Prevention of Cystoid Macular Edema After Cataract Surgery in Nondiabetic and Diabetic Patients: A Systematic Review and Meta-Analysis

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• PURPOSE: To evaluate the optimum medical strategy to prevent cystoid macular edema (CME) after cataract surgery.
• DESIGN: Systematic review and meta-analysis.
• METHODS: SETTING: Cochrane, MEDLINE, and EMBASE databases were searched to identify eligible randomized controlled trials (RCTs). STUDY POPULATION: RCTs comparing medical strategies to prevent CME after uncomplicated cataract surgery in nondiabetic and diabetic patients. OBSERVATION PROCEDURES: Data were extracted by 2 authors independently. Quality of individual RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias and Delphi criteria. MAIN OUTCOME MEASURES: Odds of developing CME within 3 months postoperatively and foveal thickness, macular volume and corrected distance visual acuity change within 3 months postoperatively, as compared to baseline.
• RESULTS: Seventeen trials reported incidence rates. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) significantly reduced the odds of developing CME as compared to topical corticosteroids in nondiabetic (odds ratio [OR] 0.11; 95% confidence interval [95% CI] 0.03–0.37) and mixed populations (OR 0.05; 95% CI 0.02–0.11). A combination of topical corticosteroids and NSAIDs significantly reduced the odds of developing CME as compared to topical corticosteroids in nondiabetic (OR 0.21; 95% CI 0.10–0.44) and diabetic patients (OR 0.17; 95% CI 0.05–0.50). Intravitreal corticosteroid or anti–vascular endothelial growth factor injections did not show any additional benefit in diabetic subjects.
• CONCLUSIONS: Topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids, in nondiabetic and mixed populations. A combination of topical NSAIDs and corticosteroids reduced the odds of developing CME in nondiabetic and diabetic patients, as compared to topical corticosteroids. (Am J Ophthalmol 2015;160(5): 968–981. © 2015 by Elsevier Inc. All rights reserved.)

FOR MANY DECADES, CATARACT HAS BEEN THE LEADing cause of blindness in the world. A major current focus in cataract surgery is how to minimize complications and improve postoperative visual recovery. Over the years, the incidence of complications has significantly decreased owing to more advanced surgical techniques. Nowadays, cystoid macular edema (CME) is one of the most prevalent postoperative complications after otherwise uncomplicated cataract surgery.

CME after cataract surgery was first reported in 1953 and is also known as the Irvine-Gass syndrome.[1,2] It usually develops within 3 months postoperatively, with a peak incidence at 4–6 weeks after surgery.[3,4] It is considered the most important cause of suboptimal visual acuity within the first weeks postoperatively and strongly affects early recovery. Although CME has been reported in up to 23% of nondiabetic subjects after regular uncomplicated cataract surgery, most cases are self-limiting and patients experience no or only minimal reduction in visual acuity.[5–8] Approximately 0%–6% of nondiabetic subjects develop visual complaints and suffer from clinically significant macular edema (CSME).[5,7,9] In contrast, incidence rates of CSME are up to 56% in diabetic patients with mild to moderate nonproliferative diabetic retinopathy (NPDR) and no CME preoperatively.[5,10–12]

In 1998, a review by Rossetti and associates reported that prophylactic anti-inflammatory interventions are effective in reducing the incidence of CME after cataract surgery.[8] Since then, many treatments have been studied in order to identify the optimal preventive treatment. Recently, Kessel and associates compared the efficacy of topical corticosteroids and topical nonsteroidal anti-inflammatory drugs (NSAIDs) in controlling postoperative inflammation and preventing CME after uncomplicated cataract surgery in nondiabetic patients.[13] The systematic review showed less postoperative inflammation and less CME in the NSAID group. This study, however, did not compare any other intervention and did not address the efficacy in diabetic patients.

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This systematic review was designed to collect and summarize the results of randomized controlled trials (RCTs) on the prevention of CME after cataract surgery. The current study compares the efficacy of preventive strategies on the odds of developing CME within 3 months after uncomplicated phacoemulsification cataract surgery with posterior chamber intraocular lens implantation in nondiabetic and diabetic patients with age-related cataract, without CME preoperatively and with no predisposing factors for developing CME. A meta-analysis and indirect treatment comparison was performed to compare the efficacy of various preventive treatments.

METHODS

THE SYSTEMATIC REVIEW AND META-ANALYSIS WAS designed using the guidelines of the Cochrane Handbook and result were reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[14,15] In accordance with Dutch guidelines, the medical ethics committee of the University Hospital Maastricht and Maastricht University decided that no institutional review board approval was required for this study.

• **SYSTEMATIC REVIEW PROCESS:** The Cochrane Library (1992 to present), MEDLINE (OVID, 1946 to present), and EMBASE (1947 to present) databases were searched in June 2013 and an update was conducted in July 2014. All search strategies included a combination of text words, including text words for cataract extraction (cataract extr*, phaco*), macular edema (irvine gass, edema, oedema), and study design (random*). The complete search strategy for the MEDLINE database is shown in Supplemental Table 1 (Supplemental Material available at AJO.com). Similar search strategies were used for the Cochrane Library and EMBASE databases. To prevent exclusion of eligible articles, there were no language, publication status, or date restrictions. Reference lists of all included trials and previously published reviews were searched for additional RCTs by 2 review authors (L.W. and V.L.) independently. No trial registries were searched for unpublished trials and no study authors were contacted to identify additional studies. All records identified were managed using Endnote X7.

Titles and abstracts were scanned for eligibility by 2 review authors (L.W. and V.L.) independently. Discrepancies were resolved by discussion between the 2 authors. Full articles were obtained for all relevant abstracts and were reviewed by the 2 authors for eligibility. Both were unmasked to authors, journal, institution, and trial results during the assessment. In order to provide a complete overview of the available evidence, all RCTs comparing at least 2 preventive strategies of any type, dosage, or form were included in this systematic review. The authors excluded trials investigating the prevention of CME after intracapsular or extracapsular cataract extraction and trials including patients with preoperative CME or a high risk of developing CME postoperatively. Trials investigating the treatment of CME were also excluded.

• **DATA EXTRACTION:** All data were extracted in duplicate by 2 authors (L.W. and V.L.) independently. A standard data extraction form was used, including the following items: study size, funding sources, eligibility criteria, type of participants, type of interventions, follow-up period, outcome definition, retinal thickness classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) retinal thickness map, macular volume (MV), and corrected distance visual acuity (CDVA).

All preventive strategies were classified into predefined treatment groups based on type of intervention and mode of administration (eg, topical corticosteroids or subconjunctival corticosteroids). All preoperative, intraoperative, and postoperative treatments were taken into account, except for once-only intraoperative eye drops that were thought not to influence the effect of additional preventive strategies. If an article included multiple study arms within the same treatment group, these arms were combined by adding the total number of participants in each group.

Risk of bias and quality of the included trials were assessed on study level by 2 reviewers independently of each other, using the Cochrane Collaboration's tool for assessing risk of bias and Delphi criteria. The Delphi list assesses the quality of RCTs based on treatment allocation (randomization and allocation concealment); baseline prognostic factors; eligibility criteria; masking of outcome assessors, care providers, and patients; presentation of point estimates and measures of variability; and inclusion of an intention-to-treat analysis.[16] The Cochrane Collaboration's tool for assessing risk of bias assesses various types of bias, including selection bias (sequence generation and allocation concealment); performance bias (masking of participants and personnel); detection bias (masking of outcome assessment); attrition bias (incomplete outcome data); and other sources of bias.[14]

• **META-ANALYSIS:** Subgroup analyses were performed for patients with and without diabetes mellitus (DM). An additional subgroup analysis was performed for all mixed populations, to compare data of studies that included both nondiabetic and diabetic patients. Trials comparing 2 identical treatment groups (eg, 2 corticosteroid eye drops) were excluded from the meta-analysis, as were data from trials that did not provide any measures of variability.

The primary outcome was the incidence of CME within 3 months after cataract surgery, using the diagnostic tools

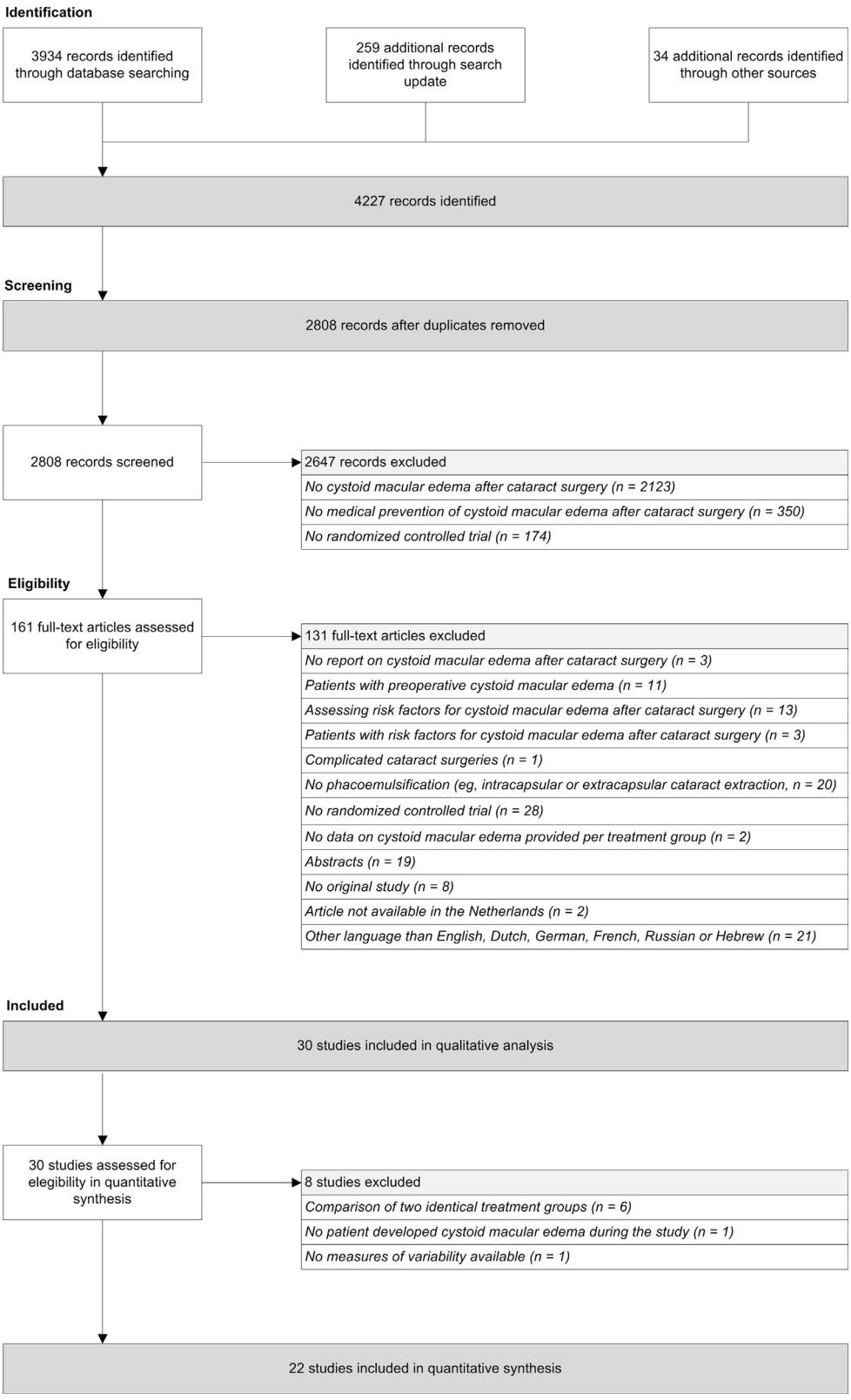

FIGURE 1. Flow chart visualizing the selection of randomized controlled trials comparing the efficacy of medical strategies to prevent the occurrence of cystoid macular edema after uncomplicated phacoemulsification cataract surgery in nondiabetic and diabetic patients, without cystoid macular edema preoperatively and with no risk factors for developing cystoid macular edema.

TABLE 1. Randomized Controlled Trials Investigating the Efficacy of Preventive Strategies on the Incidence of Cystoid Macular Edema Within Three Months After Uncomplicated Cataract Surgery in Nondiabetic Patients Without Cystoid Macular Edema Preoperatively and With No Predisposing Factors for Developing Cystoid Macular Edema

Study	Definition CME	Treatment Group	Drug	Treatment Group	Drug
Dieleman et al, 2011[46]	CME on OCT (any increase in CPT >30% compared with the preoperative baseline value developing within 4 weeks after cataract surgery) in combination with a decrease in CDVA of 2 or more lines on the ETDRS chart	Topical CS	Dexamethasone 0.1% (postop)	Subconjunctival CS	Betamethasone 5.7 mg/mL (during surgery)
Donnenfeld et al, 2006[20]	BCVA worse than 20/30 at the 2-week postoperative visit and CME diagnosed using OCT	Topical CS	Prednisolone 1% (postop)	Topical CS + topical NSAID[b]	Prednisolone 1% (postop) + ketorolac 0.4% (preop and postop)
Donnenfeld et al, 2011[19,a]	*Not given*	Topical CS + topical NSAID	Difluprednate 0.05% (postop) + nepafenac 0.1% or ketorolac 0.4% (preop and postop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + nepafenac 0.1% or ketorolac 0.4% (preop and postop)
Mathys et al, 2010[21,a]	An increase of >25 μm in macular thickness in the central 1 mm area on OCT	Topical CS + topical NSAID	Prednisolone 1% (postop) + nepafenac 0.01% (preop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + nepafenac 0.01% (preop) + nepafenac 0.1% (postop)
Miyake et al, 1999[22]	Diagnosed on FA using the Miyake classification	Topical CS	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.1% (preop and postop)
Miyake et al, 2001[24]	Diagnosed on FA using the Miyake classification	Topical CS	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.5% (preop and postop)
Miyanaga et al, 2009[27]	Decreased VA and obvious CME by OCT	Topical CS	Betamethasone 0.1% and fluorometholone 0.1% (postop)	1) Topical NSAID 2) Topical CS + topical NSAID	1) Bromfenac 0.1% (postop) 2) Betamethasone 0.1% and fluorometholone 0.1% (postop) + bromfenac 0.1% (postop)
Moschos et al, 2012[28]	*Not given*	Topical CS	Dexamethasone 0.1% (postop)	Topical CS + topical NSAID	Dexamethasone 0.1% (postop) + diclofenac 0.1% (preop and postop)
Negi et al, 2006[45]	Snellen BCVA of 6/9 or less and CME on oral FA	Oral AZ + topical CS + subconjunctival CS	AZ 250 mg (end of surgery) + betamethasone 0.1% (postop) + betamethasone 4 mg (during surgery)	Oral AZ + subconjunctival CS + sub-Tenon CS	AZ 250 mg (end of surgery) + betamethasone 4 mg (during surgery) + triamcinolone acetonide 20 or 30 mg (during surgery)
Ticly et al, 2014[29]	Diagnosed on FA using the Miyake classification; CME on OCT defined as the presence of well-defined cystic fluid pockets or a CST above 315 μm	Topical CS	Prednisolone 1% (preop and postop)	Topical CS + topical NSAID	Prednisolone 1% (preop and postop) + ketorolac 0.4% (preop and postop)

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TABLE 1. Randomized Controlled Trials Investigating the Efficacy of Preventive Strategies on the Incidence of Cystoid Macular Edema Within Three Months After Uncomplicated Cataract Surgery in Nondiabetic Patients Without Cystoid Macular Edema Preoperatively and With No Predisposing Factors for Developing Cystoid Macular Edema (*Continued*)

Study	Definition CME	Treatment Group	Drug	Treatment Group	Drug
Wang et al, 2013[43]	Impaired BCVA, macular alterations during fundus examination, and CRT of >250 μm on OCT and the presence of intraretinal cystoid space beneath the fovea	Oral CS + topical CS[b]	Prednisolone 15 mg (postop) + fluorometholone 0.1% or dexamethasone 0.1% (postop)	Oral CS+ topical NSAID[b]	Prednisolone 15 mg (postop) + bromfenac 0.1% (postop)
Yavas et al, 2007[30]	Diagnosed on FA as fluorescein leakage into the cystic space	Topical CS	Prednisolone 1% (postop)	Topical CS + topical NSAID[b]	Prednisolone 1% (postop) + indomethacin 0.1% (postop or preop and postop)

AZ = acetazolamide; BCVA = best-corrected visual acuity; CDVA = corrected distance visual acuity; CME = cystoid macular edema; CPT = center point thickness; CRT = central retinal thickness; CS = corticosteroid; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; postop = postoperatively; preop = preoperatively; VA = visual acuity.

[a]Not included in meta-analysis.

[b]Combination of more than 1 treatment group.

and definitions of the included trials. In case an article used separate definitions for CME and CSME, the occurrence of CSME was used in the meta-analysis, as this is the most clinically relevant outcome. Secondary outcome measures were the difference in optical coherence tomography (OCT)-measured central foveal thickness (FT) in the central 1-mm area of the macula and MV in the central 6-mm area of the macula within 3 months postoperatively, as compared to baseline. Moreover, this study describes the difference between treatment groups in CDVA change within 3 months postoperatively, as compared to baseline. CDVA data were converted to logMAR scale if necessary. If articles reported only absolute values of baseline and postoperative FT, MV, or CDVA, mean changes were calculated from the available information. The standard deviation (SD) for FT, MV, or CDVA change was imputed from the baseline and postoperative SD, using the methods described in the Cochrane Handbook.[14] If an outcome was measured more than once within 3 months postoperatively, the latest follow-up moment was selected for inclusion in the meta-analysis, with the intention of comparing the most long-term outcome.

Analyses were performed using Review Manager. Odds ratios (ORs) and accompanying 95% confidence intervals (95% CIs) were calculated for all dichotomous outcomes, whereas mean differences with 95% CIs were analyzed for all continuous outcome measures. As described in the Cochrane Handbook, statistical heterogeneity was assessed using the χ^2 test. I^2 was used to describe the percentage of variability in effect estimate thought to be a result of heterogeneity.[14] Whenever possible, treatment groups were compared directly using a classical pairwise meta-analysis. Some indirect comparisons could be performed using the Bucher method. This method can be used if no RCT compared 2 treatment groups directly, while both treatments have been compared to placebo or standard treatment in other trials.[17]

RESULTS

THE LITERATURE SEARCH RETRIEVED 2808 TITLES AND ABstracts. Thirty trials were included in this systematic review. Reasons for exclusion in each stage of the article selection process are shown in detail in the flow chart in Figure 1. Characteristics of included studies are listed in Supplemental Table 2 (Supplemental Material available at AJO.com). Eleven trials included only patients without DM and 7 trials included only diabetic patients. Twelve other trials included patients with and without DM or did not report the incidence of DM in the study population. These trials were clustered and referred to as "mixed populations." In the nondiabetic and mixed populations, most

TABLE 2. Randomized Controlled Trials Investigating the Efficacy of Preventive Strategies on the Incidence of Cystoid Macular Edema Within Three Months After Uncomplicated Cataract Surgery in Nondiabetic and Diabetic Patients (a Mixed Population) Without Cystoid Macular Edema Preoperatively and With No Predisposing Factors for Developing Cystoid Macular Edema

Study	Definition CME	Treatment Group	Drug	Treatment Group	Drug
Almeida et al, 2008[31,a]	*Not given*	Topical CS	Prednisolone 1% (postop)	Topical CS + Topical NSAID	Prednisolone 1% (postop) + ketorolac 0.5% (preop and postop)
Almeida et al, 2012[32]	*Not given*	Topical CS	Prednisolone 1% (postop)	Topical CS + topical NSAID[b]	Prednisolone 1% (postop) + nepafenac 0.1% or ketorolac 0.5% (preop and postop)
Cable, 2012[18,a]	*Not given*	Topical CS + topical NSAID	Prednisolone 1% (during surgery) and difluprednate (postop) + bromfenac 0.09% (preop and postop)	Topical CS + topical NSAID	Prednisolone 1% (during surgery) and difluprednate (postop) + nepafenac 0.1% (preop and postop)
Cervantes et al, 2009[33]	CSME associated with vision loss	Topical CS	Dexamethasone 0.1% (postop)	Topical CS + topical NSAID	Dexamethasone 0.1% (postop) + nepafenac 0.1% (preop and postop)
Chatziralli et al, 2011[42,a]	*Not given*	Oral AZ + topical CS + topical NSAID	Acetozolamide 125 mg (preop) + dexamethasone 0.1% (preop and postop) + ketorolac 0.5% (preop)	Oral AZ + topical CS + topical NSAID	Acetozolamide 125 mg + dexamethasone 0.1% (preop and postop) + ketorolac 0.5% (preop and postop)
Miyake et al, 2000[23]	Diagnosed on FA using the Miyake classification	Topical CS	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.1% (preop and postop)
Miyake et al, 2007[25]	Diagnosed on FA using the Miyake classification	Topical CS	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Diclofenac 0.1% (preop and postop)
Miyake et al, 2011[26]	Diagnosed on FA using the Miyake classification	Topical CS	Fluorometholone 0.1% (preop and postop)	Topical NSAID	Nepafenac 0.1% (preop and postop)
Nishino et al, 2009[41,a]	FA was performed only when CME was suspected to worsen the VA to less than 0.7	Topical NSAID	Bromfenac (preop and postop)	Topical NSAID + topical CS + subconjunctival CS	Bromfenac (preop and postop) + fluorometholone 0.1% (postop) + dexamethasone 0.5 mL (during surgery)
Weber et al, 2013[34,a]	*Not given*	Topical NSAID	Indomethacin 0.1% (preop and postop)	Topical NSAID	Ketorolac 0.5% (preop and postop)
Wittpenn et al, 2008[35,a]	Definite CME: presence of cystoid changes associated with substantial (≥40 μm) retinal thickening on OCT Probable CME: presence of changes in retinal contour and increased macular thickness relative to preoperative baseline, but without definite cystoid changes	Topical CS + topical NSAID	Prednisolone 1% (postop) + ketorolac 0.4% (preop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + ketorolac 0.4% (preop and postop)

AZ = acetazolamide; CME = cystoid macular edema; CS = corticosteroid; CSME = clinically significant macular edema; FA = fluorescein angiography; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; postop = postoperatively; preop = preoperatively; VA = visual acuity.

[a]Not included in meta-analysis.

[b]Combination of more treatment groups.

trials compared the effect of topical corticosteroids, topical NSAIDs, or a combination of both.[18–35] By contrast, many different treatments have been compared in diabetic subjects, including sub-Tenon corticosteroids,[36] intravitreal corticosteroids,[37] and intravitreal anti–vascular endothelial growth factor (anti-VEGF) injections.[38–40] A complete overview of the studied treatment groups and definitions used in the included trials are given in Tables 1–3 for nondiabetic, mixed, and diabetic populations, respectively.

Eight trials could not be included in the meta-analysis, since ORs and 95% CIs could not be calculated for the reported treatment comparisons. Quantitative measures could not be calculated because no patient developed CME in either treatment group,[41] because there were no measures of variability given by the authors,[31] or because the study compared 2 identical treatment groups as defined in this study (eg, comparing 2 different types of corticosteroid eye drops).[18,19,21,34,35,42] A complete overview of all meta-analyses is provided in Supplemental Figures 1–10 (Supplemental Material available at AJO.com) and a summary of all treatment comparisons is provided in Table 4.

• **QUALITY OF EVIDENCE:** Only RCTs were selected for inclusion in this study. Supplemental Table 2 (Supplemental Material available at AJO.com) contains an assessment of the risk of bias within studies and the quality of the included RCTs. As evident from Supplemental Figures 11 and 12 (Supplemental Material available at AJO.com), the overall quality of evidence of the included studies was low to moderate. Eleven trials used a table of random numbers to randomize the included patients,[18–21,29,34–38,43] 1 trial used centralized randomization by the pharmacy,[32] and 3 trials used envelopes.[25,29,44] The method of treatment allocation was unclear in 15 other trials. Six trials stated that the treatment allocation was concealed from the investigators.[18,19,29,32,45,46] Six trials were open-label studies.[22,23,31,43,44,46]

• **NONDIABETIC PATIENTS:** As shown in Table 1, 9 trials reporting the incidence of CME after cataract surgery in nondiabetic patients could be included in this meta-analysis. The meta-analysis in Figure 2 shows that topical NSAIDs significantly reduced the odds of developing CME after cataract surgery, as compared to topical corticosteroids. The OR was 0.11 (95% CI 0.03–0.37; I^2 0%).[22,24,27] The difference in efficacy between topical corticosteroids and NSAIDs was not statistically significant if patients also received oral prednisolone for 7 days postoperatively (OR 0.06; 95% CI 0.00–1.10).[43] A combination of topical corticosteroids and topical NSAIDs reduced the odds of developing CME as compared to topical corticosteroids as a single-drug treatment, with an OR of 0.21 (95% CI 0.10–0.44; I^2 18%).[20,27,29,30] Only 1 RCT provided a direct comparison between topical NSAIDs and a combination treatment of topical corticosteroids and NSAIDs. Unfortunately, it was not possible to include this comparison in the quantitative analyses, since no patient in either treatment group developed CME.[27] Nevertheless, using the common comparator of topical corticosteroids, it was possible to perform an indirect comparison of topical NSAIDs vs a combination treatment of topical NSAIDs and corticosteroids. This comparison showed no statistically significant difference in the odds of developing CME after cataract surgery with an OR of 0.54 (95% CI 0.13–2.20).

One study compared the efficacy of postoperative corticosteroid eye drops to subconjunctival corticosteroids at the end of cataract surgery in nondiabetic patients. This study showed no statistically significant difference in the odds of developing CME between both treatment groups (OR 1.18; 95% CI 0.53–2.62).[46]

None of the studies investigated the change in FT or MV after cataract surgery. Eight trials reported the change in CDVA within 3 months postoperatively or both the preoperative and postoperative CDVA. None of the treatment comparisons showed significant differences in CDVA change from baseline. An overview of these meta-analyses can be found in Figure 3.

• **MIXED POPULATIONS:** Four trials reported the incidence of CME after cataract surgery in mixed populations, including both diabetic and nondiabetic subjects. Table 2 provides a complete overview of the included studies. The meta-analysis shown in Figure 2 suggests that topical NSAIDs significantly reduce the odds of developing CME after cataract surgery, as compared to topical corticosteroids (OR 0.05; 95% CI 0.02–0.11; I^2 0%).[23,25,26] This finding was also confirmed by OCT, showing a significantly smaller increase in FT in the topical NSAID group as compared to topical corticosteroids (mean difference −23.20 μm; 95% CI −42.95 to −3.45 μm).[26] Other trials showed that a combination of topical corticosteroids and NSAIDs significantly reduced the postoperative change in MV, as compared to topical corticosteroids as a single-drug treatment. The mean difference was −0.25 mm^3 (95% CI −0.36 to −0.13 mm^3; I^2 0%).[32,33] There was no statistically significant difference between treatment groups in FT change from baseline (mean difference −6.00 μm; 95% CI −15.17 to 3.17 μm).[33] An indirect comparison between topical NSAIDs and a combination of topical corticosteroids and NSAIDs showed no significant difference in the FT change from baseline, with a mean difference of −17.2 μm (95% CI −38.97 to 4.57 μm).

Two trials reported change in CDVA within 3 months postoperatively. None of the comparisons showed significant differences between treatment groups in CDVA change from baseline.

TABLE 3. Randomized Controlled Trials Investigating the Efficacy of Preventive Strategies on the Incidence of Cystoid Macular Edema Within Three Months After Uncomplicated Cataract Surgery in Diabetic Patients Without Cystoid Macular Edema Preoperatively and With No Other Predisposing Factors for Developing Cystoid Macular Edema

Study	Definition CME	Treatment Group	Drug	Treatment Group	Drug
Ahmadabadi et al, 2010[37]	Subjective report of decreased vision by the patient, ophthalmoscopic detection of the presence of ME, and confirmation of the diagnosis by FA and OCT examinations at any postoperative visit	Topical CS	Betamethasone 0.1% (postop)	Topical CS + intravitreal CS	Betamethasone 0.1% (postop) + triamcinolone acetonide 2 mg (during surgery)
Chae et al, 2014[38]	>60 mm increase in CST relative to the screening CST value, as assessed by spectral-domain OCT. Diagnosed on FA using the Antcliff classification	Placebo		Intravitreal anti-VEGF	Ranibizumab 0.5 mg (during surgery)
Endo et al, 2010[44]	*Not given*	Topical CS	Betamethasone 0.1% and fluorometholone 0.1% (postop)	Topical NSAID	Bromfenac 0.1% (postop)
Fard et al, 2011[39]	Increase in CPT on OCT after cataract surgery	Placebo		Intravitreal anti-VEGF	Bevacizumab 1.25 mg (during surgery)
Kim et al, 2008[36]	Postsurgical CME was defined as decreased VA and CME on OCT	Topical CS	Prednisolone 1% (postop)	Topical CS + sub-Tenon CS	Prednisolone 1% (postop) + triamcinolone acetonide (during surgery)
Singh et al, 2012[47]	≥30% increase in CSMT relative to the presurgical baseline measurement	Topical CS	Prednisolone 1% (postop)	Topical CS + topical NSAID	Prednisolone 1% (postop) + nepafenac 0.1% (preop and postop)
Udaondo et al, 2011[40]	ME involving or threatening the center of the macula as defined by the ETDRS	Topical CS	Dexamethasone 0.1% (postop)	Topical CS + intravitreal anti-VEGF	Dexamethasone 0.1 % (postop) + ranibizumab 5 mg (during surgery)

CME = cystoid macular edema; CPT = center point thickness; CS = corticosteroid; CSMT = central subfield macular thickness; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; ME = macular edema; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; postop = postoperatively; preop = preoperatively; VA = visual acuity; VEGF = vascular endothelial growth factor.

TABLE 4. Efficacy of Various Treatment Strategies to Prevent the Occurrence of Cystoid Macular Edema After Uncomplicated Cataract Surgery in Nondiabetic, Diabetic, and Mixed Populations

			Population Studied (No. of Studies)	OR (95% CI)
Topical NSAID	>	Topical CS	Nondiabetic (3)	0.11 (0.03–0.37)
			Mixed population (3)	0.05 (0.02–0.11)
Topical NSAID	≈[a]	Topical CS & topical NSAID	Nondiabetic (n.a.)	0.54 (0.13–2.20)
Topical NSAID & topical CS	>	Topical CS	Nondiabetic (4)	0.21 (0.10–0.44)
			Diabetic (1)	0.17 (0.05–0.50)
Topical CS & intravitreal anti-VEGF	≈	Topical CS	Diabetic (1)	0.13 (0.02–1.21)
Topical CS & intravitreal anti-VEGF	≈[a]	Topical CS & intravitreal CS	Diabetic (n.a.)	0.71 (0.02–28.76)
Topical CS & intravitreal CS	≈	Topical CS	Diabetic (1)	0.09 (0.00–1.89)
Subconjunctival CS	≈	Topical CS	Nondiabetic (1)	1.18 (0.53–2.62)
Subconjunctival CS & sub-Tenon CS & oral AZ	≈	Topical CS & subconjunctival CS & oral AZ	Nondiabetic (1)	0.31 (0.03–3.16)
Topical NSAID & oral CS	≈	Topical CS & oral CS	Nondiabetic (1)	0.06 (0.00–1.10)

AZ = acetozolamide; CME = cystoid macular edema; CS = corticosteroid; n.a. = not applicable; no. = number; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; VEGF = vascular endothelial growth factor; 95% CI = 95% confidence interval.
[a]Indirect treatment comparison using the Bucher method.

• **DIABETIC PATIENTS:** Seven trials included diabetic patients with mild to severe NPDR and no diabetic macular edema preoperatively. Five trials reported the incidence of CME after cataract surgery. A complete overview of all articles is presented in Table 3. As can be seen in Figure 2, a combination of topical corticosteroids and topical NSAIDs reduced the odds of developing CME after cataract surgery as compared to topical corticosteroids as a single-drug treatment (OR 0.17; 95% CI 0.05–0.50).[47] Only 1 study compared the efficacy of topical NSAIDs vs topical corticosteroids in diabetic patients, but did not report on the incidence of CME. The difference in FT change from baseline between both treatment groups was not statistically significant (mean difference −17.00 μm; 95% CI −36.37 to 2.37 μm). Nevertheless, the study did show a statistically significantly larger improvement in CDVA in the NSAID group as compared to the topical corticosteroid group (mean difference −0.13 logMAR; 95% CI −0.24 to −0.02 logMAR). Preoperative CDVA in the NSAID and corticosteroid group was 0.24 and 0.16 logMAR (20/35 and 20/29 Snellen), respectively, and improved to −0.09 and −0.04 logMAR (20/16 and 20/18 Snellen) at 6 weeks postoperatively.[44]

While topical treatments have been studied most extensively, several trials investigated the effect of intravitreal treatments on the incidence of CME after cataract surgery in diabetic patients. Two trials showed that intravitreal anti-VEGF injections at the end of cataract surgery did not cause a statistically significant reduction in the odds of developing CME, as compared to placebo (OR 0.68; 95% CI 0.21–2.19) or as an additional treatment to topical corticosteroids (OR 0.13; 95% CI 0.02–1.21).[38,40] One RCT studied the efficacy of intravitreal triamcinolone acetonide in 41 eyes of diabetic patients who also received topical corticosteroids. Four eyes in the control group and no eyes in the triamcinolone group developed CME, but the treatment effect was not statistically significant (OR 0.09; 95% CI 0.00–1.89). CDVA improved from 0.81 and 0.98 logMAR (20/129 and 20/191 Snellen) preoperatively to 0.13 and 0.09 logMAR (20/27 and 20/25 Snellen) at 3 months postoperatively in the control group and intravitreal triamcinolone group, respectively. The difference between treatment groups in postoperative CDVA change from baseline (mean difference −0.13 logMAR; 95% CI −0.40 to 0.14) was not statistically significant.[37]

An indirect comparison showed no statistically significant difference in the odds of developing CME after intravitreal corticosteroid vs intravitreal anti-VEGF injections in diabetic patients who also received topical corticosteroids (OR 0.71; 95% CI 0.02–28.76).

DISCUSSION

THE CURRENT PAPER COMPARED THE EFFICACY OF PREDEfined preventive strategies on the incidence of CME after uncomplicated cataract surgery in nondiabetic, mixed, and diabetic populations.

In nondiabetic patients, it was found that topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids. These findings are in line with the results of a recent systematic review by Kessel and associates, reporting a significantly higher prevalence of CME in the corticosteroid group as compared

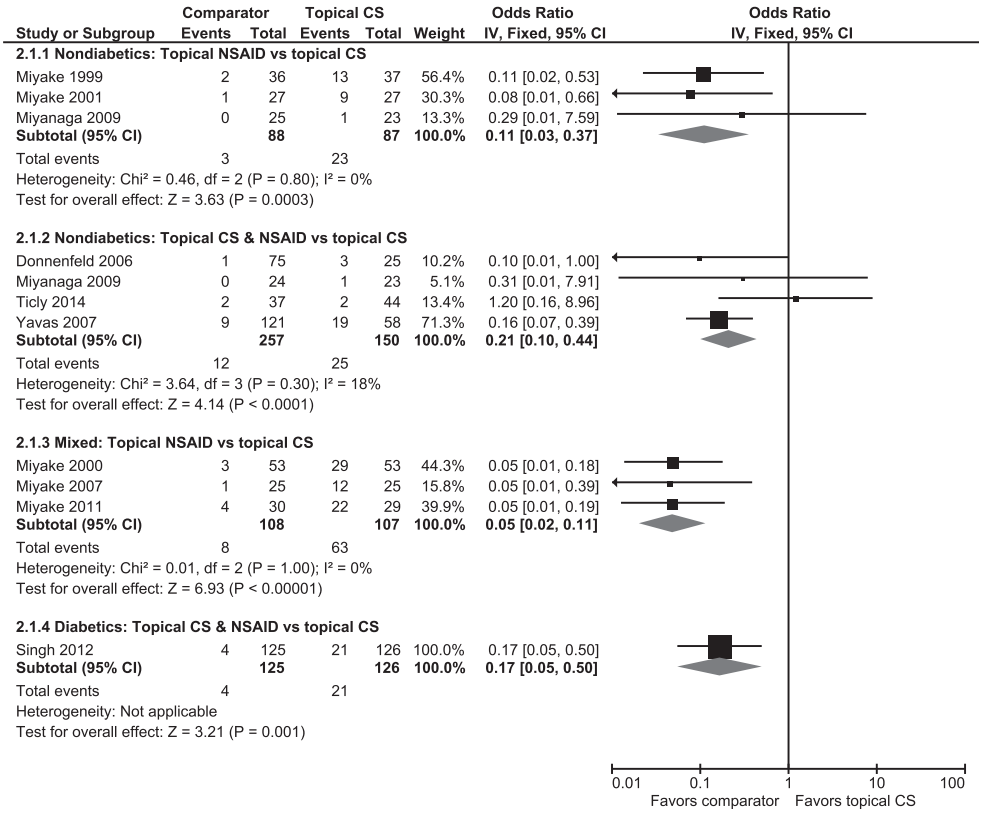

FIGURE 2. Forest plots summarizing the results of studies comparing the efficacy of topical treatments to prevent the occurrence of cystoid macular edema within 3 months after uncomplicated cataract surgery in nondiabetic, mixed, and diabetic populations. CS = corticosteroid; df = degrees of freedom; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; 95% CI = 95% confidence interval.

to the NSAID group.[13] The systematic review by Kessel and associates did not investigate the additive effects of combining topical corticosteroids and NSAIDs vs single-drug treatment. The current study demonstrated that a combination of topical NSAIDs and corticosteroids significantly reduced the odds of developing CME as compared to topical corticosteroids, while combination treatment did not show any benefit over topical NSAIDs in an indirect treatment comparison. This suggests that a topical NSAID should always be part of the preventive treatment after cataract surgery in nondiabetic patients. Whether the use of corticosteroid eye drops can be avoided cannot be concluded from these results. To establish a better evidence-based preventive strategy, the European Society of Cataract & Refractive Surgeons (ESCRS) decided to design a large multicenter study to compare the efficacy of topical NSAIDs, topical corticosteroids, and a combination treatment of both drugs to prevent the occurrence of CME after cataract surgery in nondiabetic patients.

Several factors may influence the interpretation of the current study results. Firstly, one should consider the difference in potency of various corticosteroid eye drops. It is known that fluorometholone is a corticosteroid with only low potency, owing to a lower penetration of the cornea.[48] Two of 3 RCTs comparing the efficacy of topical corticosteroids vs topical NSAIDs in the nondiabetic study population used low-potency corticosteroids, which might have caused an overestimation of the efficacy of topical NSAIDs as compared to topical corticosteroids.

The comparison of topical NSAIDs vs combination treatment with topical corticosteroids and NSAIDs was based on an indirect comparison through the common comparator of topical corticosteroids. In the absence of a direct comparison, the Bucher method can be used to compare results of different study populations. However, it should be noted that the Bucher method assumes treatment effects to be constant across different populations.[17] Most trials compared the effect of topical NSAIDs to low-potency corticosteroids, whereas the effect of topical combination treatment was compared to higher-potency corticosteroids. This may have caused an overestimation of the effect of topical NSAIDs as compared to combination treatment with topical corticosteroids and NSAIDs.

A major limitation of this study is the use of various detection methods and definitions to diagnose CME after cataract surgery. Any differences between trials in the

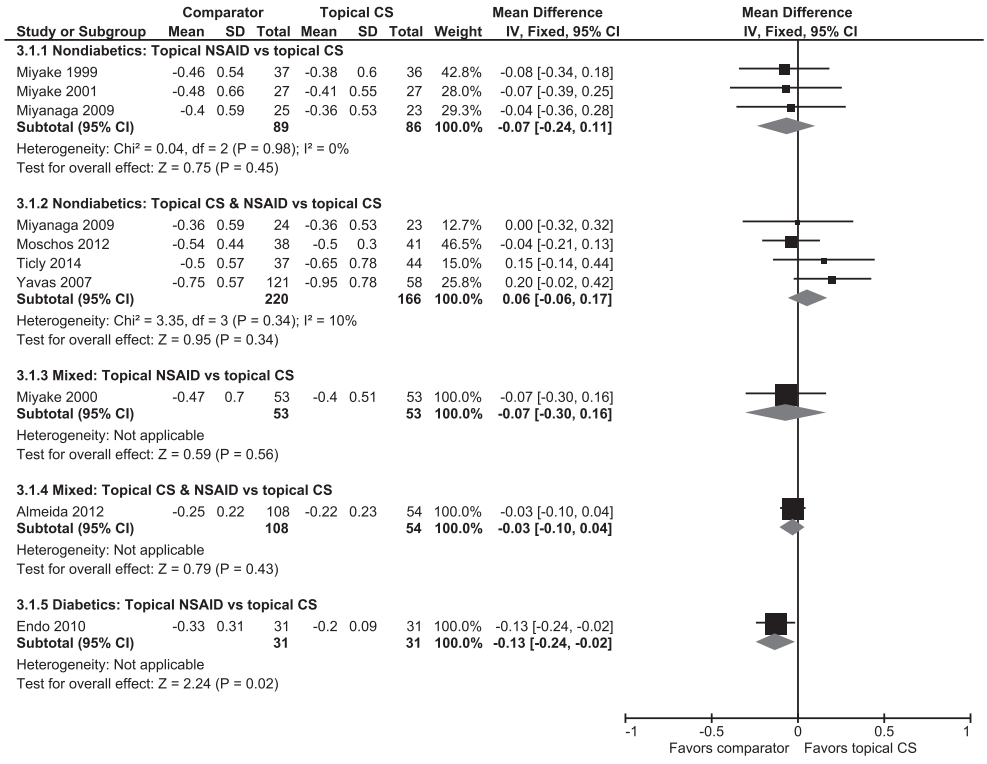

FIGURE 3. Forest plots summarizing the results of studies comparing the efficacy of topical treatments on the change in corrected distance visual acuity within 3 months after uncomplicated cataract surgery, as compared to baseline, in nondiabetic, mixed, and diabetic populations. CS = corticosteroid; df = degrees of freedom; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; 95% CI = 95% confidence interval.

efficiency of detecting CME may lead to inaccurate estimates of direct and especially indirect comparisons.[17] Four studies in the nondiabetic population used similar definitions to detect CME on FA.[22,24,29,30] OCT was used in 2 other studies, but was only performed in patients with a decreased VA.[20,27] As CME often occurs without any visual complaints, the incidence of CME will be higher in studies using FA in all patients. One should note the large differences in the incidence of CME in 3 studies using FA to detect CME (15.6%–19.2%),[22,24,30] as compared to 2 studies performing an OCT only in patients with decreased VA (1.4%–4%).[20,27] The studies using FA in all patients most likely include patients with normal CDVA and may overestimate the incidence of clinically relevant CME, since CME will resolve spontaneously in many cases.[8] Future studies would therefore benefit from standardization of the definition of CME after cataract surgery.[4]

The timing of follow-up visits is a third factor that might influence the interpretation of direct and indirect treatment comparisons. It is known that most cases of CME occur within 3 months after cataract surgery, with a peak incidence at 4–6 weeks postoperatively.[3,4] Therefore, the detection rate of CME will be highest in studies with a follow-up of 4–6 weeks postoperatively. The RCTs investigating the efficacy of topical single-drug treatments scheduled their follow-up visits closer to 4–6 weeks postoperatively, as compared to studies investigating the effect of combination treatments. Consequently, in an indirect comparison, the effect of combination treatments of topical corticosteroids and NSAIDs might be overestimated when compared to topical NSAIDs.

This study was not designed to investigate the optimal duration of pre- or postoperative topical treatments. Although the anti-inflammatory treatment is usually initiated postoperatively, it is thought that the use of preoperative NSAIDs limits the release of prostaglandins during surgery.[30] Two studies found a significantly lower incidence of CME after cataract surgery in patients starting NSAID treatment 1–3 days preoperatively as compared to patients treated only postoperatively.[20,30]

In mixed populations, topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids. All studies were performed by the same author and used the Miyake classification to diagnose CME on FA.[23,25,26] As mentioned previously, the definition used to detect CME after cataract surgery may highly influence the reported incidence rates of CME. Therefore, it would be helpful to use an objective outcome measurement (eg, change in postoperative FT or

MV) to compare the efficacy of various treatments. One study showed a significantly smaller increase in FT after cataract surgery and postoperative topical nepafenac as compared to postoperative treatment with topical fluorometholone.[26] This may suggest that a combination of topical NSAIDs and corticosteroids would also reduce the change in FT after cataract surgery as compared to topical corticosteroid treatment. However, another study could not find a statistically significant difference between eyes treated with a combination of topical nepafenac plus dexamethasone vs dexamethasone eye drops as a single-drug therapy.[33] This deviation may be caused by the use of corticosteroids of various potencies.

The present study also compared the efficacy of various treatments to prevent the occurrence of CME after cataract surgery in diabetic patients. The odds of developing CME were significantly lower after topical combination treatment with an NSAID and corticosteroid, as compared to a single-drug treatment with topical corticosteroids. One multicenter trial treating all patients with prednisolone eye drops for 2 weeks postoperatively, or longer if considered necessary to treat anterior segment inflammation, provided evidence for this observation.[47] However, an underestimation of the overall incidence of CME in this study may have occurred, as both anterior segment inflammation and CME are a consequence of the underlying inflammatory process after cataract surgery. Although none of the trials studied the efficacy of topical single-drug treatments on the odds of developing CME after cataract surgery, 1 study did investigate the efficacy of bromfenac vs fluorometholone eye drops in reducing postoperative foveal thickening. This trial reported no significant differences in FT change from baseline between the NSAID and corticosteroid treatment groups. A subanalysis including only patients with NPDR showed a statistically smaller FT change in the bromfenac group at 4 and 6 weeks postoperatively.[44] As mentioned previously, fluorometholone can be considered a corticosteroid of only low potency, which might have overestimated the effect of NSAID eye drops in this study.

Whereas different postoperative treatments did not affect CDVA in nondiabetic and mixed populations, diabetic patients showed a statistically significantly larger improvement in CDVA using topical NSAIDs as compared to topical corticosteroids.[44]

Although topical treatments have been studied most extensively, some comparisons could be made regarding the use of intravitreal treatments in diabetic patients. Three studies showed that intravitreal corticosteroid and anti-VEGF treatments might be useful to reduce the odds of developing CME after cataract surgery, but none of the studies was able to show statistically significant results owing to small sample sizes of the included studies. One study showed that a preoperative injection of 0.5 mg ranibizumab prevents the occurrence of CME after cataract surgery at 1 month postoperatively, but this difference disappeared at 3 months postoperatively.[38] This may be caused by the limited duration of the treatment effect of intravitreal ranibizumab. An indirect treatment comparison could not find a statistically significant difference in the efficacy of intravitreal corticosteroid vs intravitreal anti-VEGF injections in diabetic patients who also received a topical corticosteroid. When considering the abovementioned treatment strategies, cataract surgeons are obliged to carefully consider the adverse events reported after intravitreal injections. It should be noted that increased intraocular pressure is reported in 41.2 per 100 patients after intravitreal corticosteroid injection, whereas the incidence is much lower (0.12–0.49 per 100 patients) after intravitreal bevacizumab or ranibizumab injection.[49,50] Other safety concerns with intravitreal injections are mainly associated with the injection procedure. Endophthalmitis, the most dreaded complication after intravitreal injection, was reported in 0.04–0.05 per 100 injections in a recent systematic review summarizing the adverse events after intravitreal anti-VEGF injections reported in 278 articles.[49] Given the paucity of studies on the prevention of CME after cataract surgery in diabetic patients, the ESCRS also decided to set up a European multicenter study investigating the efficacy of intravitreal anti-VEGF and subconjunctival corticosteroid injections to prevent the occurrence of CME after cataract surgery in diabetic patients.

The purpose of this study was to summarize and integrate the results of previous RCTs on the prevention of CME within 3 months after uncomplicated phacoemulsification cataract surgery with posterior chamber intraocular lens implantation in nondiabetic and diabetic patients with age-related cataract, without CME preoperatively, and without risk factors for developing CME. Results of this meta-analysis show that topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids in nondiabetic and mixed populations. Furthermore, a combination of topical NSAIDs and corticosteroids significantly reduced the odds of developing CME in nondiabetic and diabetic patients, as compared to topical corticosteroids in a single-drug treatment. Based on an indirect treatment comparison, no difference could be found between topical combination treatment and topical NSAIDs in nondiabetic patients. None of the included studies was able to show a statistically significant effect of intravitreal corticosteroid or intravitreal anti-VEGF treatments to reduce the odds of developing CME after cataract surgery in diabetic patients.

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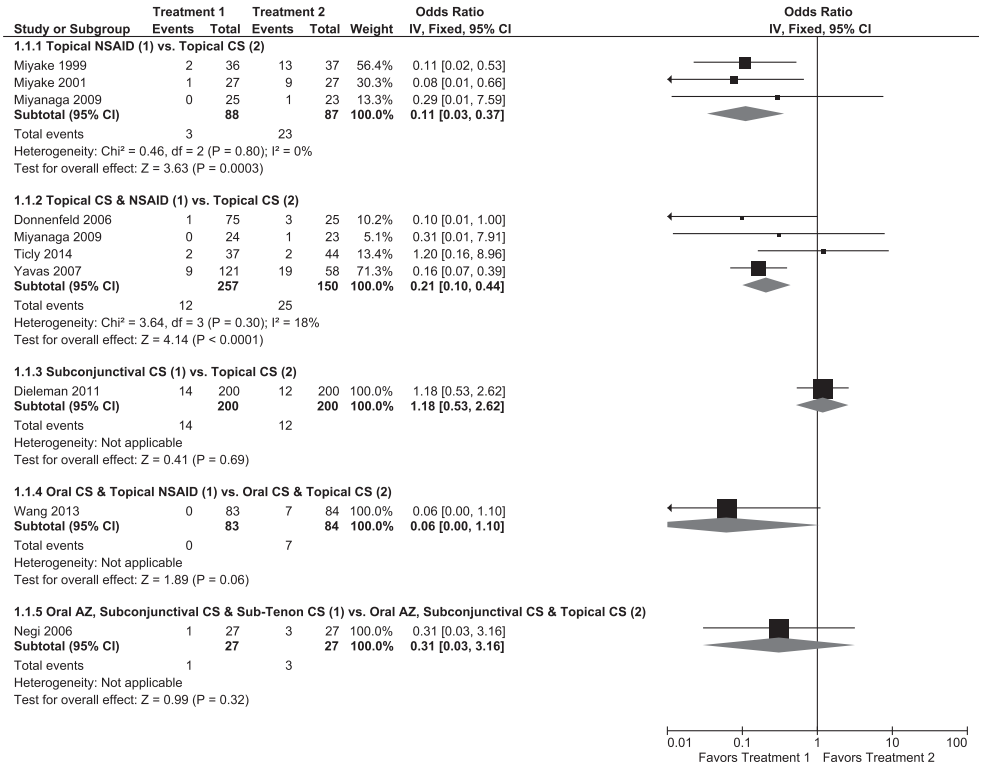
Biosketch

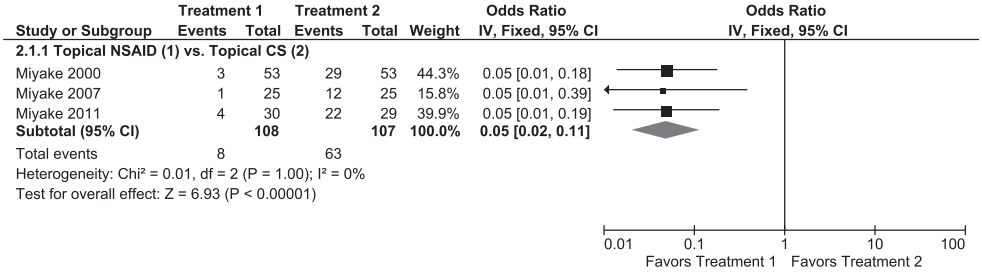
Laura H.P. Wielders, MD, received her medical degree from Maastricht University, the Netherlands in 2011. She is actively involved in clinical research at the University Eye Clinic Maastricht UMC+ and is currently working on a PhD project on the prevention of cystoid macular edema after cataract surgery.

Biosketch

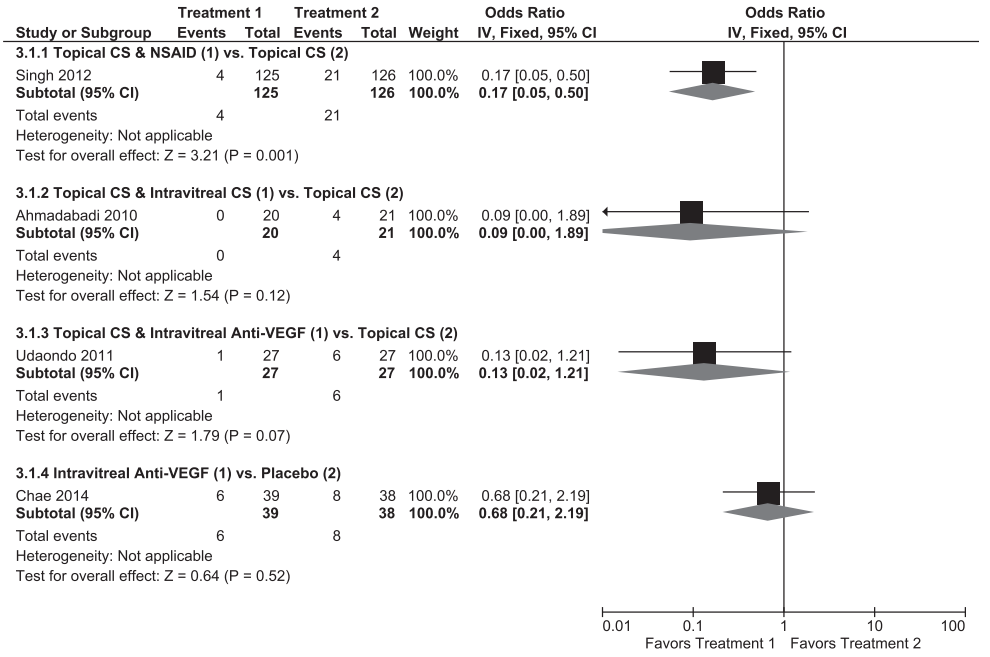
Rudy M.M.A. Nuijts, MD, PhD, is Professor of Ophthalmology and director of the Cornea Clinic and the Center for Refractive Surgery at the University Eye Clinic Maastricht UMC+, the Netherlands. His research interests are in the field of cataract, corneal and refractive surgery. He is chairman of the Netherlands IntraOcular Implant Society, and treasurer of the Dutch Corneal Society and European Society of Cataract and Refractive Surgeons.



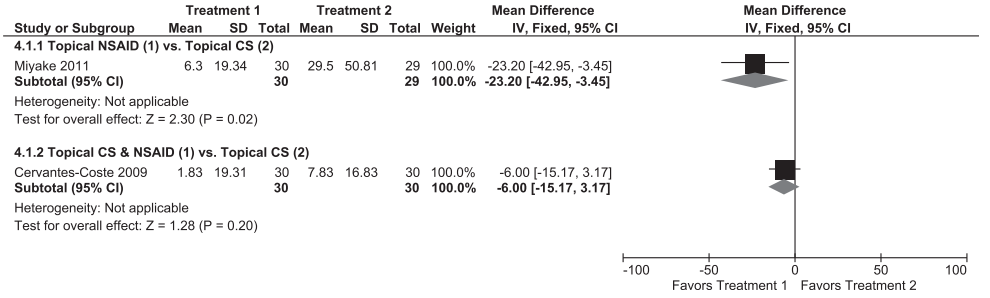
SUPPLEMENTAL FIGURE 1. Odds ratios with 95% confidence intervals for developing cystoid macular edema within 3 months after cataract surgery in nondiabetic patients. AZ = acetazolamide; CS = corticosteroid; df = degrees of freedom; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; 95% CI = 95% confidence interval.



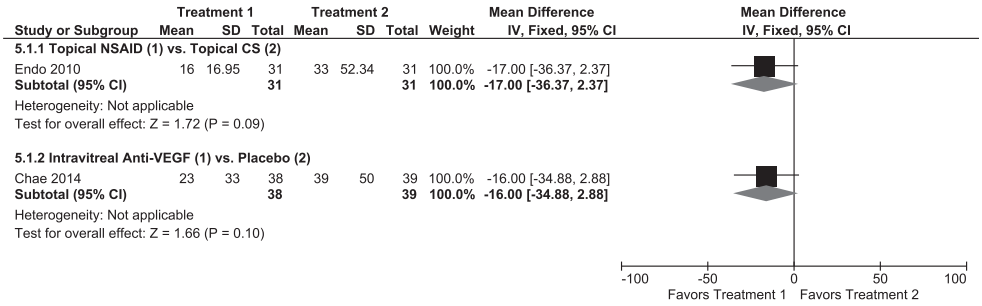
SUPPLEMENTAL FIGURE 2. Odds ratio with 95% confidence intervals for developing cystoid macular edema within 3 months after cataract surgery in a mixed population. CS = corticosteroid; df = degrees of freedom; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; 95% CI = 95% confidence interval.



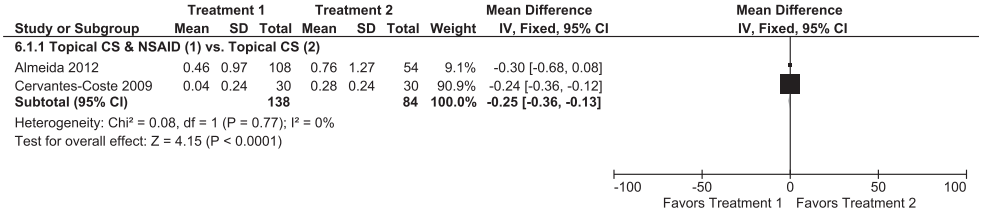
SUPPLEMENTAL FIGURE 3. Odds ratios with 95% confidence intervals for developing cystoid macular edema within 3 months after cataract surgery in diabetic patients. CS = corticosteroid; df = degrees of freedom; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; VEGF = vascular endothelial growth factor; 95% CI = 95% confidence interval.



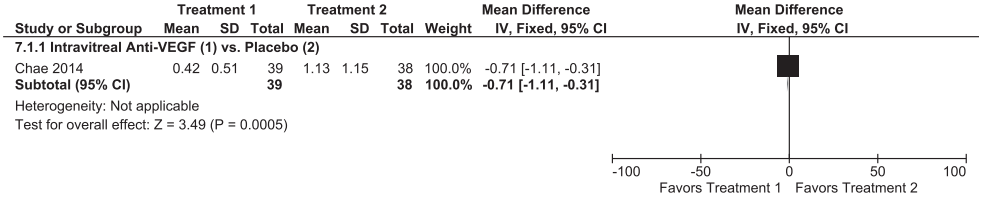
SUPPLEMENTAL FIGURE 4. Mean differences with 95% confidence intervals for change in central foveal thickness within 3 months after cataract surgery as compared to baseline in a mixed population. CS = corticosteroid; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; 95% CI = 95% confidence interval.



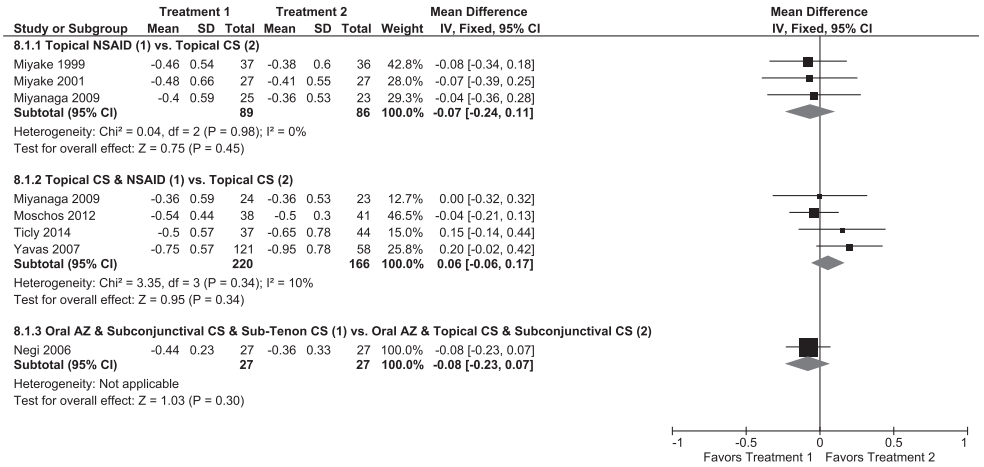
SUPPLEMENTAL FIGURE 5. Mean differences with 95% confidence intervals for change in central foveal thickness within 3 months after cataract surgery as compared to baseline in diabetic patients. CS = corticosteroid; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; VEGF = vascular endothelial growth factor; 95% CI = 95% confidence interval.



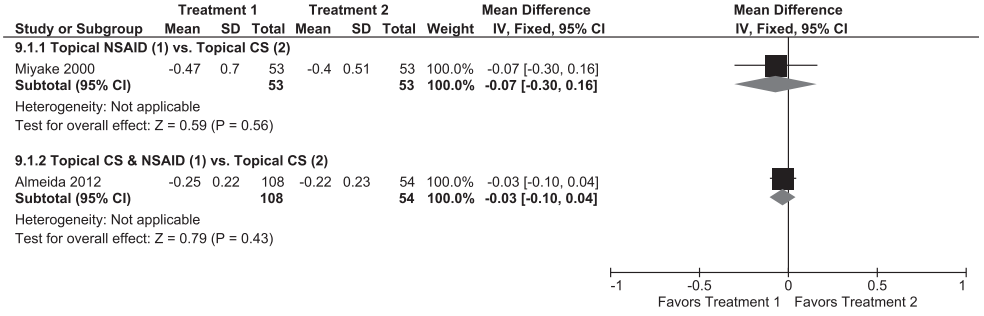
SUPPLEMENTAL FIGURE 6. Mean differences with 95% confidence intervals for change in macular volume within 3 months after cataract surgery as compared to baseline in a mixed population. CS = corticosteroid; df = degrees of freedom; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; 95% CI = 95% confidence interval.



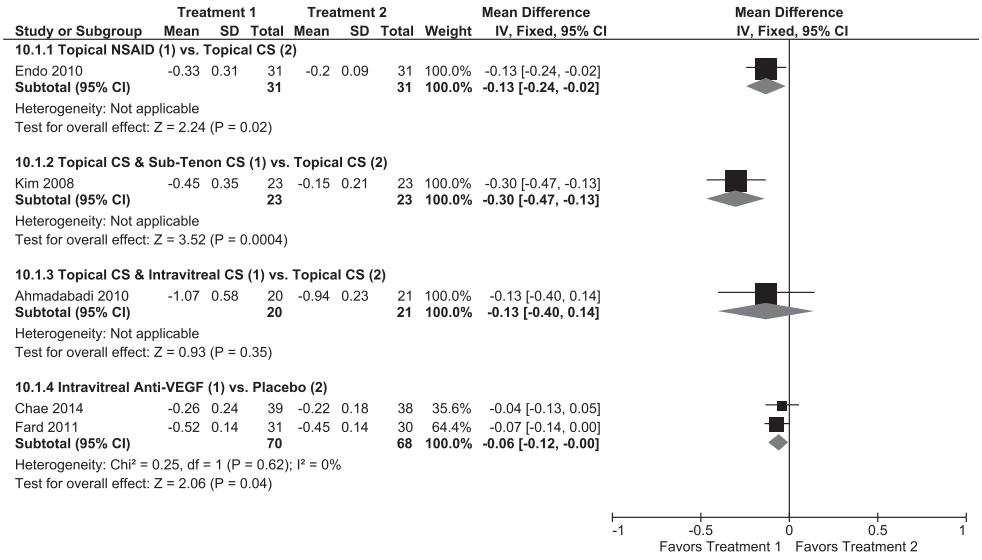
SUPPLEMENTAL FIGURE 7. Mean differences with 95% confidence intervals for change in macular volume within 3 months after cataract surgery as compared to baseline in diabetic patients. IV = inverse variance; SD = standard deviation; VEGF = vascular endothelial growth factor; 95% CI = 95% confidence interval.



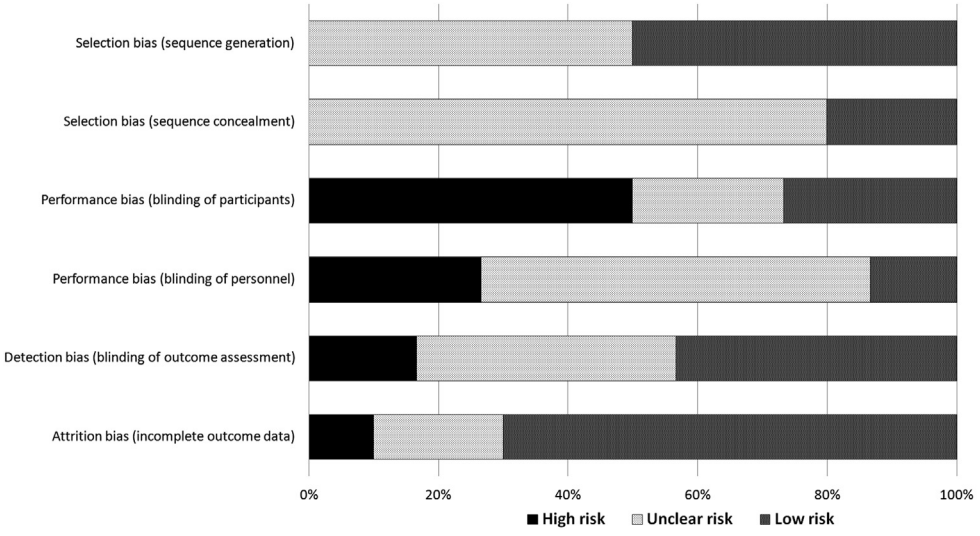
SUPPLEMENTAL FIGURE 8. Mean differences with 95% confidence intervals for change in corrected distance visual acuity within 3 months after cataract surgery as compared to baseline in nondiabetic patients. AZ = acetazolamide; CS = corticosteroid; df = degrees of freedom; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; 95% CI = 95% confidence interval.



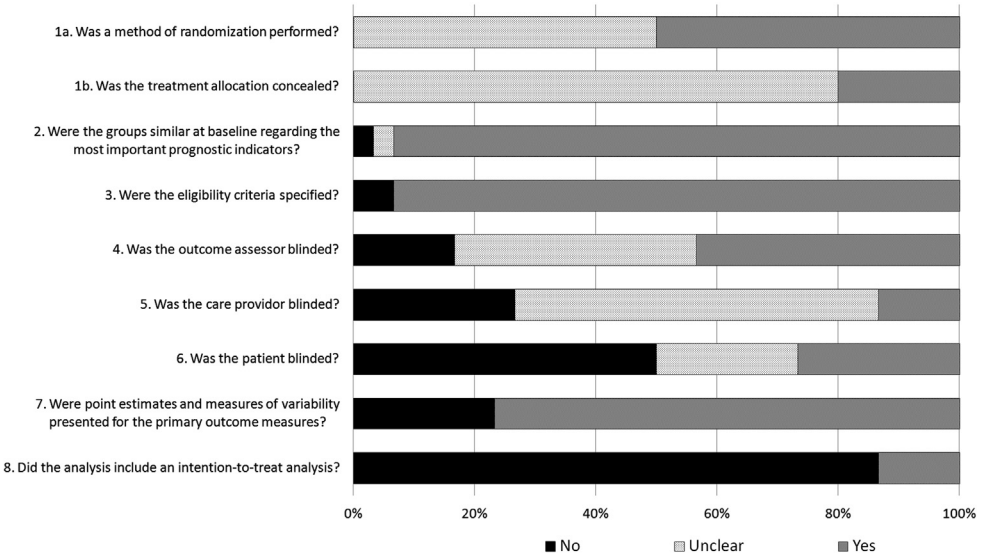
SUPPLEMENTAL FIGURE 9. Mean differences with 95% confidence intervals for change in corrected distance visual acuity within 3 months after cataract surgery as compared to baseline in a mixed population. CS = corticosteroid; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; 95% CI = 95% confidence interval.



SUPPLEMENTAL FIGURE 10. Mean differences with 95% confidence intervals for change in corrected distance visual acuity within 3 months after cataract surgery as compared to baseline in diabetic patients. CS = corticosteroid; IV = inverse variance; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; VEGF = vascular endothelial growth factor; 95% CI = 95% confidence interval.



SUPPLEMENTAL FIGURE 11. Risk-of-bias graph according to the Cochrane Collaboration's tool for assessing risk of bias, showing the risk of bias of included studies investigating the optimal strategy to prevent the occurrence of cystoid macular edema after cataract surgery in nondiabetic and diabetic patients.



SUPPLEMENTAL FIGURE 12. Quality of randomized controlled trials according to the Delphi criteria, showing the quality of included studies investigating the optimal strategy to prevent the occurrence of cystoid macular edema after cataract surgery in nondiabetic and diabetic patients.

SUPPLEMENTAL TABLE 1. Search Strategy Used for the MEDLINE Database to Identify Randomized Controlled Trials Investigating the Efficacy of Preventive Strategies on the Incidence of Cystoid Macular Edema After Cataract Surgery in Nondiabetic and Diabetic Patients

	((((((((((((((“Cataract Extraction”[Mesh]) OR “Lens Implantation, Intraocular”[Mesh]) OR “Phacoemulsification”[Mesh]) OR “Pseudophakia”[Mesh]) OR cataract extract*) OR phakectom*) OR “enzymatic zonulolysis”) OR cataract surger*) OR lens implantation*) OR intraocular lens*) OR phaco*) OR faco*) OR pseudophak*) OR pseudo-phak*) OR pseudofak*) OR pseudo-fak*)
AND	
	((((((((((((“Edema”[Mesh]) OR “Macular Edema”[Mesh]) OR edema) OR oedema) OR irvine-gass) OR “irvine gass”) OR “cystoid macular dystrophy”) OR thickn*) OR CME) OR CMO) OR PCME) OR PCMO) OR “macular volume”)
AND	
	((((((((((((((“Randomized Controlled Trial”[Publication Type]) OR “Controlled Clinical Trial”[Publication Type]) OR “Review”[Publication Type]) OR “Review Literature as Topic”[Mesh]) OR “Meta-Analysis”[Publication Type]) OR “Meta-Analysis as Topic”[Mesh]) OR randomized) OR randomised) OR placebo) OR “drug therapy”) OR random*) OR trial) OR groups) OR review) OR rct) OR meta-analysis)
NOT	
	((animals[mh]) NOT (humans[mh]))
Filters:	None

*Represents any group of characters, including no character.

SUPPLEMENTAL TABLE 2. Characteristics of Studies Investigating the Efficacy of Preventive Strategies on the Incidence of Cystoid Macular Edema After Cataract Surgery in Nondiabetic and Diabetic Patients

Nondiabetic Populations

Dieleman et al, 2011[46]

Methods	Randomized, open-label study
Participants	
n (eyes)	400
Interventions	
Topical CS	Dexamethasone 0.1% eye drops 3 times daily for a postoperative period of 4 weeks and a single administration of gentamicin–dexamethasone at the end of surgery.
Subconjunctival CS	Single subconjunctival injection of betamethasone acetate 5.7 mg/mL at the end of surgery and a single administration of gentamicin–dexamethasone at the end of surgery.
Outcome	
Detection method	OCT (time-domain)
Definition	"Clinically significant macular edema was defined as macular edema on OCT (any increase in center point thickness of more than 30% compared with the preoperative baseline value developing within 4 weeks after cataract surgery) in combination with a decrease in corrected distance visual acuity of 2 or more lines on the ETDRS chart."
Follow-up	4 weeks
Conclusion	"A single betamethasone depot at the end of uneventful cataract surgery could be a useful alternative to dexamethasone eye drops 3 times daily for 4 weeks in preventing postoperative intraocular inflammation and macular edema, especially when compliance problems seem to be an issue."
Notes	Not known how many mL of the 5.7 mg/mL betamethasone acetate were used.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Randomization […]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Low risk	"5 blocks of 80 sealed envelopes with uniform distribution […]"
Performance bias (masking of participants)	High risk	Open-label study
Performance bias (masking of personnel)	High risk	Open-label study
Detection bias (masking of outcome assessment)	High risk	Open-label study
Attribution bias (incomplete outcome data)	Unclear risk	"All excluded patients were replaced."

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; ETDRS = Early Treatment of Diabetic Retinopathy Study; OCT = optical coherence tomography; RCT = randomized controlled trial.

Donnenfeld et al, 2006[20]

Methods	Double-masked, randomized study
Participants	
n (eyes)	100
Interventions	
Topical CS	Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.

Topical CS & NSAID	Ketorolac tromethamine 0.4% 4 times daily for 3 days preoperatively, 3 times every 15 minutes in the hour before surgery, and 4 times daily for 3 weeks after the surgery; Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.
Topical CS & NSAID	Ketorolac tromethamine 0.4% 4 times daily for 1 day preoperatively, every 15 minutes in the hour before surgery, and 4 times daily for 3 weeks after the surgery; Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.
Topical CS & NSAID	Ketorolac tromethamine 0.4% every 15 minutes in the hour before surgery and 4 times daily for 3 weeks after the surgery; Topical prednisolone acetate 1% 4 times a day for 2 weeks after surgery and then twice a day for 1 additional week.
Outcome	
Detection method	OCT (type unknown)
Definition	"All patients with a BCVA worse than 20/30 at the 2-week postoperative visit had OCT at that time, which was evaluated by a masked retinal specialist."
Follow-up	3 months
Conclusion	"The preoperative use of ketorolac tromethamine 0.4% for 3 days followed by 1 day of predosing provided optimum efficacy and superior outcomes relative to 1-hour pretreatment and a placebo."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Group assignment was based on a random-number-generated protocol"
Selection bias (sequence concealment)	Unclear risk	Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Low risk	"Ocular coherence tomography was evaluated by a masked retinal specialist."
Attribution bias (incomplete outcome data)	Unclear risk	No report on drop-out

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

BCVA = best-corrected visual acuity; CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Donnenfeld et al, 2011[19]	
Methods	Multicenter, double-masked, contralateral-eye study
Participants	
n (eyes)	126 (of 63 patients)
Interventions	
Topical CS & NSAID	Difluprednate 0.05% 7 times preoperatively on the day of surgery, 3 times in surgical recovery, and 1 drop every 2 hours for the remainder of day 0. Starting on the day after surgery, 4 times daily for 1 week and twice daily for the subsequent week. Nepafenac 0.1% or ketorolac tromethamine 0.4% beginning 3 days before surgery and continuing for 4 weeks.
Topical CS & NSAID	Prednisolone 1% 7 times preoperatively on the day of surgery, 3 times in surgical recovery, and 1 drop every 2 hours for the remainder of day 0. Starting on the day after surgery, 4 times daily for 1 week and twice daily for the subsequent week. Nepafenac 0.1% or ketorolac tromethamine 0.4% beginning 3 days before surgery and continuing for 4 weeks.

Outcome	
Detection method	OCT (time-domain or spectral-domain) In all cases, each patient had the same OCT used on both eyes.
Definition	-
Follow-up	30 days
Conclusion	"In this study, difluprednate was shown to provide better results compared with prednisolone acetate in multiple end points after cataract surgery. Difluprednate improved UCVA and BCVA at 1 day after cataract surgery, reduced macular swelling at 2 and 4 weeks after surgery, and reduced endothelial cell loss at 4 weeks after surgery."
Notes	Contralateral eye study. "Patients were assigned randomly to receive either difluprednate or prednisolone for treatment of the first eye; the second eye was assigned the alternative medication."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Allocation of the medication was […] based on a random number list generated using randomizer.org."
Selection bias (sequence concealment)	Low risk	"Allocation of the medication was concealed from the investigators."
Performance bias (masking of participants)	Low risk	"Both investigators and patients were masked to the treatment condition."
Performance bias (masking of personnel)	Unclear risk	Masking of investigators is reported, but it is not given which investigators (personnel or outcome assessor) were masked.
Detection bias (masking of outcome assessment)	Unclear risk	Masking of investigators is reported, but it is not given which investigators (personnel or outcome assessor) were masked.
Attribution bias (incomplete outcome data)	Unclear risk	"Eleven patients (17.5%) were not included for the efficacy end point analysis because of protocol violations" Not specified per treatment group.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

BCVA = best-corrected visual acuity; CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial; UCVA = uncorrected visual acuity.

Mathys et al, 2010[21]	
Methods	Nonmasked, randomized, parallel-group study
Participants	
n (eyes)	84
Interventions	
Topical CS & NSAID	Nepafenac 0.01% drops thrice before surgery. Prednisolone acetate 1% 4 times a day for 1 month.
Topical CS & NSAID	Nepafenac 0.01% drops thrice before surgery and postoperatively thrice a day for 1 month. Prednisolone acetate 1% 4 times a day for 1 month.
Outcome	
Detection method	OCT (time-domain)
Definition	"Our estimate of a clinically relevant increase in central macular thickness is 25 μm."
Follow-up	8 weeks
Conclusion	"In our study of subjects without known predisposing causes of CME, the increase in postoperative macular thickness was small in both the control and treatment groups. This small increase in macular thickness had no effect on final BCVA in either group."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Using computer-generated random numbers"
Selection bias (sequence concealment)	Unclear risk	"Subjects were randomised according to the even/odd subject identification number, using computer-generated random numbers." Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	High risk	Nonmasked
Performance bias (masking of personnel)	Low risk	"Technicians, who were masked to treatment, measured ETDRS BCVA, and OCT scans were performed."
Detection bias (masking of outcome assessment)	Low risk	"Experienced ophthalmic photographers, who were masked to treatment, obtained Stratus OCT."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

BCVA = best-corrected visual acuity; CME = cystoid macular edema; CS = corticosteroid; ETDRS = Early Treatment of Diabetic Retinopathy Study; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Miyake et al, 1999[22]	
Methods	Open-label randomized controlled study
Participants	
n (eyes)	80 Eyes with ocular hypertension, normal-tension glaucoma, or primary open-angle glaucoma
Interventions	
Topical CS	0.1% fluorometholone acetate was given 4 times daily on the day of surgery and then 3 times a day until the fifth postoperative week.
Topical NSAID	0.1% diclofenac sodium was given 4 times daily on the day of surgery and then 3 times a day until the fifth postoperative week.
Outcome	
Detection method	Fluorescein angiography
Definition	"I: Slight fluorescein leakage into the cystic space, but not sufficient enough to enclose the entire fovea centralis. II: Complete circular accumulation of the fluorescein in the cystic space, but with a diameter of less than 2.0 mm. III: Circular accumulation of the fluorescein larger than 2.0 mm in diameter."
Follow-up	5 weeks
Conclusion	"Latanoprost therapy enhances disruption of the blood-aqueous barrier and increases the incidence of angiographic cystoid macular edema formation in early postoperative pseudophakias. Because administration of nonsteroidal eye drops such as diclofenac seems to prevent the adverse effects of latanoprost therapy [...] we suggest their concurrent application."
Notes	"This study consisted of a randomized double-masked trial for latanoprost and an open-label controlled trial for determining the effects of diclofenac sodium or fluorometholone eye drop use on latanoprost or its placebo." *This meta-analysis included only eyes receiving a placebo and diclofenac sodium or fluorometholone acetate*.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"[…] randomly assigned […]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	High risk	"Because fluorometholone is a milky-white substance, making it difficult to conduct this part of the study as a double-masked trial, we performed it as an open-label study."
Performance bias (masking of personnel)	High risk	Open-label study
Detection bias (masking of outcome assessment)	Low risk	"The late phase of fluorescein angiograms was graded […] in a double-masked manner."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial.

Miyake et al, 2001[24]

Methods	Single-masked, randomized study
Participants	
n (eyes)	60
	Eyes with ocular hypertension, normal tension glaucoma, or primary open-angle glaucoma
Interventions	
Topical CS	0.1% fluorometholone acetate was given 4 times daily on the day of surgery and then 3 times per day for 5 weeks after surgery.
Topical NSAID	0.5% diclofenac sodium was given 4 times daily on the day of surgery and then 3 times per day for 5 weeks after surgery.
Outcome	
Detection method	Fluorescein angiography
Definition	"I: Slight fluorescein leakage into the cystic space, but not sufficient enough to enclose the entire fovea centralis. II: Complete circular accumulation of the fluorescein in the cystic space, but with a diameter of less than 2.0 mm. III: Circular accumulation of the fluorescein larger than 2.0 mm in diameter."
Follow-up	5 weeks
Conclusion	"Timolol and its preservative, benzalkonium chloride, cause disruption of the blood-aqueous barrier in early postoperative pseudophakia and increase incidence of angiography cystoid macular edema. The concurrent administration of NSAIDs such as diclofenac prevents these adverse effects […]"
Notes	This study was "a double-masked trial for timolol with preservative, its preservative and non-preserved vehicles and a single-masked trial on the effect of diclofenac sodium and fluorometholone acetate on all three." *This meta-analysis included only eyes receiving nonpreserved vehicles and diclofenac sodium or fluorometholone acetate*.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"[…] each randomly assigned to […]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome

Performance bias (masking of participants)	High risk	"Because fluorometholone is a milky white substance, a double-masked trial was impossible in this part of the study, and we therefore settled on a single-masked trial."
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Low risk	"The late phase of fluorescein angiograms was graded […] in a double-masked manner."
Attribution bias (incomplete outcome data)	Low risk	"There was no significant difference in the incidence of patients being lost to follow-up or dropped from the study among the 6 groups."

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial.

Miyanaga et al, 2009[27]

Methods	Prospective, randomized study
Participants	
n (eyes)	72
Interventions	
Topical CS	0.1% betamethasone 4 times daily for 1 month and then 0.1% fluorometholone 4 times daily for 1 month.
Topical NSAID	0.1% bromfenac twice daily until 2 months after surgery.
Topical CS & NSAID	0.1% betamethasone 4 times daily for 1 month and then 0.1% fluorometholone 4 times daily for 1 month; 0.1% bromfenac twice daily until 2 months after surgery.
Outcome	
Detection method	OCT (time-domain)
Definition	"Decreased visual acuity and obvious cystoid macular oedema confirmed by optical coherence tomography."
Follow-up	2 months
Conclusion	"There were no significant differences in anti-inflammatory effects among the three treatments. These findings suggest that bromfenac is as effective as betamethasone in minimizing inflammatory reactions after cataract surgery."
Notes	Patients who developed clinically significant macular edema at 1 month after cataract surgery were subsequently withdrawn from the study.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Patients were randomly allocated to […]" Insufficient information to permit judgment
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes

Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Moschos et al, 2012[28]

Methods	Prospective, randomized study
Participants	
n (eyes)	79
Interventions	
Topical CS	Chloramphenicol 0.5% / dexamethasone sodium phosphate 0.1%, 1 drop 4 times a day for 28 days after phacoemulsification.
Topical CS & NSAID	Chloramphenicol 0.5% / dexamethasone sodium phosphate 0.1%, 1 drop 4 times a day for 28 days after phacoemulsification; Diclofenac sodium 0.1% 1 drop 3 times a day for 3 days before surgery and 1 drop 3 times a day for 28 days after phacoemulsification.
Outcome	
Detection method	OCT (time-domain)
Definition	-
Follow-up	28 days
Conclusion	"The addition of diclofenac did not seem to offer any additional benefit after uneventful phacoemulsification."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Patients were randomized through random number generation […]"
Selection bias (sequence concealment)	Unclear risk	"Patients were randomized through random number generation […]" Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Negi et al, 2006[45]

Methods	Prospective randomized controlled study
Participants	
n (eyes)	54
Interventions	
Oral AZ & topical CS & subconjunctival CS	A single dose of 250 mg AZ orally before discharge. Betamethasone sodium phosphate 0.1% / neomycin sulfate 0.5% drops 4 times a day for 30 days. 4 mg betamethasone injected subconjunctivally.
Oral AZ & subconjunctival CS & sub-Tenon CS	A single dose of 250 mg AZ orally before discharge. A single posterior sub-Tenon injection of 20 or 30 mg triamcinolone. 4 mg betamethasone injected subconjunctivally.

Outcome	
Detection method	Oral fluorescein angiography
Definition	"Angiograms were graded depending on the severity of fluorescein leakage as follows: Grade 1: edema less than perifoveal Grade 2: minimal perifoveal edema Grade 3: moderate perifoveal edema Grade 4: severe perifoveal edema." "Clinical cystoid macular edema was defined as Snellen BCVA of 6/9 or less."
Follow-up	90 days
Conclusion	"A single sub-Tenon's injection of 30 mg triamcinolone seems to be safe and effective as a route of steroid delivery after uneventful phacoemulsification surgery."
Notes	"Initial ethical approval was obtained for the use of 20 mg triamcinolone. However, after the first 10 patients were randomized to the injection group […] it was decided to modify the protocol. The remaining patients were injected with 30 mg of triamcinolone." "Subanalysis of the injection group revealed that of the 11 eyes that had angiographic cystoid macular edema at 30 days, 7 were in the group who had received 20 mg of triamcinolone and only 4 of 17 patients (23%) had received the 30 mg dose (p =.04)"

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Randomized controlled clinical trial" Insufficient information to permit judgment
Selection bias (sequence concealment)	Low risk	"At the end of the procedure, the operating theater nurse opened the study envelope to ascertain randomization […]"
Performance bias (masking of participants)	High risk	No placebo eye drops used in the "injection group."
Performance bias (masking of personnel)	Low risk	"[…] best corrected visual acuity on the logMAR chart by masked optometrists […]"
Detection bias (masking of outcome assessment)	Low risk	"printouts of the angiograms were read by a masked observer […]"
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

AZ = acetozolamide; BCVA = best-corrected visual acuity; CS = corticosteroid; logMAR = logarithm of minimal angle of resolution; RCT = randomized controlled trial.

Ticly et al, 2014[29]	
Methods	Single-center, prospective, double-masked, randomized clinical study
Participants	
n (eyes)	91 patients, no. of eyes included in the study was not reported (1 eye per patient assumed for this meta-analysis). "Patients with nuclear cataract density of 2 and 3 […]"
Interventions	
Topical CS	Prednisolone acetate 1% 4 times daily for 3 days preoperatively and 5 weeks postoperatively; Dextran/hypromellose (placebo) 4 times daily for 3 days preoperatively and 5 weeks postoperatively.
Topical CS & NSAID	Prednisolone acetate 1% 4 times daily for 3 days preoperatively and 5 weeks postoperatively; Ketorolac tromethamine 0.4% 4 times daily for 3 days preoperatively and 5 weeks postoperatively.
Outcome	
Detection method	OCT (spectral-domain) & fluorescein angiography

Definition	"The primary outcome measured was angiographic cystoid macular edema incidence. We classified cystoid macular edema based on fluorescein angiography using Miyake's classification. Cystoid leakage included petalloid or honeycombed patterns of hyperfluorescence and dye pooling in well-defined foveal or parafoveal spaces." "Cystoid macular edema on OCT was defined as the presence of well-defined cystic fluid pockets […] or a central subfield thickness above 315 μm."
Follow-up	5 weeks
Conclusion	"There was no difference between ketorolac tromethamine and a placebo with regard to best corrected visual acuity results or prevention of cystoid macular edema after uncomplicated cataract surgery."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Random number table […]"
Selection bias (sequence concealment)	Low risk	"A pharmacist provided the patient with a small individual envelope, and after viewing the random number, the patient took the respective eye drop bottle."
Performance bias (masking of participants)	Low risk	"All study participants were blinded to their treatment assignment."
Performance bias (masking of personnel)	Low risk	"The surgeon and the ophthalmologist who collected the data were not aware of the group assignment of the patients."
Detection bias (masking of outcome assessment)	Low risk	"The reader of fluorescein angiograms was blinded as to group allocation."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Wang et al, 2013[43]	
Methods	Prospective, randomized study
Participants	
n (eyes)	240
Interventions	
Oral CS & topical CS	Oral prednisone tablets 15 mg for 7 days; Ophthalmic fluorometholone 0.1% 3 times a day for 1 month postoperatively.
Oral CS & topical CS	Oral prednisone tablets 15 mg for 7 days; Ophthalmic dexamethasone 0.1% 3 times a day for 1 month postoperatively.
Oral CS & topical NSAID	Oral prednisone tablets 15 mg for 7 days; Ophthalmic bromfenac sodium 0.1% twice per day for 1 month postoperatively.
Oral CS & topical NSAID	Oral prednisone tablets 15 mg for 7 days; Ophthalmic bromfenac sodium 0.1% twice per day for 2 months postoperatively.
Outcome	
Detection method	OCT (time-domain)
Definition	"The patients with best-corrected visual acuity impairment and macular alterations were considered possible cystoid macular edema patients and the diagnosis was final confirmed by OCT […] Cystoid macular edema was defined as central retinal thickness >250 μm and the presence of intraretinal cystoid space beneath the foveal, with the diagnosis confirmed by the same retinal specialist."

Follow-up	2 months
Conclusion	"Bromfenac sodium was more effective and safer than fluorometholone and dexamethasone as an anti-inflammatory, decreasing macular thickness and preventing cystoid macular edema in age-related cataract patients after cataract surgery."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Random-numbers table"
Selection bias (sequence concealment)	Unclear risk	"Randomly and prospectively assigned […] by a random-numbers table." Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	High risk	"The drugs were applied […] open-labeled."
Performance bias (masking of personnel)	High risk	"The drugs were applied […] open-labeled."
Detection bias (masking of outcome assessment)	High risk	"The drugs were applied […] open-labeled."
Attribution bias (incomplete outcome data)	Unclear risk	Missing outcome data balanced in numbers across intervention groups. Reasons for drop-out not reported.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Yavas et al, 2007[30]

Methods	Prospective, randomized study
Participants	
n (eyes)	189 Right eyes of 189 patients
Interventions	
Topical CS	1 drop of topical prednisolone acetate 1% 4 times daily for 1 month postoperatively.
Topical CS & NSAID	1 drop of topical prednisolone acetate 1% 4 times daily for 1 month postoperatively; 1 drop of topical indomethacin 0.1% 4 times daily for 3 days preoperatively and 4 times daily for 1 month postoperatively.
Topical CS & NSAID	1 drop of topical prednisolone acetate 1% 4 times daily for 1 month postoperatively; 1 drop of topical indomethacin 0.1% 4 times daily for 1 month postoperatively.
Outcome	
Detection method	Fluorescein angiography
Definition	"Slight fluorescein leakage into the cystic space without enclosing the entire central fovea or complete fluorescein accumulation in the cystic space was diagnosed as angiographic cystoid macular edema."
Follow-up	3 months
Conclusion	"Nonsteroidal anti-inflammatory drugs decreased the incidence of CME, and their efficacy increased when begun preoperatively."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Patients were randomized into 3 groups." Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	High risk	Frequency of administration varied between treatment groups.

Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Low risk	"Fluorescein leakage to diagnose angiographic cystoid macular edema was evaluated by a masked observer."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	No
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CME = cystoid macular edema; CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial.

Mixed Populations

Almeida et al, 2008[31]

Methods	Open-label nonmasked randomized study
Participants	
n (eyes)	106
Interventions	
Topical CS	A 14-day course of prednisolone acetate 1% 4 times a day for 1 week followed by twice a day for 1 week.
Topical CS & NSAID	A 14-day course of prednisolone acetate 1% 4 times a day for 1 week followed by twice a day for 1 week. 1 drop of ketorolac tromethamine 0.5% (Acular) 4 times a day beginning 2 days before surgery and for 29 days after surgery, for a total of 31 days.
Outcome	
Detection method	OCT (time-domain)
Definition	-
Follow-up	1 month
Conclusion	"Used prophylactically after cataract surgery, ketorolac 0.5% was efficacious in decreasing postoperative macular edema."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Random number assignment"
Selection bias (sequence concealment)	Unclear risk	"Random number assignment" Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	High risk	"Open-label nonmasked study"
Performance bias (masking of personnel)	High risk	"Open-label nonmasked study"
Detection bias (masking of outcome assessment)	High risk	"Open-label nonmasked study"
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Almeida et al, 2012[32]	
Methods	Prospective placebo-controlled parallel-assignment double-masked randomized clinical trial
Participants	
n (eyes)	193
Interventions	
Topical CS	Prednisolone 1% drops, started on the day of surgery, 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and 1 time a day for 1 week. Placebo eye drops 4 times a day, beginning 1 day before surgery and continued for 4 weeks.
Topical CS & NSAID	Prednisolone 1% drops, started on the day of surgery, 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and 1 time a day for 1 week. Nepafenac 0.1% eye drops 4 times a day, beginning 1 day before surgery and continued for 4 weeks.
Topical CS & NSAID	Prednisolone 1% drops, started on the day of surgery, 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and 1 time a day for 1 week. Ketorolac 0.5% eye drops 4 times a day, beginning 1 day before surgery and continued for 4 weeks.
Outcome	
Detection method	OCT (time-domain)
Definition	-
Follow-up	1 month
Conclusion	"One month after uneventful phacoemulsification, there was no difference in macular volume between the placebo, ketorolac, and nepafenac. Thus, for patients without risk factors having routine surgery, prophylactic topical NSAIDs are not recommended."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Patients were randomly assigned to […]" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Low risk	"[…] identical generic drop bottles that were individually made by the hospital investigational pharmacy division."
Performance bias (masking of participants)	Low risk	"Identical generic drop bottles"
Performance bias (masking of personnel)	Unclear risk	"Double masked." Unclear whether personnel and/or outcome assessor were masked.
Detection bias (masking of outcome assessment)	Unclear risk	"Double masked." Unclear whether personnel and/or outcome assessor were masked.
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Unclear
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Cable, 2012[18]	
Methods	Prospective, randomized, investigator-masked, parallel-group, comparative clinical study
Participants	
n (eyes)	20 Patients without preexisting macular or retinal edema or more than 2 microaneurysms within the fundus
Interventions	
Topical CS & NSAID	Prednisolone acetate 1% intraoperatively; Difluprednate once daily for 3 weeks postoperatively; Bromfenac ophthalmic solution 0.09% once daily. Dosing began 3 days before cataract surgery, continuing to day 21 postsurgery.

Topical CS & NSAID	Prednisolone acetate 1% intraoperatively. Difluprednate once daily for 3 weeks postoperatively. Nepafenac ophthalmic suspension 0.1% 3 times daily. Dosing began 3 days before cataract surgery, continuing to day 21 postsurgery.
Outcome	
Detection method	OCT (time-domain)
Definition	-
Follow-up	6 weeks
Conclusion	"Both bromfenac and nepafenac resulted in positive clinical outcomes of ETDRS visual acuities. Postoperative measurements of macular volume and retinal thickness of bromfenac subjects showed a trend toward improved vision, less retinal thickening, and more stable macular volumes overall."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"[…] according to a computer-generated randomization list […]"
Selection bias (sequence concealment)	Low risk	"The investigator and technicians recording study data were masked to treatment group assignment for the duration of the trial […]"
Performance bias (masking of participants)	Unclear risk	"Subjects were masked to the study drug identity for the entirety of the trial" However, the frequency of administration varied between treatment groups.
Performance bias (masking of personnel)	Low risk	"All measurements were completed by masked observers."
Detection bias (masking of outcome assessment)	Low risk	"The investigator and technicians recording study data were masked to treatment group assignment for the duration of the trial […]"
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	Yes

CS = corticosteroid; ETDRS = Early Treatment Diabetic Retinopathy Study; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Cervantes-Coste et al, 2009[33]	
Methods	Prospective, randomized, single-masked comparative study
Participants	
n (eyes)	60
Characteristics	Patients without noncontrolled diabetes mellitus, based on clinical history and blood glucose level; proliferative diabetic retinopathy; and/or macular edema.
Interventions	
Topical CS	Dexamethasone treatment 4 times daily for 10 days after surgery.
Topical CS & NSAID	Dexamethasone treatment 4 times daily for 10 days after surgery. 1 drop of nepafenac 0.1% 3 times daily 1 day prior to surgery, every 15 minutes 1 hour prior to surgery, and 3 times daily for 6 weeks afterward.
Outcome	
Detection method	OCT (time-domain)
Definition	"Clinically significant macular edema associated with vision loss."
Follow-up	6 weeks
Conclusion	"Prophylactic use of nepafenac was effective in reducing macular edema after cataract surgery and in maintaining trans-operative mydriasis."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"[…] patients were randomly selected […]" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (masking of personnel)	High risk	"The identity of patients receiving nepafenac was concealed form the surgeon." Other personnel were not masked (single-masked study).
Detection bias (masking of outcome assessment)	High risk	Other personnel were not masked (single-masked study).
Attribution bias (incomplete outcome data)	Low risk	"All patients completed the follow-up visits over a 6-week period."

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Chatziralli et al, 2011[42]

Methods	Randomized study
Participants	
n (eyes)	145
Interventions	
Oral AZ & topical CS & NSAID	Half a tablet of acetazolamide 250 mg the night prior to surgery and on the morning before surgery. Ketorolac tromethamine 0.5% 3 times daily, 3 days before surgery. Dexamethasone 0.1% 5 times daily, 3 days before surgery, and 1 drop 4 times per day 28 days after surgery.
Oral AZ & topical CS & NSAID	Half a tablet of acetazolamide 250 mg the night prior to surgery and on the morning before surgery. Ketorolac tromethamine 0.5% 3 times daily, 3 days before surgery and 28 days after surgery. Dexamethasone 0.1% 5 times daily, 3 days before surgery, and 1 drop 4 times per day 28 days after surgery.
Outcome	
Detection method	Funduscopy & Amsler grid test
Definition	-
Follow-up	42 days
Conclusion	"The addition of ketorolac did not seem to offer any additional benefit in terms of inflammation-related signs. Four weeks appeared as an adequate treatment interval."
Notes	"In case 1 inflammation-related sign (corneal edema, conjunctival hyperemia or Tyndall reaction) was present on day 28, the treatment was continued. Irrespective of continuation, on day 42 all patients underwent fundoscopy and an Amsler grid test, so as to trace any suspicious signs for the development of clinically significant cystoid macular edema."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"The patients were randomized […]" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	Low risk	"The study was masked to the patients […]"
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this outcome.

Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	No
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

AZ = acetozolamide; CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial.

Miyake et al, 2000[23]

Methods	Multicenter, prospective open clinical study
Participants	
n (eyes)	118
Characteristics	Eyes without complications from diabetes mellitus
Interventions	
Topical CS	0.1% fluorometholone at 3 hours, 2 hours, 1 hour, and 30 minutes, prior to surgery; and 3 times a day for 8 consecutive weeks following surgery.
Topical NSAID	0.1% diclofenac at 3 hours, 2 hours, 1 hour, and 30 minutes, prior to surgery; and 3 times a day for 8 consecutive weeks following surgery.
Outcome	
Detection method	Fluorescein angiography
Definition	"I: minimal fluorescein leakage into the cystic space but not surrounding the entire fovea; II: fluorescein leakage surrounding nearly the entire fovea but less than 2.0 mm in diameter; III: fluorescein leakage surrounding the fovea and larger than 2.0 mm in diameter."
Follow-up	8 weeks
Conclusion	"These findings suggest that diclofenac effectively prevents CME following cataract surgery and that CME is closely related to the breakdown of the blood–aqueous barrier."
Notes	"Five to 15 consecutive patients were enrolled at each site […]"

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"[…] eyes were assigned to […]" The authors assumed that the trial was randomized, because baseline factors were equal in both treatment groups in a study population of >100 subjects. Nevertheless, there was insufficient information to permit judgment about the sequence generation process.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	High risk	"Open trial"
Performance bias (masking of personnel)	High risk	"Open trial"
Detection bias (masking of outcome assessment)	Low risk	"CME was evaluated in a double-masked fashion […]"
Attribution bias (incomplete outcome data)	High risk	Visual acuity was available for approximately half of the study subjects.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CME = cystoid macular edema; CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial.

Miyake et al, 2007[25]

Methods	Prospective, double-masked, randomized study
Participants	
n (eyes)	62
Interventions	
Topical CS	Fluorometholone eye drops 4 times before surgery (3 hours, 2 hours, 1 hour, and 30 minutes) and 3 times a day for 5 weeks after surgery.
Topical NSAID	Diclofenac eye drops 4 times before surgery (3 hours, 2 hours, 1 hour, and 30 minutes) and 3 times a day for 5 weeks after surgery.
Outcome	
Detection method	Fluorescein angiography
Definition	"1: slight dye accumulation in the cystic space and incompletely surrounding the fovea; 2: dye accumulation surrounding the fovea with a diameter of less than 2 mm; 3: dye accumulation surrounding the fovea with a diameter greater than 2 mm."
Follow-up	5 weeks
Conclusion	"Reduction of choroidal blood flow, disruption of the blood-aqueous barrier, and incidence of cystoid macular edema in early postsurgical pseudophakic eyes were more effectively prevented chronologically in eyes treated with diclofenac than in those treated with fluorometholone."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Each patient was randomly assigned […] using the envelope method"
Selection bias (sequence concealment)	Unclear risk	"Each patient was randomly assigned […] using the envelope method" Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	Unclear risk	"Double masked study […]" Unknown whether participants were masked.
Performance bias (masking of personnel)	Unclear risk	"Double masked study […]" Unknown whether personnel were masked.
Detection bias (masking of outcome assessment)	Low risk	"Cystoid macular edema […] was analyzed by one of the authors in a masked fashion."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial.

Miyake et al, 2011[26]

Methods	Randomized double-masked single-center clinical study
Participants	
n (eyes)	60
Characteristics	Patients without diabetic retinopathy
Interventions	
Topical CS	Fluorometholone 0.1% 1 drop 3 times a day starting the day before surgery until 5 weeks postoperatively. An additional 1 drop was given on the day of surgery.
Topical NSAID	Nepafenac 0.1% 1 drop 3 times a day starting the day before surgery until 5 weeks postoperatively. An additional 1 drop was given on the day of surgery.
Outcome	
Detection method	OCT (spectral-domain) & fluorescein angiography

Definition	"I: slight fluorescein leakage into the cystic space, but not enough to enclose the entire fovea centralis. II: there is complete circular accumulation of the fluorescein in the cystic space, but the diameter of the accumulation is smaller than 2.0 mm. III: the fluorescein leakage surrounds the fovea and is larger than 2.0 mm in diameter."
Follow-up	5 weeks
Conclusion	"Nepafenac was more effective than fluorometholone in preventing angiographic cystoid macular edema and blood-aqueous barrier disruption, and results indicate nepafenac leads to more rapid visual recovery."
Notes	No definition of cystoid macular edema on OCT given.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Randomized to" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	Low risk	"The 2 drugs had identical outer appearances and could not be differentiated."
Performance bias (masking of personnel)	Low risk	"Fluorescein angiography was used to confirm the presence of cystoid macular edema […] in a double masked manner."
Detection bias (masking of outcome assessment)	Low risk	"[…] physician determined and graded the severity […] in a double-masked manner."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Nishino et al, 2009[41]

Methods	Single-masked, randomized, prospective study
Participants	
n (eyes)	28 (of 21 patients)
Interventions	
Topical NSAID	Topical bromfenac sodium every 20 minutes 2 hours prior to surgery and from the day after surgery, twice daily.
Topical CS & NSAID & subconjunctival	0.1% topical fluorometholone 4 times daily;
CS	Topical bromfenac sodium every 20 minutes 2 hours prior to surgery and from the day after surgery, twice daily. Subconjunctival injection of approximately 0.5 mL phosphoric acid dexamethasone was injected at the end of the surgery.
Outcome	
Detection method	Fluorescein angiography
Definition	"Fluorescein fundus angiography was performed only when cystoid macular edema was suspected to worsen the visual acuity to less than 0.7."
Follow-up	1 month
Conclusion	"Topical steroid medication may not be absolutely essential after uneventful phaco-emulsification/aspiration plus intraocular lens implantation."
Notes	"Cystoid macular edema was not found in any of patients."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"All participants were prospectively evaluated by randomizing into 2 groups." Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	High risk	Frequency of administration varied between treatment groups.
Performance bias (masking of personnel)	Unclear risk	"Single-blind study." Unknown whether personnel was blinded.
Detection bias (masking of outcome assessment)	Unclear risk	"Single-blind study." Unknown whether outcome assessor was masked.
Attribution bias (incomplete outcome data)	Unclear risk	No report on drop-out

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial.

Weber et al, 2013[34]

Methods	Prospective, multicenter, investigator-masked, parallel-group, randomized, active-controlled clinical study
Participants	
n (eyes)	123
Characteristics	Patients without diabetic retinopathy
Interventions	
Topical NSAID	Indomethacin 0.1% 1 drop 4 times daily for 3 weeks, beginning 24 hours prior to surgery.
Topical NSAID	Ketorolac 0.5% 1 drop 4 times daily for 3 weeks, beginning 24 hours prior to surgery.
Outcome	
Detection method	OCT (time-domain)
Definition	-
Follow-up	90 days
Conclusion	"Indomethacin 0.1% was at least as effective as ketorolac 0.5% at day 1 and more effective than ketorolac 0.5% at day 7 in treating ocular inflammation after uncomplicated cataract surgery."
Notes	"Corticosteroids were to be administered at follow-up visits in the following cases: conjunctival hyperaemia grade ≥3, ciliary flush grade ≥3, fibrinoid exudate, hypopyon, retrocorneal precipitates or posterior synechiae in the study eye." Noninferiority trial: the trial was designed to investigate the noninferiority of indomethacin to ketorolac.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Treatment was determined by a unique randomization table"
Selection bias (sequence concealment)	Unclear risk	"Allocation of treatment was determined by a unique randomization table […]" Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	Low risk	"Both drugs were labelled identically to preserve masking […] with the patients being masked to the treatment name."
Performance bias (masking of personnel)	Unclear risk	"The study was investigator-masked […]" Unknown whether personnel were masked.

Detection bias (masking of outcome assessment)	Unclear risk	"The study was investigator-masked […]" Unknown whether the outcome assessor was masked.
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	Yes

NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Wittpenn et al, 2008[35]

Methods	Prospective, randomized, investigator-masked, multicenter study.
Participants	
n (eyes)	546
Characteristics	Patients with no ocular manifestations of systemic diseases.
Interventions	
Topical CS & NSAID	Four doses of ketorolac 0.4% during the 1 hour prior to surgery Prednisolone acetate 1% 4 times daily after surgery until patients exited the study at weeks 4–6. Artificial tear solution (placebo).
Topical CS & NSAID	Ketorolac 0.4% 4 times daily for 3 days prior to surgery, 4 doses every 15 minutes 1 hour preoperatively, and 4 times daily until they exited the study at weeks 4–6. Prednisolone acetate 1% 4 times daily after surgery until 1 5-mL bottle was empty.
Outcome	
Detection method	OCT (type unknown)
Definition	"Definite CME: Presence of cystoid changes associated with substantial (≥40 μm) retinal thickening on OCT. Probable CME: Presence of changes in retinal contour and increased macular thickness relative to preoperative baseline, but without definite cystoid changes. Possible CME: Mild to moderate changes in retinal thickness or contour without cystoid changes."
Follow-up	4–6 weeks "Patients were exited from the study when the surgeon felt the patient had achieved best-obtainable visual acuity and no inflammation was present."
Conclusion	"This study suggests that adding perioperative ketorolac to postoperative prednisolone significantly reduces the incidences of CME and macular thickening in cataract surgery patients already at low risk for this condition."
Notes	"Patients could also be exited from the study if, on postoperative day 1, the surgeon felt the amount of inflammation was greater than expected and, in his best clinical judgment, more aggressive anti-inflammatory treatment was indicated."

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"[…] using a randomly generated list"
Selection bias (sequence concealment)	Unclear risk	"[…] using a randomly generated list" Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	Low risk	"The labels were covered. Patients would only have been unmasked if they researched the type and shape of the different bottles."
Performance bias (masking of personnel)	High risk	"The technical staff was unmasked."
Detection bias (masking of outcome assessment)	Low risk	"OCT-based diagnosis of CME was made by an experienced and masked retina specialist"
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CME = cystoid macular edema; CS = corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Diabetic Populations

Ahmadabadi et al, 2010[37]

Methods	Prospective randomized controlled study
Participants	
n (eyes)	41
Characteristics	"Patients with type 2 diabetes and moderate nonproliferative diabetic retinopathy"
Interventions	
Topical CS	Betamethasone 0.1% eye drops 6 times a day for 1 week. After 1 week, the betamethasone was tapered over 4 weeks.
Topical CS & intravitreal CS	Betamethasone 0.1% eye drops 6 times a day for 1 week. After 1 week, the betamethasone was tapered over 4 weeks. Injection of 2 mg of triamcinolone acetonide 3.5 mm posterior to the inferotemporal limbus.
Outcome	
Detection method	OCT (time-domain) & fluorescein angiography
Definition	"Clinical cystoid macular edema was defined as a subjective report of decreased vision by the patient, ophthalmoscopic detection of the presence of macular edema, and confirmation of the diagnosis by fluorescein angiography and OCT examinations at any postoperative visit."
Follow-up	6 months
Conclusion	"Intravitreal injection of triamcinolone reduced the amount of increase in center point thickness and central 1.0 mm subfield mean thickness after phacoemulsification in eyes of diabetic patients. Although it also reduced the incidence of CME, it had no effect on visual acuity gain."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"Using computer-generated random numbers […]"
Selection bias (sequence concealment)	Unclear risk	"Using computer-generated random numbers […]" Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	Unclear risk	The study did not address this outcome.
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes (partial)
Intention-to-treat analysis included?	No

CME = cystoid macular edema; CS = corticosteroid; OCT = optical coherence tomography; RCT = randomized controlled trial.

Chae et al, 2014[38]

Methods	Prospective randomized study
Participants	
n (eyes)	80

Characteristics	"Patients with stable diabetic retinopathy without significant macular edema"
Interventions	
Placebo	The needle tip was only touched to the conjunctiva surface.
Intravitreal anti-VEGF	0.05 mL of a solution containing 0.5 mg of ranibizumab was injected intravitreally at the sclera from 3 mm posterior to the limbus
Outcome	
Detection method	OCT (spectral-domain) & fluorescein angriography
Definition	"Postoperative diabetic macular edema was defined as a >60 mm increase in central subfield thickness relative to the screening central subfield thickness value, as assessed by spectral domain OCT." "Using fluorescein angiography, postoperative diabetic macular edema was scored as follows: (method of Antcliff et al): Grade 0: no perifoveal hyperfluorescence Grade 1: incomplete perifoveal hyperfluorescence Grade 2: mild 360° hyperfluorescence Grade 3: severe 360° hyperfluorescence with the hyperfluorescent area being ≈ 1 disk diameter."
Follow-up	6 months
Conclusion	"In patients with stable diabetic retinopathy without significant macular edema, intravitreal ranibizumab injection at cataract surgery may prevent the postoperative worsening of macular edema and may improve the final visual outcome without affecting safety."
Notes	The authors do not mention any (standard) anti-inflammatory treatment, used in addition to the intravitreal or sham injection.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"[…] patients were randomly assigned […] using a table of random numbers."
Selection bias (sequence concealment)	Unclear risk	"[…] patients were randomly assigned […] using a table of random numbers." Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	Low risk	"In the sham group, the needle tip touched the conjunctiva surface."
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	High risk	The number of drop-outs reported does not match the number of eyes at baseline and endpoint. Percentages, total number of patients, and number of patients with cystoid macular edema reported in the article do not match.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

OCT = optical coherence tomography; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

Endo et al, 2010[44]	
Methods	Prospective open-label study
Participants	
n (eyes)	75
Characteristics	Diabetic patients, no severe diabetic retinopathy
Interventions	
Topical CS	Betamethasone sodium phosphate 4 times daily for 1 week followed by fluorometholone 0.1% for steroid withdrawal 4 times daily for 5 weeks.
Topical NSAID	Bromfenac eye drops were instilled twice daily until week 6.

Outcome	
Detection method	OCT (time-domain)
Definition	-
Follow-up	6 weeks
Conclusion	"Bromfenac suppressed anterior chamber inflammation and increasing retinal thickening after cataract surgery in patients with nonproliferative diabetic retinopathy."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"[…] using the envelope method."
Selection bias (sequence concealment)	Unclear risk	"[…] using the envelope method." Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	High risk	"open-label study"
Performance bias (masking of personnel)	High risk	"open-label study"
Detection bias (masking of outcome assessment)	High risk	"open-label study"
Attribution bias (incomplete outcome data)	Unclear risk	Drop-outs not specified per treatment group

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	No (significantly higher HbA1c in bromfenac group)
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; HbA1c = hemoglobin A1c; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Fard et al, 2011[39]

Methods	Prospective randomized study
Participants	
n (eyes)	63
Characteristics	Patients with preexisting moderate or severe nonproliferative diabetic retinopathy and a preoperative central macular thickness of <200 μm on OCT
Interventions	
Placebo	Standardized procedure of phacoemulsification with intraocular lens implantation alone.
Intravitreal anti-VEGF	1.25 mg intravitreal bevacizumab at the end of surgery.
Outcome	
Detection method	OCT (time-domain)
Definition	"Increase in center point thickness on OCT after cataract surgery."
Follow-up	6 months
Conclusion	"Intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is effective just for the short term and 6-month results are the same as the control group."
Notes	Standardized procedure not described. The authors do not mention any (standard) anti-inflammatory treatment, used in addition to the intravitreal or sham injection.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Patients were randomized to […]" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	Unclear risk	The study did not address this outcome.
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this for the primary outcome measurement (OCT). "Progression of diabetic retinopathy was based on assessment in a masked fashion by a retina specialist."

Attribution bias (incomplete outcome data)	High risk	Number of patients lost to follow-up was higher in the control group. No reasons for drop-out were given.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

OCT = optical coherence tomography; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

Kim et al, 2008[36]

Methods	Prospective randomized controlled study
Participants	
n (eyes)	46 (of 23 patients)
Characteristics	Non-insulin-dependent diabetic patients and mild to moderate nonproliferative diabetic retinopathy or no retinopathy
Interventions	
Topical CS	Prednisolone acetate eye drops 1%, 1 drop 4 times daily from the day of surgery until 1 month and 1 drop 2 times daily for the following 2 weeks.
Topical CS & Sub-Tenon CS	Prednisolone acetate eye drops 1%, 1 drop 4 times daily from the day of surgery until 1 month and 1 drop 2 times daily for the following 2 weeks; Sub-Tenon capsule injection of triamcinolone acetonide at the end of cataract surgery.
Outcome	
Detection method	OCT (type unknown) & fluorescein angiography
Definition	"Postsurgical cystoid macular edema was defined as decreased visual acuity and cystoid macular edema on OCT."
Follow-up	6 months
Conclusion	"A posterior sub-Tenon injection of triamcinolone acetonide lowered the incidence of cystoid macular edema after cataract surgery in diabetic patients, improved visual recovery, and reduced the amount of central macular thickness increase in the short term (≤1 month postoperatively). However, triamcinolone acetonide did not affect DR progression over the 6-month follow-up."
Notes	

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Low risk	"The assignment […] was made using computer-generated random numbers."
Selection bias (sequence concealment)	Unclear risk	"The assignment […] was made using computer-generated random numbers" Unknown whether appropriate safeguards were used.
Performance bias (masking of participants)	Unclear risk	The study did not address this outcome.
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	Paired eye comparison

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; DR = diabetic retinopathy; OCT = optical coherence tomography; RCT = randomized controlled trial.

Singh et al, 2012[47]	
Methods	Multicenter, randomized, double-masked, vehicle controlled study
Participants	
n (eyes)	263
Characteristics	Diabetic (type 1 or type 2) patients with an existing diagnosis of nonproliferative diabetic retinopathy
Interventions	
Topical CS	Prednisolone acetate ophthalmic suspension 4 times daily for 2 weeks postsurgery or longer if considered necessary to treat anterior segment inflammation.
Topical CS & NSAID	Prednisolone acetate ophthalmic suspension 4 times daily for 2 weeks postsurgery or longer if considered necessary to treat anterior segment inflammation. Nepafenac ophthalmic suspension 0.1% 3 times daily on the day prior to cataract surgery, on the day of surgery and for 90 days thereafter.
Outcome	
Detection method	OCT (time-domain)
Definition	"Macular edema was defined as ≥30% increase in central subfield macular thickness relative to the presurgical baseline measurement."
Follow-up	90 days
Conclusion	"Nepafenac demonstrated statistically significant and clinically relevant advantages compared with vehicle in preventing macular edema and maintaining visual acuity in diabetic patients following cataract surgery. These advantages were seen at multiple time points over the course of the 90-day therapy period."
Notes	Prednisolone eye drops were used longer if considered necessary to treat postoperative inflammation.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Enrolled patients were randomized to […]" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	Low risk	"Double masked, vehicle controlled study"
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Low risk	"Morphological features, including intraretinal cysts, were analyzed by the reading center in a masked fashion."
Attribution bias (incomplete outcome data)	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	No
Intention-to-treat analysis included?	No

CS = Corticosteroid; NSAID = nonsteroidal anti-inflammatory drug; OCT = optical coherence tomography; RCT = randomized controlled trial.

Udaondo et al, 2011[40]	
Methods	Prospective randomized controlled intervention study
Participants	
n (eyes)	54
Characteristics	"Patients with some degree of diabetic retinopathy without macular involvement"
Interventions	
Topical CS	Dexamethasone eye drops 4 times a day for 1 month.
Topical CS & Intravitreal anti-VEGF	Dexamethasone eye drops 4 times a day for 1 month; An intravitreal injection of ranibizumab (0.5 mL of solution at 10 mg/mL) at the end of surgery.
Outcome	

Detection method	OCT (spectral-domain)
Definition	"Clinically significant macular edema was defined as macular edema involving or threatening the centre of the macula as defined by the ETDRS."
Follow-up	3 months
Conclusion	"The combination of intravitreal ranibizumab and uncomplicated phacoemulsification avoids the macular thickening measured by OCT in mild to moderate diabetic retinopathy patients without previous macular involvement."
Notes	Postoperative central subfield thickness is only reported for eyes that developed central subfield macular thickness.

Risk of bias (Cochrane Collaboration's tool for assessing risk of bias)

Bias	Authors' Judgment	Support for Judgment
Selection bias (sequence generation)	Unclear risk	"Randomized study" Insufficient information to permit judgment.
Selection bias (sequence concealment)	Unclear risk	The study did not address this outcome.
Performance bias (masking of participants)	Unclear risk	The study did not address this outcome.
Performance bias (masking of personnel)	Unclear risk	The study did not address this outcome.
Detection bias (masking of outcome assessment)	Unclear risk	The study did not address this outcome.
Attribution bias (incomplete outcome data)	Low risk	No drop-outs

Quality of RCT (additional items Delphi List)

Quality Measure	Authors' Judgment
Prognostic indicators similar at baseline?	Yes
Eligibility criteria specified?	Yes
Point estimates and measures of variability given?	Yes
Intention-to-treat analysis included?	No

CS = corticosteroid; ETDRS = Early Treatment Diabetic Retinopathy Study; OCT = optical coherence tomography; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.