was a significantly greater reduction of 55.43 endothelial cells/mm² for the MCS comparator before versus after surgery (P = 0.006; Fig 2P).

Prostaglandin Concentration and Mean Aqueous Flare

Across 2 studies by the same research team, total prostaglandin concentration was greater for eyes receiving FLACS relative to MCS (P < 0.001; Fig 2Q). In addition, between-study heterogeneity was noted for this outcome (P < 0.001; I² = 96%). For mean aqueous flare, meta-analysis revealed a nonsignificant difference between comparators (P = 0.28; Fig 2R).

Safety Analysis

Analysis of the overall incidence of complications showed that there was no statistically significant difference between comparators (P = 0.16; Fig 3A); however, there was significant heterogeneity between studies (P < 0.001; I² = 95%). The same result was maintained for other end points: capsular complications except for posterior capsular tears (P = 0.14; heterogeneity, P < 0.001; I² = 88%; Fig 3B), corneal complications (P = 0.27; heterogeneity, P < 0.001; I² = 85%; Fig 3D), and pupillary complications (P = 0.10; heterogeneity, P = 0.006; I² = 81%; Fig 3E). Eyes that underwent MCS had a significantly lower incidence of posterior capsular tears when compared with those that underwent FLACS (P = 0.005; Fig 3C).

Discussion

The purported efficacy and safety benefits of FLACS relative to MCS are based on its ability to produce more accurate, reproducible capsulotomies and clear corneal incisions, as well as to reduce the ultrasound energy and intraocular manipulation required for lens fragmentation and removal. From an efficacy standpoint, we were unable to detect a difference between MCS and FLACS for UDVA, CDVA, and MAE. In reviewing the literature, visual and refractive outcomes are the most patient-important end points from a clinical perspective. However, we do note that our analysis was limited to the outcomes that were reported. For future research, an editorial by Hoffer et al. reminds authors to zero the mean arithmetic error for their study populations, to compare median not mean absolute errors, to report categorical outcomes of patients within reasonable refractive targets, to report manifest refractions only for patients with vision of 20/40 or better, to account for correlation between eyes, and to report the instruments used to obtain various study measurements. Furthermore, we welcome novel studies addressing other measures of visual quality, including higher-order aberrations, contrast sensitivity, and dysphotopsia. For instance, Mihaltz et al.
found some evidence that the Strehl ratio and modulation transfer function were higher in eyes undergoing FLACS relative to MCS. Mixed results were found when examining the ability of FLACS to produce more circular capsulotomies. Given the 2 definitions that currently exist, it is recommended that future studies standardize the definition of circularity to facilitate better interstudy comparison. When comparing mean deviation from the intended diameter, FLACS produced capsulotomies that were significantly closer to the intended diameter relative to MCS. This difference may be attributed to variability in surgical technique and the effect of corneal magnification when performing manual capsulorhexis, which does not apply to the FLACS capsulotomy. Further, FLACS capsulotomies may not be uniform between patients; Dick et al demonstrated an age-dependent variability in capsulotomy size with pediatric FLACS procedures. Our meta-analysis also showed that IOLs implanted in FLACS patients had significantly better horizontal centration, presumably because of a more centered and circular capsulotomy. Previous authors have asserted that FLACS delivers greater accuracy and precision of the capsulotomy, which may make for a more predictable effective lens position, thus improving visual and refractive outcomes. Theoretically, capsule overlap throughout the entire circumference of the IOL optic may prevent pea-podding, Figure 2.

<table>
<thead>
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<th>A</th>
<th>Study or Subgroup</th>
<th>FLACS</th>
<th>Mean</th>
<th>SD</th>
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<th>MCS</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
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<td>1481</td>
<td>100.0%</td>
<td>-0.01 [-0.02, 0.00]</td>
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<td>Favors (FLACS)</td>
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<td>0.25</td>
<td>387</td>
<td>23.8%</td>
<td>-0.03 (-0.06, 0.00)</td>
<td>2098</td>
<td>1489</td>
<td>100.0%</td>
<td>-0.02 [-0.07, 0.04]</td>
<td>Favors (FLACS)</td>
</tr>
<tr>
<td>D</td>
<td>Study or Subgroup</td>
<td>FLACS</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>MCS</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Weight</td>
<td>Mean Difference</td>
<td>IV, Random, 95% CI</td>
<td>Mean Difference</td>
</tr>
<tr>
<td>Chee et al. 2015</td>
<td>0.94</td>
<td>3.47</td>
<td>100</td>
<td>6.5</td>
<td>4.3</td>
<td>76</td>
<td>11.1%</td>
<td>-5.56 [-7.64, -4.18]</td>
<td>2098</td>
<td>1489</td>
<td>100.0%</td>
<td>-0.02 [-0.07, 0.04]</td>
<td>Favors (FLACS)</td>
</tr>
<tr>
<td>Conrad-Hengerer et al. 2015</td>
<td>0.16</td>
<td>0.24</td>
<td>61</td>
<td>0.37</td>
<td>0.24</td>
<td>29</td>
<td>14.2%</td>
<td>-0.02 [-0.04, 0.00]</td>
<td>2098</td>
<td>1489</td>
<td>100.0%</td>
<td>-0.02 [-0.07, 0.04]</td>
<td>Favors (FLACS)</td>
</tr>
</tbody>
</table>
reducing the risk of myopic shift or astigmatism resulting from anterior optic displacement and tilt. Although Reddy et al. found that capsulorrhexis centration was improved significantly for FLACS eyes relative to MCS eyes, so far it is only possible to center the capsulotomy on the pupil. Ideally, the visual axis should be used for centration, which can be performed with MCS by using corneal markers that take advantage of Purkinje images to center the capsulorrhexis on the visual axis. In addition, the notion of circularity and centration materially affecting

Figure 2. (continued).
refractive outcomes is still being debated. For instance, in an observational study, Okada et al did not detect a significant correlation between either circularity or centration with target spherical equivalent and cylinder 1 month and 1 year after surgery. Nonsignificant findings in refractive outcomes may be attributable to numerous sources of error in refractive predictability, including preoperative measurement, choice of IOL formula, and methods used for prediction error assessment, which could hide any true difference resulting from a consistent capsulotomy. Furthermore, complete capsule—optic overlap also has been shown to reduce the rate of posterior capsular opacification and dysphotopsia. However, only 1 published study has investigated differences in the rate of posterior capsular opacification between FLACS and MCS. We encourage future research in this area.

Although average surgical time was nonsignificantly different between comparators, FLACS produced a shorter
effective phacoemulsification time, which signifies a lower total amount of energy delivered to the eye. Between studies, differences in surgical equipment, surgeon skill, patient selection, and definitions of terms may have led to significant heterogeneity in the total procedure time and effective phacoemulsification time outcomes. At the same time, the pooled treatment effect of studies reporting on CDE showed no significant difference between FLACS and MCS (Fig 2G). The contradictory results between effective phacoemulsification time and CDE could be explained by methodologic variation in the included studies, by differences in surgical techniques, or by the differential number of included studies, which may have introduced reporting bias into the findings. Another confounding factor is between-study variability in energy delivery parameters, which affects the calculation for CDE differently. Specifically, the formula for calculating CDE assigns only 40% of the actual torsional effective phacoemulsification time to the sum, whereas the effective phacoemulsification time for longitudinal ultrasound remains the same.

The meta-analysis demonstrated that there was a statistically significant difference in favor of FLACS over MCS in surgery-induced corneal endothelial cell loss. However, it is uncertain whether this mean difference of 55.43 cells/mm² carries any clinical significance. For instance, this difference may be attributed to instrument bias, given the poor repeatability of specular microscopy. Notwithstanding, corneas were significantly thinner in the early postoperative period in patients undergoing FLACS, which may suggest less surgically-induced corneal stress. Studies evaluating corneal endothelial changes after femtosecond LASIK suggest that this procedure is safe for the endothelium. In contrast, a study by Abell et al found that eyes undergoing FLACS with laser-automated corneal incisions had a greater endothelial cell loss at 6 months than eyes undergoing FLACS, but with manual corneal incisions (P < 0.001); eyes with 0 effective phacoemulsification time (EPT) and manual incisions had the least endothelial cell loss (P < 0.001). Differences in findings between studies comparing femtosecond LASIK and FLACS may be explained by the deeper...
energy penetration at the level of the endothelium when performing clear corneal incisions compared with LASIK flaps.71 The safety analysis showed no significant differences between FLACS and MCS for overall, capsular, pupillary, and corneal complications. However, there was a significantly greater incidence of posterior capsular tears after FLACS relative to MCS. Given that many of the included studies were published early after the introduction of FLACS, the surgeon learning curve may have influenced these results. Nonetheless, posterior capsular tears are associated with complications like retinal detachment, endophthalmitis, and cystoid macular edema. Beyond the evaluated outcomes, there are also complications unique to femtosecond lasers that have been noted in past case reports, including interface corneal stromal irregularities, corneal perforation, and incomplete laser-assisted capsulotomy and fragmentation resulting from silicone oil in the anterior chamber.72

Femtosecond laser-assisted cataract surgery was shown to be associated with a significantly greater concentration of intraocular prostaglandins relative to MCS ($P < 0.001$).29,39 Schultz et al.39 note that, despite the significant concentrations of prostaglandins synthesized by the iris and ciliary body, the specific location of prostaglandin release currently is uncertain. They hypothesize that the microplasma of gas and water generated by the focused FLACS laser spot may trigger the release of prostaglandins. Prostaglandins have been shown to be associated with inflammation-induced miosis and may be a causative factor in the development of cystoid macular edema and uveitis after cataract surgery.39

Comparing the present analysis with the only previous meta-analysis in the published literature, we found that the previous study screened only 297 articles (present meta-analysis, 2802 articles).11 Our broader screening strategy led to the inclusion of 6 additional randomized controlled trials. These randomized controlled trials, in addition to the inclusion of 22 observational studies, led to an increase in sample size from 989 to 14567. Our design also included additional outcomes not reported previously: mean absolute error, total surgery time, balanced salt solution volume, capsule opening diameter, absolute mean deviation from intended diameter, decentration, total prostaglandin concentration, mean aqueous flare, and various complication parameters.

Beyond efficacy and safety, the cost effectiveness of FLACS is an important consideration that is not addressed in the present meta-analysis. In their comparative cost-effectiveness analysis of FLACS and MCS, Abell and Vote76 reviewed complication rates in the literature. In their hypothetical cohort of patients between 6 months to 1 year after cataract surgery, there was a quality-adjusted life-year gain of 0.06 units for FLACS compared with MCS. However, this equated to a cost per quality-adjusted life-year of $102,691, which was not viewed as cost effective.

Recently, the updated European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) case control data concerning the efficacy and safety of FLACS was presented (Barry P. ESCRS femto laser assisted cataract surgery (FLACS): case control study. Paper presented at: 33rd Congress of the ESCRS, September 5–9, 2015; Barcelona). Although the study remains unpublished, it is notable for reporting on a large number of eyes (2814 vs. 4987 eyes after FLACS and MCS, respectively) derived from a registry-based database. Their findings corroborate the results of the current meta-analysis: higher complication rates (3.4% vs. 2.3%) and a similar proportion of eyes with an improvement in CDVA (86.0% vs. 89.3%) after FLACS relative to MCS. We look forward to the publication of their results.

This meta-analysis is the most comprehensive review of the published literature investigating the efficacy and safety of FLACS.
of FLACS relative to MCS. As such, the analysis benefits from a large sample size (n = 14,567) and a high number of published studies (n = 37). Further, all included studies contained an MCS arm; based on descriptive statistics, preoperative parameters were comparable between the FLACS and MCS cohorts.

Despite these advantages, the study is subject to certain limitations. In terms of limitations related to the study designs of extracted articles, many observational studies were included (22 of 37 studies [59.5%]; 12,967 of 14,567 eyes [89.0%]). This may have introduced confounding by indication, information bias, and selection bias into the findings. Adjusted effect estimates could not be extracted because of the limitations in the reporting of individual observational studies, which may have introduced confounding. However, one may hypothesize that the combination of confounding and information bias would skew the results in favor of FLACS, a finding that largely was not present in this meta-analysis. We found that 15 of 37 (40.5%) included studies disclosed that at least some patients contributed 2 eyes to the individual analysis. Of these 15, only 8 (53.3%) noted that patients who contributed 2 eyes were treated independently. The other 7 (46.7%) studies should have taken into account that there is some within-patient correlation between eyes of the same patient. For our visual outcome analysis, we reported data as they were analyzed in the existing literature, understanding the limitations of this parametric analysis.77

We encourage future studies to provide broader detail on their visual outcomes and to consider using clinically significant cutoffs in their reporting.28 In terms of limitations related to the selection of included studies, this meta-analysis considered only published data to ensure that the rigors of peer review were met for each included article. We recognize that a consequence of this approach is the potential for publication bias (i.e., not including unpublished negative studies). Also, there might have been language bias because the meta-analysis considered only studies published in English. Finally, in terms of limitations related to variability in clinical reporting, it was difficult to control for different technologies and surgeon experience because of a large between-study variance and lack of reporting of these parameters. There was significant variability in the duration of reported follow-up in the included studies; as such, we used the last available follow-up for analysis of postoperative outcomes. This decision was supported by the work of Conrad-Hengerer et al.,46 who showed that there was no significant change in the mean refractive spherical equivalent between 1 week and 1 month after FLACS and between 1, 2, 3, and 6 months after either FLACS or MCS. Our results also showed that there was significant heterogeneity across numerous outcomes and that the effect sizes of certain end points (e.g., corneal thickness) were smaller than the known variability in the accuracy of measurement.

In summary, this meta-analysis found that there were no significant differences between FLACS and MCS in terms of key postoperative visual and refractive outcomes, specifically UDVA, CDVA, and MAE. There were mixed results regarding secondary surgical end points, in which a nonsignificant difference between comparators was found for certain parameters like CDE, capsule opening diameter, and vertical IOL centration, whereas there was a statistically significant difference in favor of FLACS for effective phacoemulsification time, absolute mean deviation from intended capsule diameter, horizontal IOL centration, and postoperative central corneal thickness. There was a significant difference in favor of MCS in terms of prostaglandin concentration. Safety analysis revealed that FLACS and MCS were nonsignificantly different in the incidence of overall, capsular, corneal, and pupillary complications; however, there was a significant difference in favor of MCS over FLACS in the incidence of posterior capsular tears. In general, it is important to consider the clinical significance of the measured differences when interpreting these findings.

There may be certain clinical scenarios, such as cases in which a manual capsulorrhexis is harder to perform (e.g., subluxated lens), in which FLACS may have specific advantages.78 Furthermore, there may be applications and modifications of the IOL technology in the future that may favor FLACS over MCS. Because of the continual evolution of the femtosecond laser technology, it is likely that there will be continued head-to-head comparisons between these 2 techniques. We await this evidence and recommend that a subsequent re-evaluation be performed after a significant number of well-designed randomized trials are introduced into the literature. Through this process, the authors hope a more definitive conclusion can be reached regarding the role of femtosecond lasers in cataract surgery.

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Data collection: Popovic, Campos-Möller, Schlenker, Ahmed
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Overall responsibility: Popovic, Campos-Möller, Schlenker, Ahmed

Abbreviations and Acronyms:
CCI = clear corneal incision; CDE = cumulative dissipated energy; CDVA = corrected distance visual acuity; CI = confidence interval; EUREQUO = European Registry of Quality Outcomes for Cataract and Refractive Surgery; FLACS = femtosecond laser-assisted cataract surgery; IOL = intraocular lens; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; MAE = mean absolute error; MCS = manual cataract surgery; NOS = Newcastle-Ottawa Quality Assessment Scale; RR = relative risk; UDVA = uncorrected distance visual acuity; WMD = weighted mean difference.

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Pictures & Perspectives

Merkel Cell Carcinoma of the Eyelid
An 81-year-old immunocompetent man presented with a 5-week history of a rapidly growing left upper eyelid lesion (Fig 1, arrow). Eight years prior, he had a Merkel cell carcinoma (MCC) of the left cheek that was treated with repeat wide local excision, limited neck dissection with negative sentinel lymph nodes, and postoperative radiation therapy. Histopathology revealed small blue cells (Fig 2), numerous mitotic figures, large oval nuclei, prominent nucleoli, and salt and pepper dense chromatin (Fig 3). Merkel cell carcinoma of the eyelids display an aggressive clinical course with a high rate of local recurrence (14%), regional lymph node invasion (20%), and metastasis (5%).

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