



# Clinical Efficacy and Safety of Propranolol in the Prevention and Treatment of Retinopathy of Prematurity: A Meta-Analysis of Randomized Controlled Trials

Haibo B. Kong<sup>1</sup>, Guoyuan Y. Zheng<sup>2</sup>, Baomei M. He<sup>1</sup>, Ying Zhang<sup>1</sup> and Qin Zhou<sup>1\*</sup>

<sup>1</sup> Department of Pediatrics, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, China, <sup>2</sup> Department of Neuroelectrophysiology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, China

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> \*Correspondence: Qin Zhou

2013032039@hmc.edu.cn

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Kong HB, Zheng GY, He BM, Zhang Y and Zhou Q (2021) Clinical Efficacy and Safety of Propranolol in the Prevention and Treatment of Retinopathy of Prematurity: A Meta-Analysis of Randomized Controlled Trials. Front. Pediatr. 9:631673. doi: 10.3389/fped.2021.631673 **Objective:** To perform a meta-analysis of randomized controlled trials verifying clinical efficacy and safety of propranolol in pre-term newborns with retinopathy of prematurity (ROP).

**Methods:** We searched the literature databases (Pubmed, Embase, The Cochrane Library, Web of Science, CNKI, WanFang, VIP, CBM) for publications before August 10, 2020, and the World Health Organization's International Clinical Trials Registry and ClinicalTrials.gov for ongoing trials. Randomized controlled trials (RCTs) of propranolol for the prevention or treatment of ROP were included. The quality of the included studies was primarily assessed by the RCT tool of the Cochrane Collaboration. The included studies were quantified using a meta-analysis of relative risk (RR) estimated with a random effect model.

**Results:** Our original search identified 171 articles, and five studies met our criteria. A meta-analysis was performed that showed that infants orally treated with propranolol had a decreased risk of disease progression: stage progression had an RR = 0.65 [95% confidence interval (Cl), 0.47–0.88]), plus disease had an RR = 0.43 [95% Cl, 0.22–0.82]. The demands for additional treatments had similar protective results: laser photocoagulations had an RR = 0.55 [95% Cl, 0.35–0.86]), and intravitreal injection of anti-vascular endothelial growth factor had an RR = 0.45 [95% Cl, 0.22–0.90]). The oral administration of propranolol was associated with an increased risk of adverse events (RR = 2.01 [95% Cl, 1.02–3.97]). High-risk adverse events included bradycardia, hypotension, not gaining enough weight, bronchospasm, hypoglycemia, apnea, and increasing ventilator need. Subgroup analysis of ROP phases and stages found that the risk in stage 2 ROP of the second phase and the individual risk factors (stage progression, RR = 0.42 [95% Cl, 0.27–0.65]; plus disease, RR = 0.40 [95% Cl, 0.17–0.93]; laser photocoagulation, RR = 0.31 [95% Cl, 0.14–0.68]) have statistically significant differences compared with other phases and stages.

1

**Conclusions:** Pre-term newborns with ROP, especially in stage 2 ROP of the second phase, who were orally given propranolol have a reduced risk of disease progression and demand for additional treatments, but the safety needs more attention.

Keywords: retinopathy of pre-maturity, propranolol, clinical efficacy, safety, meta-analysis

# INTRODUCTION

Retinopathy of pre-maturity (ROP) is a complex eye disease involving immature development, oxygen, inflammation, and other factors, and it leads to microvascular lesions, resulting in new blood vessels and ultimately leading to retinal detachment (1). Globally, it is estimated that more than 20,000 babies are blinded by ROP each year, and another 12,300 have mild-tomoderate visual impairment (2). In addition to visual loss, ROP can lead to a wide range of other visual impairments, including reduced contrast sensitivity, visual field deficits, color vision deficits, strabismus, and refractive errors (3). With the rapid development and application globally of neonatal intensive care technology, pre-term infants' survival rate has been significantly increased, and the incidence of common complications, such as ROP, has also increased accordingly (4).

ROP is a biphasic disease with two phases, including blood vessel growth arrest that leads to ischemia and uncontrolled proliferation of blood vessels (5). Currently, the treatment is mainly focused on the second phase of ROP, including laser photocoagulation and intraocular injection of vascular endothelial growth factor (VEGF)-neutralizing antibodies (6). However, despite these treatments, an increasing number of clinical studies report that laser photocoagulation (7) and intravitreal injection of anti-VEGF therapy (8, 9) do have some limitations, which can cause several side effects. Therefore, it is necessary to search for new therapeutic alternatives that avoid or reduce complications or sequelae due to laser photocoagulation and intravitreal injection of anti-VEGF therapy.

In 2008, French scholars accidentally discovered that propranolol could effectively control infantile hemangioma proliferation and promote its regression (10). Since then, many scholars from a variety of countries have studied propranolol. In 2010, the first study suggested that propranolol has a potential efficacy on ROP (11). In 2015, propranolol was suggested for early prevention of ROP and treatment of existing ROP in pre-term neonates (12). However, there is no consensus about either the benefit or the concerns of using propranolol for ROP treatment. Several randomized controlled trials (RCTs) have recently been published. This study aimed to conduct a meta-analysis on the clinical efficacy and safety of propranolol to prevent and treat ROP.

## **METHODS**

## **Protocol and Registration**

According to a pre-published protocol on PROSPERO (CRD42020204510), we performed this meta-analysis following the methodology suggested by Q Zhou et al., the Cochrane

Handbook for Systematic Reviews of Interventions, and the PRISMA statement.

# **Eligibility Criteria**

The inclusion criteria were as follows: (1) RCTs were considered for inclusion irrespective of blinding, publication status, or sample size; (2) the pre-term patients had a high risk of developing ROP or had been diagnosed with ROP by the international classification of ROP (13) regardless of their underlying disease; (3) the experimental intervention was propranolol, independent of propranolol dose, manner of administration, and duration of treatment; and (4) the control intervention was either a placebo or no treatment. (5) Primary outcomes were disease progression (stage progression and plus disease), the demands for additional treatments (laser photocoagulation and intravitreal injection of anti-VEGF), and adverse events.

The exclusion criteria were as follows: (1) duplicate studies and data, (2) studies with incomplete or missing data or studies that were only an abstract with no full text, (3) studies not reported in Chinese or English.

## **Data Sources and Searches**

We searched the following databases for relevant English language literature: PubMed, EMBASE, the Cochrane Library, and Web of Science and Chinese language literature: CNKI, WanFang, VIP, and CBM. The search string was built as follows (such as Pubmed): ("retrolental fibroplasia"[Title/Abstract] OR ("retinopathy"]Title/Abstract] AND "prematur\*"[Title/Abstract]) OR "Retinopathy of Prematurity" [MeSH Terms]) AND (("Propranolol" [Title/ Abstract] OR "Inderal" [Title/Abstract] OR "Avlocardyl" [Title/Abstract] OR "Dexpropranolol"[Title/Abstract] OR "Dociton" [Title/Abstract] OR "anaprilin\*"[Title/Abstract] OR "Betadren" [Title/Abstract] OR "ay 20694" [Title/Abstract] "obsidan" [Title/Abstract] OR "obzidan" [Title/Abstract] OR OR "propanolol" [Title/Abstract]) OR "Propranolol" [MeSH Terms]). References of the identified studies were screened to identify further relevant trials by two reviewers (HB Kong and GY Zheng). In addition, we searched the World Health Organization's International Clinical Trials Registry and ClinicalTrials.gov for ongoing trials. The search was last updated on August 10, 2020 (The retrieval strategy is detailed in Supplement 1 in Supplementary Material).

## Data Extraction and Quality Assessment Data Extraction

Two authors (HB Kong and GY Zheng) independently extracted the study data. Any disagreement was resolved by discussion until consensus was reached or by consulting a third author (Q Zhou). The following data were extracted: author, year of publication, county, original inclusion and exclusion criteria, the total number of people included in the study, doses of propranolol and time of application, numbers of progression to higher ROP stage, numbers of progression with plus disease, numbers of treatment with laser photocoagulation, numbers of treatment with intravitreal injection of anti-VEGF, and adverse events.

#### **Quality Assessment**

Two reviewers (HB Kong and GY Zheng) independently assessed the quality of the selected studies according to

the Cochrane Collaboration's tool for RCTs. Papers were evaluated in three categories: low risk of bias, unclear bias, and high risk of bias. The following characteristics were evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases; results were graphed and assessed using Review Manager 5.3. In addition, the studies were graded by quality assessment methods (14) as low, high, or moderate quality to facilitate the subgroup analysis and sensitivity analysis.



#### TABLE 1 | Characteristics of included randomized trials.

References	Country	Inclusion	Exclusion criteria	Phase and				Intervention	group				Contr	rol group		Outcome
		criteria		stage	Sample size	Gestational age (weeks)	Male (%)	Intervention	Dose	Way	Duration	Sample size	Gestational age (weeks)	Male (%)	Control	
Filippi et al. (17)	Italy	GA < 32 w; Stage 2 ROP without plus in zone II.	Congenital or acquired cardiovascular anomalies, renal failure or cerebral hemorrhage ROP in zone I, more advanced stage than Stage 2 without plus in zone II.	Second phase-stage 2	26	26.5 ± 2.2	17 (65)	Propranolol	0.5 or 0.25 mg/kg/q6h	Oral	Until complete retinal vascularization, not more than 90 days.	26	26.2 ± 1.7	15 (58)	Standard treatment alone	1. Progression to higher stage; 2. with plus; 3. Treatment with laser photocoagulation; 4 Treatment with intravitreal injection of anti-VEGF; 5. Adverse events.
Makhoul et al. (18)	Israel	24 w < GA < 28 w, BW < 1,500 g, Stage 1 (zone ), Stage 2 or higher (zones I or II), and/or plus disease.	None.	Second phase-stage 1 or higher	10	None	None	Propranolol	0.16 mg/kg/q8 h to 0.67 mg/kg/q8h	Oral	Given for 4 weeks or until ROP resolution or hospital discharge.	10	None	None	Placebo (sucrose 5%)	1. Progression to higher stage; 2. Treatment with laser photocoagulation; 3 Treatment with intravitreal injection of anti-VEGF; 4. Adverse events.
Korkmaz et al. (16)	Turkey	GA < 32 w, BW < 1,500 g, Stage 0, 1, 2 ROP.	Cardiovascular anomaly, renal failure, apnea, hypoglycemia, bradycardia, not take medicine, parents' request, not gain sufficient weight.	Second phase-stage 0,1,2	89	28.3 ± 2.03	None	Propranolol	0.5 mg/kg/q6h	Oral	Until complete retinal vascularization.	91	28.6 ± 1.82	None	Physiological saline	1. Treatment with laser photocoagulation; 2 Treatment with intravitreal injection of anti-VEGF; 3. Adverse events.
Sanghvi et al. (19)	India	$26 w < GA < 32 w, \le 7 days$ old.	Recurrent episodes of bradycardia, atrioventricular blocks, hypotension, refractory hypoglycaemia and major congenital malformations.	First phase	55	$29.54 \pm 1.69$	24 (44)	Propranolol	0.5 mg/kg/q12h	Oral	Utill a corrected gestational age of 37 weeks or complete retinal vascularisation.	54	29.12 ± 1.74	1 29 (54)	Calcium carbonate	1.progression to higher stage; 2.with plus; 3.treatment with laser photocoagulation; 4.treatment with intravitreal injection of anti-VEGF; 5.Adverse events.
Ozturk and Korkmaz, (15) [Supplement the Korkmaz et al. (16) data]	Turkey	GA < 32 w, BW < 1,500 g, Stage 0, 1, 2 ROP.	Cardiovascular anomaly, renal failure, apnea, hypoglycemia, bradycardia, not taken their medicine, not gain sufficient weight, and their parents' request.	Second phase-stage 0,1,2	58	28.4 ± 1.23	32 (55)	Propranolol	2 mg/kg/d	Oral	Until complete retinal vascularization.	68	28.6 ± 1.54	39 (57)	Physiological saline	1. Progression to higher stage; 2. With plus;3. Adverse events.
Sun et al. (20)	China	GA < 32 w, Stage 2 ROP without plus in zone II or III.	Genetic metabolic diseases, congenital dysplasia, congenital heart disease, severe chronic lung disease, septicemia and renal failure, severe bradycardia and hypotension within 0.5–1 h after taking propranolol, and their parents' request.	Second phase-stage 2	41	29.9 ± 1.8	28 (68)	Propranolol	0.25 mg/kg/q12h	Oral	Until complete retinal vascularization, or hospital discharge, not more than 30 days.	43	30.1 ± 1.7	27 (63)	Physiological saline	1. Progression to higher stage; 2. Treatment with lase photocoagulation; 3 Treatment with intravitreal injection of anti-VEGF; 4. Adverse events.

# **Data Synthesis and Analysis**

#### Meta-Analysis

Relative risks (RR) and the random effect model (weighted by the Mantel-Haenszel) were used. Results were assessed using forest plots and presented as RRs for the primary outcomes. Significant differences (test of interaction p < 0.05) were considered statistically significant. Statistical analyses were conducted using the Review Manager software (Review Manager 5.3, Cochrane Collaboration, Nordic Cochrane Centre, London, United Kingdom).

#### Assessment of Heterogeneity

Between-study heterogeneity was assessed using the  $\tau^2$ ,  $\chi^2$  (Cochran Q), and  $I^2$  statistics. Consistent with the Cochrane handbook, the  $I^2$  was interpreted as non-important (<30%), moderate (30–60%), and substantial (>60%). The heterogeneity was statistically significant (test of interaction  $p \leq 0.10$  and  $I^2 > 50\%$ ). Clinical heterogeneity was explored by conducting explorative subgroup analysis or sensitivity analysis.

#### Subgroup Analysis

We conducted subgroup analysis to determine whether substantial heterogeneity or clinical significance existed between trials. We performed subgroup analyses for primary outcomes: (1) ROP phase and stage starting to prevent or treat and (2) propranolol dose. Statistically significant subgroup differences (test of interaction P < 0.05) could provide evidence of an intervention effect within the subgroup.

#### Sensitivity Analysis

Sensitivity analyses were performed to determine heterogeneity or stability using the meta-analysis results by excluding different research quality (low quality), transforming different inclusion criteria (exclude the first phase ROP study), or shifting different effect models (fixed-effect model).

#### **Publication Bias**

If there were 10 or more studies in the meta-analysis, we would investigate reporting biases (such as publication bias) using funnel plots.

# RESULTS

## **Study Selection**

Our search strategy identified 171 papers and included 161 papers in English (Pubmed 35, Embase 59, Cochrane Library 24, Web of Science 43) and 10 papers in Chinese (CNKI 3, WanFang 3, VIP 2, CBM 2). After the removal of duplicates and eliminating apparently unrelated studies by reading the titles and abstracts, 12 records remained. Six records were excluded based on full text, and the remaining six records were included. Among these articles, the study Ozturk and Korkmaz (15) was a supplement to Korkmaz et al. (16) and their data complement each other. Finally, five RCTs (six articles) with 445 patients were included in the quantitative synthesis (**Figure 1**).

## **Characteristics of the Included Studies**

Detailed characteristics of the five included trials are presented in **Table 1**. The year of publication ranged from 2013 to 2018. Four trials were reporting in English and one in Chinese. One trial was published as a letter only. There were three single-center and two multicenter trials (**Table 1**).

## **Bias Risk Assessment**

The risk of bias for the included RCTs was assessed using the Cochrane Risk of Bias tool. Random sequence generation, allocation concealment, blinding participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases (defined by the Cochrane tools as including bias due to problems not covered elsewhere, such as a particular trial design, alleged fraud, or other problems) were evaluated. In addition, quality assessment methods were performed as follows: (1) If randomization or allocation concealment was considered to have a high risk of bias without considering the risks of other items, the trial



quality was considered to be low; (2) when both randomization and allocation concealment were assessed to have a low risk of bias and all other items were assessed to have a low or unclear risk of bias, the trial quality was considered to be high; (3) tests that did not meet high- or low-quality standards were considered to be moderate quality (14). Sanghvi et al. (19) was high quality, Filippi et al. (17) and Sun et al. (20) were moderate quality, and Korkmaz et al. (16) [Ozturk and Korkmaz (15)] and Makhoul et al. (18) were low quality (**Figure 2**).

### Meta-Analysis Clinical Efficacy

In all studies, the main outcomes of clinical efficacy were prevention of disease progression and reduction of additional treatments. Disease progression included stage progression and



FIGURE 3 | Clinical efficacy of propranolol oral administration in the prevention and treatment of retinopathy of prematurity based on disease progression and the demands for additional treatment. (A) Disease progression and (B) Demands for additional treatment.

plus disease. The demands for additional treatment included laser photocoagulation and intravitreal injection of anti-VEGF. The propranolol group was significantly better than the control group for stage progression (RR = 0.65; P = 0.006;  $I^2 = 37\%$ ), plus disease (RR = 0.43; P = 0.01;  $I^2 = 0\%$ ), laser photocoagulation (RR = 0.55; P = 0.009;  $I^2 = 0\%$ ), and intravitreal injection of anti-VEGF (RR = 0.45; P = 0.02;  $I^2 = 0\%$ ) (**Figure 3**).

#### Safety

For the five included studies, those from Filippi et al. (17), Korkmaz et al. (16) [Ozturk and Korkmaz (15)], and Sanghvi et al. (19) report several adverse events, but those from Makoul et al. (18) and Sun et al. (20) report no adverse events. Details of these adverse events are shown in Table 2. A meta-analysis of the five trials evaluated the safety of propranolol in the course of treatment. Propranolol was associated with an increased RR for overall adverse events (RR = 2.01 [95% confidence interval (CI), 1.02 to 3.97]). Sun et al. (20) and Makoul et al. (18) had no adverse events during propranolol treatment. The other studies report adverse events, including death (RR = 1.01 [95% CI, 0.30-3.47]), bradycardia (RR = 11.42 [95% CI, 0.66-196.40]), hypotension (RR = 7.27 [95% CI, 0.39-133.95]), hypoglycemia (RR = 3.10 [95% CI, 0.33-29.27]), increasing ventilator need (RR = 1.71 [95% CI, 0.18-16.07]), apnea (RR = 2.00 [95% CI, 0.11-34.81]), not gaining enough weight (RR = 3.52 [95% CI, 0.38 to 32.90]), and bronchospasm (RR = 3.12 [95% CI, 0.13-73.06]) (Figure 4).

TABLE 2   Adve	rse events in included Studies.	
References	Intervention group (22/221)	Control group (11/224)
Filippi et al. (17)	1 case of death, 1 case of increasing ventilator need, 3 cases of serial apnea, bradycardia, and hypotension, 1 case of severe apnea and bradycardia, 1 case of bradycardia with H1N1 infection, 1 case of bronchospasm, and 1 case of unknown reason (unreported).	2 cases of death and 2 cases of increasing ventilator need.
Makhoul et al. (18)	None.	None.
Korkmaz et al. (16) [Ozturk and Korkmaz (15)]	1 case of apnea, 2 cases of increasing ventilator need, 3 cases of hypoglycemia and increasing ventilator need, and 3 cases of not getting enough weight.	2 cases of apnea, 1 case of increasing ventilator need and hypoglycemia, and 1 case of not getting enough weight.
Sanghvi et al. (19)	4 cases of death.	3 cases of death.
Sun et al. (20)	None.	None.

## Subgroup Analysis

After assessment of heterogeneity, the heterogeneity among studies was not statistically significant (p > 0.10 and  $I^2 <$ 50%), but the timing and dosage of propranolol are clinical concerns. Different ROP phases and stages starting to prevent or treat and different propranolol doses would be subgroup analyzed. Subgroup analysis showed the following risks in Stage 2 ROP of the second phase: (stage progression, RR = 0.42[95% CI, 0.27-0.65]; plus disease, RR = 0.40 [95% CI, 0.17-0.93]; laser photocoagulation, RR = 0.31 [95% CI, 0.14-0.68]). Stage 2 ROP of the second phase had statistically significant differences for these variables although the other phases and stages did not. Different starting doses of oral propranolol to prevent or treat ROP showed that the risk in the low dose (0.5 mg/kg/d, stage progression, RR = 0.46 [95% CI, 0.21-1.00]; laser photocoagulation, RR = 0.26 [95% CI, 0.06-1.16]; intravitreal injection of anti-VEGF (RR = 0.66 [95% CI, 0.23-1.84]) or high dose (2 mg/kg/d, stage progression, RR = 0.73 [95% CI, 0.46-1.17]; plus disease, RR = 0.50 [95% CI, 0.14–1.86]; laser photocoagulation, RR = 0.49 [95% CI, 0.21-1.13; intravitreal injection of anti-VEGF (RR = 0.36) [95% CI, 0.06-2.29]) had no statistically significant difference (Figures 5, 6).

## Sensitivity Analysis

Sensitivity analysis by research quality, inclusion criteria, and effect model was performed. In the research quality, when lowquality studies (15, 16, 18) were removed, the results showed that the propranolol group had a significantly better effect than the control group with stage progression (RR = 0.58 [95%) CI, 0.35–0.97]), plus disease (RR = 0.41, [95% CI, 0.19–0.86]), laser photocoagulation (RR = 0.54 [95% CI, 0.32-0.90]), and intravitreal injection of anti-VEGF (RR = 0.46 [95% CI, 0.22-0.98]). For the inclusion criteria study, when we removed the study (19) that used propranolol in the first phase of ROP, our results showed that the propranolol group had a significantly better effect than the control group with stage progression (RR = 0.56 [95% CI, 0.40-0.77]), plus disease (RR = 0.42 [95% CI, (0.19-0.93]), and laser photocoagulation (RR = 0.44 [95% CI, 0.24-0.83]). When we used the fixed-effect model, the results showed that the risk in the propranolol group was significantly better than in the control group with stage progression (RR =0.64 [95% CI, 0.51-0.81]), plus disease (RR = 0.43 [95% CI, 0.23-(0.82]), laser photocoagulation (RR = 0.52 [95% CI, 0.33-0.82]), and intravitreal injection of anti-VEGF (RR = 0.43 [95% CI, 0.22-0.84]) (Figure 7).

## **Publication Bias**

All outcome indicators were analyzed in  $<\!10$  studies, so publication bias was not examined.

## DISCUSSION

According to the five included studies on ROP treatment, we found that the RR of disease progression and the demands for additional treatment were significantly lower compared with that without propranolol. However, we found an



increased RR for adverse events compared with those without propranolol. In subgroup analysis, it was found that, when the propranolol is initiated at Stage 2 ROP, the propranolol had the most significant clinical effect in stage progression, plus disease, and laser photocoagulation compared with other phases or stages. In addition, our analysis found no significant difference in clinical effects in different therapeutic doses. The sensitivity analysis found that the research results were stable according to the research quality, inclusion criteria, and effect model changes.

ROP, initially known as retinal fibrosis, is characterized by vasoproliferative retinopathy and primarily affects newborns born at <32 weeks of gestation. Pre-term birth (low gestational age, low birth weight), hyperoxygen supplementation, poor post-partum weight gain, hyperglycemia, low IGF-1 concentration, blood transfusion, and infection are associated with developing ROP (21). ROP's complex pathogenesis occurs in 2 phases. In the first phase, the blood vessel stops growing and leads to

ischemia; in the second phase, blood vessel proliferation occurs (5). Neovascularization is related to a variety of growth factors, such as VEGF, platelet-derived factor, interleukin-8, and others. VEGF is a kind of endothelial cell-selective mitogen and is a key factor in a series of continuous reactions causing vascular leakage and angiogenesis (22, 23). Adrenergic receptors, such as beta2- and beta3-adrenal receptors, play an essential role in regulating the VEGF level (24, 25). Propranolol is a nonselective beta-adrenal receptor blocker, which has antagonistic effects on sympathetic excitation and catecholamine and can affect angiogenesis.

Animal experiments confirm that propranolol can reduce the excessive production of VEGF in the hypoxic retina. However, it does not affect the VEGF level in the normal oxygenated retina and serum, suggesting that VEGF's regulation mechanism at the average oxygen level is different from that in the hypoxic state (26). In addition, the administration of propranolol at the first phase (the ischemic phase), when the level of VEGF is too low,



is probably risky for more aggressive ROP development. On the contrary, the administration of propranolol at the second phase (the proliferative phase), when the level of VEGF is usually too high, is rational (27). In Sanghvi et al. (19), pre-term newborns with a gestation age between 26 and 32 weeks and <7 days old were included. Propranolol was given starting from 7 days of age during the first phase of ROP. Although no adverse events were reported, its clinical efficacy was uncertain. Therefore, propranolol is effective in ROP theoretically, particularly at Stage 2 ROP of the second phase because it primarily affects the VEGF levels in the hypoxic retina instead of those in the normal retina. Our study particularly validated such a speculation through a subgroup analysis of the starting point of propranolol treatment.

In infants and children, propranolol, a relatively safe and well-tolerated drug in clinical practice for many years, is commonly used to treat heart disease, neonatal hyperthyroidism, and so on (28). However, for infants with unstable conditions, especially premature infants with moderate-to-severe risk of bronchopulmonary dysplasia, septicemia, dyspnea, or incomplete recovery under anesthesia, propranolol can cause adverse events, such as hypotension and bradycardia (29, 30). Our study found an increased relative risk of adverse events over the patients who did not take propranolol. However, our study found no difference in our baseline data, including complications in premature infants. Propranolol administration route, dose, and duration may be related to the adverse events. Our study also found that adverse events are focused primarily on the Filippi et al. (17) and Korkmaz et al. (16) [Ozturk and Korkmaz (15), the same study as Korkmaz et al. (16)] studies. In Filippi's study, newborns who initially experienced adverse events after receiving high-dose propranolol were reassigned into the low-dose group. Therefore, in these two studies, the propranolol dose was mostly 2 mg/kg/d, which was higher than that in most of the other studies. Although high-dose propranolol was also used in Makhoul's study, the dose was gradually increased, and the follow-up time was significantly insufficient. However, the administration route and duration were similar to other studies, so the extremely high drug dose might cause the adverse events. In addition, no significant difference in the clinical effects was

Propranolol Control R <sup>i</sup> iy or Subgroup Events Total Events Total Weight M-H, F	isk Ratio R Random, 95% CI Year M-H, R	isk Ratio andom, 95% CI St	Plus Disease Propranol itudy or Subgroup Events T	lol Contro Fotal Events	ol Total Weight M-H	Risk Ratio I, Random, 95% CI Y	'ear	Risk Ratio M-H, Random, 95% Cl
Propranoiol 0.5mg/kg/d	0.46 [0.21, 1.00] 2018 0.46 [0.21, 1.00]	4. Sa Su Tru Hu Tru	k.3.2 Propranolol 1mg/kg/d ianghvi 2017 4 iubtotal (95% Cl) otal events 4 feterogeneity: Not applicable "est for overall effect: Z = 1.43 (f	51 9 51 9 9 P = 0.15)	51 100.0% 51 100.0%	0.44 [0.15, 1.35] 24 0.44 [0.15, 1.35]	017	-
Propranolol Img/kg/d         Vi         2017         29         51         35         51         100.0%         0           vi         2017         29         51         35         51         100.0%         0           events         29         35         35         00.0%         0           orgeneity: Not applicable         0         0         0         0           or overall effect.         2         1.22 (P = 0.22)         0         0	0.83 [0.61, 1.12] 2017 3.83 [0.61, 1.12]	4. 0: 5s To HH	A.3.3 Propranolol 2mg/kg/d Dzturk 2018 3 iubtotal (95% CI) Total events 3 deterogeneity: Not applicable Test for overall effect: Z = 1.03 (f	58 7 58 7 P = 0.30)	68 100.0% 68 100.0%	0.50 [0.14, 1.86] 2 0.50 [0.14, 1.86]	018	-
Propranolol 2mg/kg/d         1         7         10         52.4%         Cl           vul 2014         6         1         7         10         52.4%         Cl           val 2014         5         19         68         47.6%         Cl           val 305%Cl)         68         78         100.0%         Cl           events         26         26         78         100.0%           openeity: Tau <sup>2</sup> = 0.00, Chi <sup>2</sup> = 0.55, df = 1 (p = 0.46); i <sup>2</sup> = 0.4         ov         ov         ov	0.86 [0.45, 1.64] 2014 0.62 [0.31, 1.22] 2018 	Te	"est for subgroup differences: CP	ni² = 0.02, df =	= 1 (P = 0.89), $I^2 = 0.9$	×	0.01	0.1 1 10 propranolol control
		+ +						
for subgroup differences: $Chi^2 = 1.95$ , $df = 2$ (P = 0.38), $I^2 = 0\%$	0.01 0.1 propran	1 10 100 blol control						
for subgroup differences: Chi <sup>2</sup> = 1.95, df = 2 (P = 0.38), l <sup>2</sup> = 0% <b>Demands for Additional Treatm</b>	ent	I 10 100 Jol control						
for subgroup differences: $Chi^2 = 1.95$ , $df = 2 (P = 0.36)$ , $l^2 = 0.6$ <b>Demands for Additional Treatment</b> <b>Laser Photocollistication</b>	ent	Jol Control	Intravitreal Inje	ection o	f Anti-Vas	cular Endo	thelial (	Growth Factor
or subgroup differences: Chi <sup>2</sup> = 1.95, df = 2 (P = 0.38), l <sup>2</sup> = 0% <b>Demands for Additional Treatm</b> <b>Laser Photocoggulation</b> Propranolol Control or Subgroup Events, Total Weight M-H, R Monemanded Control Net State St	0.01 0.1 propran P <b>CHI</b> Isk Ratio Random, 95% CI Year M-H, R	isk Ratio	Intravitreal Inje Proprano itudy or Subgroup Events T 21 Bosenvello Serei (kr./d	e <b>ction o</b> Iol Contro Fotal Events	<i>f Anti-Vasi</i> ol Total Weight M-H	C <b>ular Endo</b> Risk Ratio I, Random, 95% CI	<i>thelial</i> (	Growth Factor Risk Ratio M-H, Random, 95% CI
for subgroup differences: Chi <sup>2</sup> = 1.95, df = 2 (P = 0.38), l <sup>2</sup> = 0% <b>Demands for Additional Treatm</b> <b>Laser Photocoagulation</b> Propranolo Control R ror Subgroup Events Total Events Total Weight M-H, R ror Subgroup Events Total Events Total Weight M-H, R ror Subgroup Events Total Events Total Weight M-H, R versis 2 8 43 100.0% genetic, Not applicable or overall effect: 2 - 1.76 (P = 0.08)	Ul Ul propran ent isk Ratio SZ (0.06, 1.16) 2018	isk Ratio isk Ratio sk Ratio	Intravitreal Inje Propranol Indig or Subgroup Events T 3.3.1 Propranolo Song Ikg/ ubtotal (05% C) 5 steterogenetity. Not applicable est for overall effect: 2 = 0.80 (05%)	All     Bit       Iol     Contro       Iol     Contro       Iol     Events       41     8       8     8       P = 0.42)     0.42	<b>f</b> Anti-Vase ol Total Weight M-H 43 100.0% 43 100.0%	Cular Endo Risk Ratio I, Random, 95% CI Y 0.66 [0.23, 1.84] 0.66 [0.23, 1.84]	<i>thelial</i> ( 'ear <sup>D18</sup>	Growth Factor Risk Ratio M-H, Radom, 95% (1
for subgroup differences: Chi <sup>2</sup> = 1.95, df = 2 ( $P = 0.38$ ), l <sup>2</sup> = 0% <b>Demands for Additional Treatm</b> <b>Accel Photocoagulation</b> Propranolog Control R Programoly Control R Programoly 2 Programoly 2 Programoly 2 Programoly 2 Programoly 2 1 8 43 100.00% ( 0 cal (95% c) 41 8 43 100.00% ( 0 cal (95% c) 2 16 8 43 100.00% ( 0 cal (95% c) 2 16 9 0.08) Programoly 1 Programoly 1 Prog	UI UI propram ent isk Ratio (andom, 55% CI Year M-H, R M-H, R M-H, R 0.33 (0.04, 2.48) 2013 0.69 (0.35, 1.33) 2017	isk Ratio isk Ratio sandom 55% CI 5% 5% 5% 5% 5% 5% 5% 5% 5% 5%	Intravitreal Inje Propranol 13.1 Propranola O.Sing/Keyri 13.1 Propranola O.Sing/Keyri ubtotal (95% CI) 5 5 5 5 5 5 5 5 5 5 5 5 5	Section 0         O           lol         Contro           d1         Events           41         8           P         0.42)           51         8           51         8           P         0.07)	<b>f</b> Anti-Vasa ol Total Weight M-H 43 100.0% 51 100.0% 51 100.0%	Cullar Endo Risk Ratio , Random, 95% CI Y 0.66 [0.23, 1.84] 2 0.66 [0.23, 1.84] 0.25 [0.06, 1.12] 2 0.25 [0.06, 1.12]	<b>thelial (</b> 'ear 018	Growth Factor Risk Ratio M-H, Random, 55% Cl
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	U01 U1 propram ent isk Ratio R Random, 555 U Vear M-4, R 0.26 (0.06, 1.16) 0.18 0.26 (0.06, 1.16) 0.18 0.26 (0.04, 1.20) 0.13 0.64 (0.34, 1.20) 0.13 0.55 (0.14, 1.40) 2.013 0.55 (0.17, 1.69) 2.014 0.53 (0.25, 1.09) 0.16	isk Ratio isk Ratio andom, 95% CI 55 55 55 55 55 55 55 55 55 55 55 55 55	Intravitreal Injec Propranol tudy or Subgroup Events T 3.3 Propranolol O.Smg/kg/d un Holing 2018 5 Valle vents T 5 teterogeneity. Not applicable fest for overall effect: Z = 0.80 (f 3.3.2 Propranolol Img/kg/d whotal (95% C) 2 teterogenity. Not applicable fest for overall effect: Z = 1.81 (f 3.3.3 Propranolol Zmg/kg/d dakhoul 2014 0 orkemaz 2016 1 ubtotal (95% C) 1 teterogenity. Tau <sup>2</sup> = 0.00; (cf) teter for overall effect: Z = 1.08 (f sto for overall effect: Z = 1.08 (f	$\begin{array}{c} \text{Perfine} & 0 \\ \text{Iol} & \text{Contro} \\ \text{Total Events} \\ \begin{array}{c} 41 \\ 1 \\ 8 \\ 8 \\ \end{array} \\ \begin{array}{c} 8 \\ 8 \\ 8 \\ \end{array} \\ \begin{array}{c} 8 \\ 8 \\ 8 \\ \end{array} \\ \begin{array}{c} 8 \\ 8 \\ 8 \\ \end{array} \\ \begin{array}{c} 9 \\ 8 \\ 9 \\ 9 \\ 9 \\ 4 \\ 9 \\ 9 \\ 0.28 \\ \end{array} \\ \begin{array}{c} 8 \\ 8 \\ 8 \\ 8 \\ \end{array} \\ \begin{array}{c} 8 \\ 8 \\ 8 \\ 8 \\ \end{array} \\ \begin{array}{c} 8 \\ 8 \\ 8 \\ 8 \\ 8 \\ 8 \\ 8 \\ 8 \\ 8 \\ 9 \\ 9$	<b>f</b> Anti-Vasc ol Total Weight M-H 43 100.0% 51 100.0% 51 100.0% 10 40.0% 90 60.0% 100 100.0%	Cular Endo Risk Ratio Random, 95% CI Y 0.66 [0.23, 1.84] 0.66 [0.23, 1.84] 0.25 [0.06, 1.12] 2 0.25 [0.06, 1.12] 2 0.25 [0.06, 1.12] 2 0.25 [0.06, 1.12] 2 0.26 [0.01, 3.70] 2 0.20 [0.01, 3.70] 2	thelial (           */ear           018           017           014	Growth Factor Risk Ratio M-H, Random, 95% Cl

found among different therapeutic doses; good clinical efficacy may also be achieved at low doses.

Compared with previous systematic reviews (31, 32), our study has some advantages. First, this study conducted a comprehensive search, including English databases, such as PubMed, Cochrane Library, EMBASE, and Web of Science, and Chinese databases, such as CNKI, CBM, VIP, and WanFang. Second, this study included 5 RCT studies, which was more than previous studies, and we found that Ozturk and Korkmaz (15) is the same study as Korkmaz et al. (16), which supplements the data from Ozturk and Korkmaz (15) study. Third, in this study, the clinical efficacy and safety of propranolol in ROP treatment were evaluated by multiple indicators including disease progression (stage progression and plus disease), the demands for additional treatment (laser photocoagulation and intravitreal injection of anti-VEGF), and adverse events, all of which have been shown on the forest map. Fourth, although the heterogeneity among studies was low, subgroup analysis was conducted considering clinical attention issues, such as treatment timing and treatment dose.

Similarly, there are still some deficiencies in this study. One RCT study (33) reported by a meeting abstract was excluded because the data were not available. Second, there were fewer than 10 studies included in this study, so publication bias could not be evaluated. Third, in this study, long-term adverse events were not analyzed due to insufficient data. Propranolol has

been reported to cause memory loss in chickens through the blood-brain barrier (34). VEGF has the function of protecting neurons. It was found that repeated vitreous injection of VEGF antagonist Bevacizumab could induce retinal neuronal apoptosis (35). Whether propranolol causes damage to retinal neurons or the nervous system remains to be further studied. Fourth, we conducted a quantitative meta-analysis mainly based on secondary data, leading to inaccurate results due to insufficient individual patient data. Fifth, all the randomized controls included in this study were through oral administration. Because no RCT was available before now, other administration routes, such as eye drops, could not be analyzed in this study. However, it is demonstrated that propranolol administered with eye drops reaches the retina (36), and explorative trials with propranolol eye microdrops provide prospective encouraging results (27, 37). Therefore, RCTs using propranolol through eye drops might be expected to show better efficacy and safety than oral approaches.

This study drew the following conclusions: Oral administration of propranolol is effective in preventing or treating ROP. Treatment may be the most effective at the start of ROP Stage 2 of the second phase, and low doses (0.5 mg/kg/d) may have the same therapeutic effect as high doses (2 mg/kg/d). Also, the treatment of ROP with propranolol has some potential safety issues. However, due to the lack of current research, caution should be exercised in interpreting

dv or Subaroup	Propranolol Events Total Ev	Control	Risk Ratio 4-H. Random, 95% Cl	Year	Risk Ratio M–H. Random, 95% Cl		Study or Subgroup	Propranolol Events Total	Control Events Total We	Risk Ratio	5% Cl Year	R M-H. R	isk Ratio andom, 95% Cl	
ppi 2013 khoul 2014 nghvi 2017	9 25 6 10 29 51	22 26 32.5% 7 10 0.0% 35 51 43.9%	0.43 [0.25, 0.74] 2 0.86 [0.45, 1.64] 2 0.83 [0.61, 1.12] 2	2013 2014 2017			Filippi 2013 Sanghvi 2017 Ozturk 2018	4 25 4 51 3 58	11 26 55 9 51 4 7 68	5.1% 0.38 [0.14, 4.9% 0.44 [0.15, 0.0% 0.50 [0.14,	1.03] 2013 1.35] 2017 1.86] 2018	-	F	
n Huiqing 2018 turk 2018	7 41 10 58	16 43 23.5% 19 68 0.0%	0.46 [0.21, 1.00] 2 0.62 [0.31, 1.22] 2	2018 2018			Total (95% CI)	76	77 100	0.0% 0.41 [0.19,	0.86]	-	•	
tal (95% CI) tal events	117 45	120 100.0%	0.58 [0.35, 0.97]		•		Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	o 0.00; Chi <sup>2</sup> = 0.0 Z = 2.37 (P = 0	04, df = 1 (P = 0.83) (.02)	; $I^2 = 0\%$		0.01 0.1 propran	i 10 olol control	10
terogeneity: Tau <sup>2</sup> = st for overall effect:	0.13; Chi <sup>2</sup> = 5.79, Z = 2.09 (P = 0.04)	If = 2 (P = 0.06); I <sup>2</sup> = 1	55%	0.01	0.1 i 10 propranolol control	100								
Removin	g the first Propranolol	phase studie	2S Risk Ratio		Risk Ratio		b. Removing	the first Propraholol	t phase stu	dies Risk Ratio		R	isk Ratio	
ppi 2013	Events Total Ev 9 25	22 26 35.0%	1-H, Random, 95% CI 0.43 [0.25, 0.74] 2	Year 2013	M-H, Random, 95% CI		Study or Subgroup Filippi 2013	Events Total 4 25	Events Total Wei 11 26 67	ight M-H, Random, 95 2.9% 0.38 [0.14,	% CI Year 1.03] 2013	M-H, R	Indom, 95% Cl	
khoul 2014 Johni 2017	6 10 29 51	7 10 25.0%	0.86 [0.45, 1.64] 2	2014	-		Sanghvi 2017 Ozturk 2018	4 51 3 58	9 51 0 7 68 3	0.0% 0.44 [0.15, 7.1% 0.50 [0.14,	1.35] 2017 1.86] 2018		<b>→</b>	
Huiging 2018	7 41	16 43 17.4%	0.46 [0.21, 1.00] 2	2018			Total (95% CI)	83	94 10(	0.0% 0.42 [0.19,	0.93]	-	-	
IUTK 2018	10 56	19 08 22.7%	0.62 [0.31, 1.22] 2	2018			Total events Heteroneneity: Tau <sup>2</sup> =	7 0.00: Chi <sup>2</sup> = 0.1	18 11 df = 1 (P = 0.73)	· 1 <sup>2</sup> = 0%				
al events	32	64	0.36 [0.40, 0.77]		· •		Test for overall effect:	Z = 2.13 (P = 0.1)	.03)	1 - 04	i	0.01 0.1 proprane	1 10 Jol control	10
erogeneity: Tau <sup>2</sup> = t for overall effect:	0.00; Chi <sup>2</sup> = 3.01, Z = 3.52 (P = 0.000	if = 3 (P = 0.39); I <sup>2</sup> = 0 (4)	ж	0.01	0.1 1 10 propranolol control	100								
Fixed eff	fect model						c. Fixed effe	ct model	l					
udv or Subaroun	Propranolol Events Total E	Control	Risk Ratio	(03r	Risk Ratio		Study or Subgroup	Propranolol Events Total	Control	Risk Ratio	KCI Year	Ri M-H	sk Ratio Fixed 95% CI	
opi 2013	9 25	22 26 22.3%	0.43 [0.25, 0.74] 20	013			Filippi 2013	4 25	5 11 26	41.1% 0.38 [0.14, 1	.03] 2013		E	
ghvi 2014 ghvi 2017	29 51	35 51 36.2%	0.86 [0.45, 1.64] 20 0.83 [0.61, 1.12] 20	014	-		Ozturk 2018	3 58	3 7 68 7	24.6% 0.50 [0.14, 1	.86] 2018		<b></b>	
i Huiqing 2018 :urk 2018	7 41 10 58	16 43 16.2% 19 68 18.1%	0.46 [0.21, 1.00] 20 0.62 [0.31, 1.22] 20	018 018			Total (95% CI)	134	145 10	0.0% 0.43 [0.23, 0	.82]	-	•	
tal (95% CI)	185	198 100.0%	0.64 [0.51, 0.81]		•		Total events Heterogeneity: Chi <sup>2</sup> =	11 0.12, df = 2 (P	27 = 0.94); I <sup>2</sup> = 0%		Ŀ.		<u> </u>	
al events	61	99					Test for overall effect:	Z = 2.54 (P = 0)	0.01)			proprane	lol control	1
erogeneity: Chi <sup>2</sup> =	0.50, ul = 4 tr = 0	(17)(1) = 3726												
terogeneity: Chi <sup>2</sup> = st for overall effect Laser Pho Removin	stocoagula g low qual	tion ity studies		0.01	0.1 1 10 propranolol control	100	D Intravitrea a. Removing	l Injectio low qua	on of Anti- ılity studie.	Vascular En s	ndotheli	al Growth	Factor	
terogeneity: Chi <sup>2</sup> = st for overall effect Laser Pho . Removin dy or Subgroup	construction of the second sec	tion ity studies ontrol nts Total Weight M	Risk Ratio 1-H, Random, 95% Cl	0.01 Year	0.1 10 propranolol control Risk Ratio M-H, Random, 95% Cl	100	D Intravitreau a. Removing	l Injectio Low qua Propranolol Events Total	0 <b>n of Anti-</b> 1lity studie. Control Events Total Wei	Vascular Er S Risk Ratio ght M-H, Random, 95	<i>idotheli</i> %Cl Year	al Growth	Factor ik Ratio ndom, 95% CI	
terogeneity: Chi <sup>2</sup> = st for overall effect <b>Laser Pho</b> <b>Removin</b> dy or Subgroup opi 2013 thoul 2014	$\begin{array}{c} \text{OSS, ul = 4 (F = 0.000)} \\ \text{Orogranula} \\ \text{Orogranula} \\ \text{Orogranula} \\ \text{Propranolol} \\ \frac{4}{2} \\ 2 \\ 10 \end{array}$	ity studies           ontrol           nts Total Weight M           10         26           3         10	Risk Ratio 1-H, Random, 95% CI 0.42 [0.15, 1.16] 2 0.67 [0.14, 3.17] 2	0.01 Year 2013 2014	0.1 10 propranolol control Risk Ratio M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014	l Injectio Propranolol Events Total 2 25 0 10	on of Anti- ility studies Control Events Total Wei 5 26 23 2 10 0	Vascular Er S Risk Ratio ght M-H, Random, 95 .2% 0.42 [0.09, 1 .0% 0.20 [0.01, 1	<b>Motheli</b> <u>% CI Year</u> 1.95] 2013 3.70] 2014	<i>ial Growth</i> м-н, <sub>Ra</sub>	Factor	
terogeneity: Chi <sup>2</sup> = st for overall effect <b>Laser Pho</b> <b>Removin</b> dy or Subgroup ppl 2013 thoul 2014 kmuz 2016 ghvi 2017	0.33, 01 - 4 (F - C           Z = 3.72 (P = 0.00           ptoccoagula           glow quai           Propranolol           Q           4           2           10           4           2           1           51	III): F = 37%           tion           tity studies           ontrol           nts         Total           Veight N           10         26           26         26.0%           3         10           16         51           16         51	Risk Ratio I-H, Random, 95% CI 0.42 [0.15, 1.16] 2 0.67 [0.14, 3.17] 2 0.63 [0.17, 1.69] 2 0.69 [0.35, 1.33] 2	0.01 Year 2013 2014 2016 2017	0.1 10 propranolol control M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017	l Injectio Iow qua Propranolol Events Total 2 25 0 10 1 84 2 51	on of Anti- uity studie. Control <u>Events Total Wei</u> 5 26 23 2 10 0 2 90 0 8 51 24	Vascular Er. S Risk Ratio ght M-H, Random, 95 2% 0.42 (0.09, 1 0% 0.20 (0.01, 1 0% 0.54 (0.05, 1 7% 0.25 (0.06, 1	<b>K CI Year</b> 1.951 2013 3.701 2014 5.801 2016 1.122 2017	ial Growth <sub>м-н, ва</sub>	Factor	
terogeneity: Chi <sup>2</sup> = tr for overall effect <b>Laser Pho</b> <b>Removin</b> dy or Subgroup upi 2013 houl 2014 kmaz 2016 ghvi 2017 Huiqing 2018	$\begin{array}{c} 0.35, 0.1 - 4 (F = 0.00) \\ z = 3.72 (P = 0.00) \\ \hline \                                 $	Introl         Introl           Internal         Weight M           10         26         26.0%           3         10         0.0%           6         51         61.8%           8         80.0%         16           51         61.8%         8	Risk Ratio 1-H, Random, 95% Cl 0.42 [0.15, 1.16] 2 0.67 [0.14, 3.17] 2 0.63 [0.14, 3.17] 2 0.69 [0.35, 1.33] 2 0.26 [0.06, 1.16] 2	0.01 Year 2013 2014 2016 2017 2018	0.1 10 propranolol control M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiqing 2018	l Injectio Propranolol Events Total 2 25 0 10 1 84 2 51 5 41	Events         Total         Wei           5         26         23           2         10         0           2         90         0           8         51         24           8         43         52	Vascular Er. S Risk Ratio ght M-H, Random, 95 2% 0.42 (0.09, 0% 0.54 (0.05, 1% 0.25 (0.06, 1% 0.66 (0.23, 1% 0.66 (0.23,	<b>% CI Year</b> 1.95) 2013 3.70) 2014 5.80) 2016 1.12) 2017 1.84] 2018	<i>al Growth</i> 	sk Ratio ndom, 95% CI	
terogeneity: Chi <sup>2</sup> = tr for overall effect <b>Laser Phot</b> <b>Removin</b> dy or Subgroup pip 2013 thou! 2014 kmaz 2016 ghvi 2017 Huiding 2018 al (95% Cl) al events	2 3.72 (P = 0.00 <b>ptocoagula</b> <b>glow quai</b> <b>Propranolol</b> <b>events Total Event</b> <b>4</b> 25 2 10 4 83 11 51 2 41 117 17	Introl         Introl           ity studies         ontrol           ints Total         Weight N           10         26         26.0%           3         10         0.0%           8         80.0%         0.0%           8         43         12.2%           120         100.0%         34	Risk Ratio 1-H, Random, 95% CI 0.42 [0.15, 1.16] 2 0.67 [0.14, 3.17] 2 0.53 [0.17, 1.69] 2 0.69 [0.35, 1.33] 2 0.26 [0.06, 1.16] 2 0.54 [0.32, 0.90]	0.01 Year 2013 2014 2016 2016 2017 2018	0.1 1 10 propranolol control M-H, Random, 95% CI	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiqing 2018 Total (95% Cf) Total (95% Cf)	l Injectic Propranolol Events Total 2 25 0 10 1 84 2 51 5 41 117 9	on of Anti- Lity studie. Control Events Total Wei 2 00 0 8 51 24 8 43 52 120 100 21	Vascular Er. S Risk Ratio ght M-H, Random, 95 22% 0.42 (0.09, 1 0% 0.54 (0.05, 1 7% 0.25 (0.06, 1 7% 0.66 (0.23, 1 0% 0.46 (0.22, 0	<b>CI Year</b> 1.95] 2013 3.70] 2014 5.80] 2016 1.12] 2017 1.84] 2018 <b>0.98</b> ]	ial Growth	Factor	
terogeneity: Chi <sup>2</sup> = st for overall effect <b>Laser Phot</b> <b>Removin</b> dy or Subgroup pi 2013 choul 2014 kmaz 2016 ghvi 2017 Huiqing 2018 al (95% Cl) al events erogeneity: Tau <sup>2</sup> = t for overall effect:	$\begin{array}{c} 0.38, \ (n+4) \in 0\\ z = 3.72 \ (P=0.00\\ \hline z = 3.72 \ (P=0.00\\ \hline z = 0.00\\ \hline z = 0.00$	$\begin{array}{l} I(r)_{1}(r=3/\pi)\\ \hline (22)\\ \hline (22)$	Risk Ratio 1-0, 42 [0.15, 1.16] 2 0.67 [0.15, 1.16] 2 0.67 [0.17, 1.69] 2 0.59 [0.35, 1.33] 2 0.26 [0.06, 1.16] 2 0.54 [0.32, 0.90]	0.01 Year 2013 2014 2014 2017 2018 0.01	Risk Ratio M-H, Random, 95% CI	100	D Intravitreau a. Removing Filippi 2013 Makhoul 2014 Korkmaz 2016 Sang Huling 2018 Total (95% C) Total events Heterogeneity: Tau' = Test for overall effect:	l Injectic Propranolol Events Total 2 25 0 10 1 84 2 51 5 41 917 2.0.0; Chi <sup>2</sup> = 1.1 2 - 2.01 (P - 0.	on of Anti- lity studie. Contol Events Total Wei Events Total Wei Events Total Wei Events Total Wei 2 10 0 2 90 0 2 90 0 2 90 0 2 90 0 2 90 0 2 10 00 21 2. df = 2 (P = 0.57); 04	Vascular Er. S Risk Ratio ght M-H, Random, 95 2.2% 0.42 [0.09, 0.0% 0.20 [0.01, 1.1% 0.66 [0.23, 1.1% 0.66 [0.23, 0] 0.46 [0.22, 0] 1 <sup>2</sup> = 0%	X CI Year 1.95] 2013 1.70] 2014 1.80] 2016 1.12] 2017 1.84] 2018 3.98]	ial Growth м-н, ка .01 0.1 логоглар	Factor	10
ti for overall effect ti for overall effect <b>Laser Photo</b> <b>Removin</b> dy or Subgroup pi 2013 houl 2014 kmaz 2016 givi 2017 Huiqing 2018 al (95% Cl) al events arogeneity: Tau <sup>2</sup> to ro overall effect: <b>Removin</b>	0.38, (ii = 4(r = 0 z = 3.72 (P = 0.00 ptoccoagula g low quai Propranolo ( <u>Events Total Events</u> 4 25 2 11 4 83 11 51 2 41 117 10.00; (chi <sup>2</sup> = 1.70, 0 z - 2.35 (P = 0.02) g the first	17);   = 37% tion iity studies ontrol nts Total Weight N 10 26 26.0% 3 10 0.0% 8 43 12.2% 120 100.0% 4 5 2 (P = 0.43); l <sup>2</sup> = ( phase studie)	Risk Ratio 1-H, Random, 95% C1 0-42 [0:13, 1.16] 2 0-67 [0:14, 3.17] 0-59 [0:05, 1.16] 2 0-59 [0:05, 1.16] 2 0.54 [0:32, 0.90] % 25	0.01 Year 2013 2014 2016 2017 2018 0.01	0.1 10 propranolol control	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghri 2018 Total (95% CD) Total (95% CD)	l Injectic Propranolol Events Total 2 25 0 10 1 84 2 51 5 41 117 0.00; Chi <sup>2</sup> = 1.1 2 - 2.01 (P = 0. the first	on of Anti- lity studie. Control Events Total Wei Events Total Wei Events Total Wei Events Total Wei 2 10 00 2 3 10 100 21 120 100 21 2. df = 2 (P = 0.57): 04 t phase stu	Vascular Er. S Risk Ratio pht M+1, Random, 92 200 0, 02 201 0, 02 100 0	% CI         Year           1.951         2013           3.701         2014           1.801         2016           1.121         2017           1.841         2018           2.98]         50	ial Growth м-н, ка .01 0.1 proprano	Factor sk Ratio ndom, 95% Cl	10
treogeneity: Chi <sup>2</sup> = tt for overall effect <b>Laser Phot</b> <b>Removin</b> dy or Subgroup pi 2013 houl 2014 kmaz 2016 givi 2017 Huiqing 2018 al (95% Cl) al events arogeneity: Tau <sup>2</sup> = tor overall effect: <b>Removin</b> dy or Subgroup	2 = 3.72 (P = 0.00 ptocoagula glow quai Propranolol 2 10 2 10 4 25 2 10 4 25 2 10 4 33 11 51 117 100: Chi <sup>2</sup> = 1.70, ( 2 - 2.35 (P = 0.02) g the first Propranolol Comparison of the first Propranolol	1/):         - 3 /%           02)         02)           02)         02)           03)         04           04)         05           05         04           05         04           06         05           07         04           08         04           08         04           120         100.0%           41         2 (P = 0.43); l <sup>2</sup> = C           0         04           0         05           0         05           0         05           0         04           0         05	Risk Ratio 1-H, Random, 95% CI + 0-42 (0.15, 1.16) 0-47 (0.14, 3.17) 2 0-53 (0.06, 1.16) 2 0-54 (0.32, 0.90) % 25 Risk Ratio H. Random, 95% CI + 25	0.01 Year 2013 2014 2016 2017 2016 2017 2018 0.01 Year	0.1 10 propranolol control M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2018 Sanghvi 2018 Total (195K C) Total events Heterogeneity: Tau <sup>4</sup> = Test for overall effect: <b>b. Removing</b>	Unjectic           Propranolo           Events Total           2         25           0         100           1         84           2         51           5         41           117         9           0.00; Chi² = 1.1         2           2         2.01 (P = 0.           the first         Propranolo	on of Anti- zlity studie. Control Events Total Wei 2 10 c 2 90 0 8 51 24 8 43 52 120 100 21 120 100 120 100 120 100 100 100 1	Vascular Er. S Risk Ratio MH-H, Random, 95 0.2% 0.42 [0.09, 0.54 [0.05, 7] 0.25 [0.06, 1] 0.66 [0.22, 0] 1% 0.66 [0.22, 0] 1% 0.65 [0.22, 0] 1% 0.66 [0.22,	% CI         Year           1.951         2013           1.701         2014           1.801         2016           1.121         2017           1.841         2018           9.981         5	RI M-H, Ra .01 0.1 proprano	Factor sk Ratio ndom, 95% CI	10
terogeneity: Ch <sup>2</sup> = st for overall effect Laser Photo Removin dy or Subgroup ppl 2013 choul 2014 kmaz 2016 ghvi 2017 Huiqing 2018 al (95% Cl) al events crogeneity: Tau <sup>2</sup> = c for overall effect: dy or Subgroup ppl 2013 dy or Subgroup ppl 2013	$\sum_{i=1}^{2} \sum_{j=1}^{2} \sum_{i=1}^{2} \sum_{j=1}^{2} \sum_{j=1}^{2} \sum_{i=1}^{2} \sum_{j=1}^{2} \sum_{j=1}^{2} \sum_{i=1}^{2} \sum_{i$	$\begin{array}{l} 10(1) = -3.7\% \\ \text{(ii)} = -3.7\% \\ \text{(iii)} =$	Risk Ratio 1-H, Random, 95% Cl - V 0-42 (0.15, 1.16) 2 0-57 (0.14, 3.17) 2 0-58 (0.17, 1.69) 2 0-54 (0.32, 0.90) 0 54 (0.32, 0.90) 0 1-H, Random, 95% Cl - 1 0-42 (0.15, 1.16) 2 0-42 (0.15,	0.01 Year 2013 2014 2014 2014 2016 2017 2016 0.01 Year Year 2013	0.1 10 propranolol control M-H, Random, 95% Cl 0.1 10 morparalol control M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiqing 2018 Total (195K CD) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>b. Removing</b>	Injectic           Image: Image of the second secon	on of Anti- tity studie. Control Events Total Wei Events Total Wei 2 01 0 2 2 00 0 0 2 90 0 0 2 0 0 0 0	Vascular Er. S mk-H, Random, 95 2.2% 0.42 [0.09, 0.42 [0.09, 0.42 [0.09, 0.42 [0.02, 0.42 [0.02, 0.42 [0.02, 0.46 [0.22, 0] dics Risk Ratio ght M-H, Random, 95 Risk Ratio	% CI         Year           1.951         2013           3.701         2014           5.001         2016           1.121         2017           8.841         2018           5.983         6           % CI         Year           1.951         2013	RI M-H, Ra .01 0.1 proprano	Factor sk Ratio ndom, 95% CI sk Ratio ndom, 95% CI sk Ratio ndom, 95% CI	10
erogeneity: Chi <sup>2</sup> = t for overall effect Laser Phic Removin y or subgroup p) 2013 houl 2014 maz 2016 houl 2014 maz 2016 hour 2017 Hunging 2018 at (95% Cf) levents Removin ty or subgroup p) 2013 houl 2014 maz 2016	$\begin{array}{c} 0.38, \ \text{in - } V(F=0,0)\\ 2=3.72 \ (P=0,0)\\ \hline \mbox{tocoagula}\\ \mbox{glow} \ \mbox{qluai}\\ \mbox{propanola}\\ \mbox{random}\\ \mbox{qluai}\\ \mbox{random}\\ \mbox{random}\\ \mbox{qluai}\\ \mbox{random}\\ rand$	$\begin{array}{c} 10, (-3.78)\\ 10, (-3.78)\\ \hline \mbox{tion}\\ \mbox{iii}\\ \mbox{tion}\\ \mbox{iii}\\ \mbox{stabular}\\ $	Risk Ratio 1-H, Random, 95% CI 0-42 (0.15, 1.16) 0-67 (0.14, 3.17) 2 0-53 (0.17, 1.69) 2 0-54 (0.32, 0.90) % S Risk Ratio 1-H, Random, 95% CI 0-42 (0.15, 1.16) 2 0-63 (0.17, 1.69) 2 0-53	0.01 Vear 2013 2014 2014 2016 2017 2018 0.01 Vear 2013 0.01	0.1 10 propranolol control M-H, Random, 95% Cl	100	D Intravitreau a. Removing Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiging 2018 Total (95% CI) Total (95% CI)	$\begin{array}{c} I \ Injectic \\ Iow \ quarker \\ Propranol0 \\ \hline 2 \ column{2}{2} \\ 2 \ column{2}{2} \\ 2 \ column{2}{2} \\ 2 \ column{2}{2} \\ 1 \ 8 \ 4 \\ 2 \ column{2}{2} \\ 1 \ 8 \ 4 \\ 2 \ column{2}{2} \\ 1 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \ 7 \ 7 \ 7 \\ \hline 7 \ 7 \ 7 \ 7 \ 7 \ 7 \ 7 \ 7 \ 7 \ 7$	on of Anti- ality studie. Control Events Total Wei 2 00 c 2 00 c 2 00 c 2 00 c 2 10 20 2 120 100 12 df = 2 (P = 0.57); 04) Events Total Wei 2 0 00 12 df = 2 (P = 0.57); 04) Events Total Wei 2 0 00 2 0 0 c 2 0 c 2 0 0 c 2 0 0 c 2 0 c	Vascular Er. S Risk Ratio ph. M-H, Random, 95 128 0.42 (0.03) 0.54 (0.05) 1.96 0.54 (0.05) 1.96 0.66 (0.23) 0.66 (0.23) 0.66 (0.23) 1.96 0.66 (0.23) 0.66 (0.23) 1.96 0.66 (0.23) 1.96 0.65 (0.23) 1.96 0.65 (0.23) 1.96 0.66 (0.25) 1	% CI         Year           1.951         2013           1.701         2014           1.801         2016           1.121         2016           1.121         2017           8.801         2018           9.981         6           % CI         Year           1.951         2013           3.701         2014           5.601         2014	Al Growth Ri M-H, Ra 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1	Factor	10
ierogeneity: Chi <sup>2</sup> = t t for overalle effect <b>Laser Photo</b> <b>Removin</b> dy or sbugroup pt 2013 40 or sbugroup pt 2013 huiding 2018 at 69% Chi at 69% Chi a	0.35. MIL + 07 = 0.00 27 = 3.72 (P = 0.00 27 occaagula g low quai Propranoid 2 to 4 as 11 51 2 41 117 10.00: Chi' = 1.70, 2 2 - 3.35 (P = 0.02) g the first 4 constant 2 - 2.35 (P = 0.02) g the first 2 - 2.35 (P = 0.02) 2 - 2.35 (P = 0.02) 3 -	$\begin{array}{c} 10), (-3.78)\\ \hline (10), (-3.78)\\ \hline $	Risk Ratio           1-H, Radio 15, 141           0-47 (01-4, 317)           0-57 (01-4, 317)           0-58 (00-51, 161)           0-54 (0.32, 0.90)           %           25           Risk Ratio           1-H, Risk Ratio           0-54 (0.31, 116)           0-54 (0.31, 116)           0-54 (0.31, 116)           0-54 (0.31, 117)           0-56 (0.5, 116)           0-58 (0.5, 116)           0-58 (0.5, 116)           0-58 (0.5, 116)	0.01 Year 2013 2014 2015 2017 2018 0.01 Year 2013 2014 2013 2014 2013 2014 2013 2014 2013 2014 2015 2015 2015 2016 2017 2018	0.1 1 10 propranolol control M-H. Random, 95% Cl 0.1 10 propranolol control Risk Ratio M-H. Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Korkmaz 2016 Sanghi 2017 Sun Huiqing 2018 Total eversi Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>b. Removing</b> Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghiv 2017 Sun Huiqing 2018	$\begin{array}{c} I \ Injectic \\ Iow \ quarker \\ Propranol0 \\ \hline \\ \frac{Events}{2} \ constraints \\ \hline \\ 2 \ constraints \\ 2 \ constraints \\ 2 \ constraints \\ 2 \ constraints \\ \hline \\ 9 \ 0.00; \ Chi^2 = 1.1 \\ 2 \ constraints \\ \hline \\ 9 \ 0.00; \ Chi^2 = 1.1 \\ 2 \ constraints \\ \hline \\ 117 \ 9 \\ 9 \ 0.00; \ Chi^2 = 1.1 \\ 2 \ constraints \\ \hline \\ 9 \ 0.00; \ Chi^2 = 1.1 \\ 2 \ constraints \\ \hline \\ 117 \ 9 \\ \hline \\ 9 \ 0.00; \ Chi^2 = 1.1 \\ 2 \ constraints \\ \hline \\ 9 \ 0.00; \ Chi^2 = 1.1 \\ \hline \ \ 0.00; \ Chi^2 = 1.1 \\ \hline \ \ 0.1 \\ \hline \ 0.00; \ 0.00; \ 0.00; \ 0.00; \ 0.00; \ 0.00; \ 0.00; \ 0.00; \ 0.00; \ 0.00; $	on of Anti- ality studie. Events Total Wei Events Total Wei 2 00 C 8 51 24 8 43 52 120 100 12 df = 2 (P = 0.57); 001 2 df = 2 (P = 0.57); 001 Events Total Wei S 2 6 25 2 10 7 2 10 7 8 51 C 8 51 C 8 51 C	Vascular Er. S Risk Rato pt. H. 4, 8andom 95 2.2% 0.42 [0.01, 0.5% 0.42 [0.02, 1.2% 0.42 [0.02, 1.3% 0.42 [0.02, 1.3% 0.46 [0.23, 0.5% 0.46 [0.23, 0.5% 0.46 [0.23, 1.3% 0.46 [0.24, 1.3% 0.46 [0.24, 1.4% 0.42 [0.04, 1.4% 0.4] [0.04, 1.4% 0.4% 0.4] [0.04, 1.4% 0.4% 0.4] [0.04, 1.4% 0.4% 0.4] [0.04, 1.4% 0.4% 0.4% 0.4% 0.4% 0.4% 0.4% 0.4% 0	% CI         Year           1.951         2013           1.701         2014           1.801         2016           1.121         2017           1.841         2018           0.988         0	ial Growth м-н, ка .01 0.1 ргоргало м-н, ка	Factor sk Ratio sk Ratio loi control sk Ratio ndom, 95% cl	10
torogeneity: Chi <sup>2</sup> = to for overall effect Laser Phic Removin dy or subgroup phi 2013 hou 2016 phine 2018 da (95% Chi Philosophi 2018 da (95% Chi	2.5. Min + 0 = 0.0 <b>All Cocaguida</b> <b>g low quai</b> <b>Propranoloi</b> <b>4</b> 25 <b>2</b> 41 <b>117</b> <b>117</b> <b>100</b> : Chi <sup>2</sup> = 1.70, (2) <b>31</b> <b>31</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>32</b> <b>43</b> <b>31</b> <b>51</b> <b>2</b> <b>43</b> <b>31</b> <b>15</b> <b>17</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b> <b>70</b>	$\begin{array}{c} 10,  1-3/8  \\ (2)$	Risk Ratio           1-H, Random, 95% C1           0.42 (0.13, 1.16)           0.53 (0.17, 1.66)           0.53 (0.17, 1.66)           0.53 (0.17, 1.66)           0.54 (0.32, 0.90)           %           ZS           Risk Ratio           1-H, Random, 95% C1           0.54 (0.13, 1.16)           0.57 (0.14, 1.17)           0.67 (0.14, 1.17)           0.67 (0.14, 1.17)           0.69 (0.35, 1.33)           0.26 (0.06, 1.16)           0.26 (0.06, 1.16)           0.26 (0.06, 1.16)           0.26 (0.06, 1.16)           0.26 (0.06, 1.16)	0.01  Year  2013 2014 2016 2017 2018  0.01  Year  2013 2014 2013 2014 2017 2013 2014 2017 2018  2016 2017 2018  2016 2017 2018  2018 2016 2017 2018  2018 2018 2018 2018 2018 2018 201	0.1 10 propranolol control	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2016 Sanghu 2017 Sun Huiqing 2018 Total events Heterogeneity: Tau' = Text for overall effect: <b>b. Removing</b> Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghui 2017 Sun Huiqing 2018	L Injectic Low quue Propranolo Events Total 2 225 0 100 2 51 5 41 117 9 00° CP <sup>2</sup> = 1.1 2 - 2.20.1 (P - 0.0) 10 2 - 2.01 (P -	on of Anti- alicy studie. Control Events Total Wei Events Total Wei Events Total Wei Events Total Wei 2 10 00 21 10 100 21 20 100 20 20 20 20	Vascular Er. S Risk Ratio MH-H, Random, 55 2.26 0.42 [0.09, 0.25 [0.05, 1.37 0.66 [0.23, 0.05 0.46 [0.22, 0 1 <sup>2</sup> = 0% Michael Strategy Michael Str	% CI         Year           1.951         2013           3.701         2014           8.601         2016           1.841         2018           9.961         1014           1.951         2013           3.701         2014           5.962         1014           1.951         2013           3.701         2014           5.801         2016           1.121         2017           1.841         2018           1.141	ial Growth MH, Ra 0.01 0.1 proprano	Factor sk Ratio ndom, 95% Cl	10
icropeneity: Chi <sup>2</sup> = it for overall effect. Laser Photo Removin dy or subgroup pi 2013 thild of the subgroup pi 2013 thild of the subgroup di (5% Ci) a levents di (5% Ci) a levents dy or subgroup pi 2013 a levents dy or subgroup a levents dy or subgroup dy a levents dy a lev	$\begin{array}{c} 0.38, \ \text{in-t}\ \text{it-g}=0.00\\ \textbf{y}=0.00, \ \textbf{y}=0.00\\ \textbf{y}=$	$\begin{array}{c} 10); (1-3/2)\\ (2); (2); (2); (2); (2); (2); (2); (2);$	Risk Ratio           -H, Random, 95% Cl           0.42 (0.15, 1.16)           0.67 (0.14, 1.17)           0.67 (0.14, 1.17)           0.69 (0.05, 1.16)           0.69 (0.05, 1.16)           0.69 (0.05, 1.16)           0.64 (0.032, 0.90)           %           ZS           Risk Ratio           -4.4 (2.05, 1.16)           0.66 (0.03, 1.33)           0.66 (0.03, 1.33)           0.66 (0.03, 1.33)           0.66 (0.05, 1.16)           0.44 (0.24, 0.83)	0.01 Vear 2013 2014 2016 2016 2017 2013 2014 0.01 Vear 2015 2017 2013 2015 2015 2015 2015 2017 2017 2017 2017 2017 2017 2017 2016 2017 2016 2017	0.1 10 propranolol control M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hudging 2018 Total (95% C) Total events Heterogeneity: Tau' = Test for overall effect: b. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hudging 2018 Total (95% C) Total events Heterogeneity: Tau' =	l Injectic low qua Propranolol Events Total 2 235 0 10 0 44 2 51 1 5 41 117 9 0.00; Ch <sup>2</sup> = 1.1 2 2.5 0 10 1 6 1 6 1 7 2 25 0 11 1 7 1 7 1 7 1 7 1 7 1 7 1 7	on of Anti- alicy studie. Control Events Total Wei Events Total Wei Events Total Wei Events Total Wei 2 12 12 of 100 2 2 12 of 100 2 2 12 of 100 2 2 12 of 100 2 2 10 0 12 df 2 0 12 df 2 0 10 0 12 df 2 0 10 0 12 df 2 0 10 0 10 0 10 0 10 0 10 0 10 0 10 0	Vascular Elt           S           Risk Ration           MH-H, Random, 55           2.3%         0.42 [0.09, 0.00]           0.8         0.20 [0.01, 1.00]           0.8         0.20 [0.01, 1.00]           0.8         0.20 [0.01, 1.00]           0.8         0.42 [0.09, 1.00]           1.9         0.66 [0.22, 1.00]           1.9         0.66 [0.22, 1.00]           1.9         0.46 [0.22, 1.00]           1.8         Ratio           1.8         0.42 [0.00, 1.10]           1.8         0.42 [0.02, 1.00]           1.8         0.42 [0.02, 1.00]           1.8         0.42 [0.02, 1.00]           1.8         0.42 [0.02, 1.00]           1.8         0.42 [0.02, 1.00]           1.8         0.42 [0.02, 1.00]           1.8         0.42 [0.02, 1.00]           1.8         0.54 [0.02, 1.00]           0.88         0.66 [0.23, 1.00]           0.96         0.53 [0.24, 1.10]           1.97         0.53 [0.24, 1.10]	% CI         Year           1.951         2013           3.701         2014           8.601         2016           8.601         2016           8.641         2018           9.981         0           % CI         Year           1.551         2013           3.701         2014           5.501         2016           1.121         2017           1.841         2018           1.121         1	ial Growth MH, R 0.01 0.1 proprano	Factor sk Ratio ndom, 95% Cl lo control sk Ratio	10
icropentity: Chi <sup>2</sup> = t for overall effect Laser Phot Removin dy of subgroup pi 2013 with 2017 Huilaing 2018 a (5% Ct) effective and a (5% Ct) effecti	$\begin{array}{c} 0.38, \ \text{in-t} \ \text{if} = 0.00\\ 2 = 3.72 \ (\text{P} = 0.00\\ \text{Molecular proposal of } \\ \text{Propranolol} \\ \text{Propranolol} \\ Verms Total Events T$	$\begin{array}{c} 10), (1-3/8)\\ 10), (2-3/8)\\ \hline \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Risk Ratio           1-H, Random, 95% CI         4           0.42 (0.15, 1.16)         2           0.43 (0.16, 1.16)         2           0.45 (0.14, 3.17)         2           0.46 (0.06, 1.16)         2           0.56 (0.32, 0.590)         6           75         7           Risk Ratio         -           -H, Random, 95% CI         4           0.47 (0.14, 3.17)         2           0.54 (0.32, 0.590)         6           6.57 (0.14, 3.17)         2           0.58 (0.31, 3.13)         2           0.59 (0.35, 1.33)         2           0.59 (0.35, 1.33)         2           0.59 (0.35, 1.33)         2           0.59 (0.35, 1.33)         2           0.44 (0.24, 0.83)         5	0.01 Vear 2013 2014 2015 2017 2018 0.01 Vear 2013 0.01 Vear 0.01 0.01 0.01	0.1 10 propranolol control M-H, Random, 95% Cl 0.1 propranolol control M-H, Random, 95% Cl 0.1 propranolol control M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiging 2018 Total 095K CO Total events Heterogeneity: Tau' = Test for overall effect: B. Removing Study or Subgroup Filippi 2013 Korkmaz 2016 Sanghvi 2017 Sun Huiging 2018 Contal events Heterogeneity: Tau' = Total events Heterogeneity: Tau' = Test for overall effect:	Injectic           Iow quia           Propranolol           Propranolol           2 55           0           0           117           9           0.00: Chi <sup>2</sup> = 1.1           117           Propranolol           Events Total           0           117           117           Propranolo           Events Total           0           1           14           2           15           11           15           11           14           2           15           11           15           11           15           11           160           0.00: Chi <sup>2</sup> = 0.62 (P = 0.1)	on of Anti- ality studie. Control Events Total Wei Yents Total Wei 2 90 c 3 10 2 2 90 c 3 5 124 8 43 52 120 100 12, df = 2 (P = 0.57); .04) Events Total Wei Events Total Wei Events Total Wei 8 43 55 169 100 19, df = 3 (P = 0.87); .11)	Vascular Er. S 1848 Raio 1944, H., Random, 95 2.2% 0.42 [0.09, 0.42 [0.09, 0.42 [0.09, 0.42 [0.09, 0.42 [0.09, 0.42 [0.09, 0.42 [0.09, 0.45 [0.22, 0] 19 0.66 [0.23, 0.46 [0.22, 0] 19 0.46 [0.22, 0] 19 0.46 [0.22, 0] 19 0.46 [0.22, 0] 10 0.45 [0.06, 0] 10 0.45 [0.06, 0] 10 0.45 [0.06, 0] 10 0.45 [0.24, 0] 10 0.45 [	% CI         Year           1.951         2013           3.701         2014           3.801         2016           1.121         2017           1.841         2018           3.958         50           3% CI         Year           1.951         2013           3.012         2016           1.121         2017           1.141         2018	.01 0.1 MH, R OI Proprano R MH, R OI Proprano	Factor sk Ratio ndom, 95% CI	10
icrogeneity: Chi <sup>2</sup> = t for overall effect Laser Photo Removin by of subgroup pr2013 thuising 2018 at 05% C1) at 05% C1) thuising 2018 at 05% C1) thor overall effect: Fixed eff	$\begin{array}{c} 0.38, \ \text{in - 4} \ \text{($P$-0.05$)}\\ 2 = 3.72 \ ($P$-0.05$)\\ \hline \textbf{M} \ \textbf{Cocaguila}\\ \textbf{g low quai}\\ \textbf{Propranolol}\\ \textbf{Vernts} \ \textbf{Total} \ \textbf{Eve}\\ \textbf{Vernts} \ \textbf{Vernts} \ \textbf{Vernts} \ \textbf{Vernts}\\ \textbf{Vernts} \ Ve$	$\begin{array}{c} 10(1) = 3.7\% \\ 110(1) =$	Risk Ratio           1-H, Random, 95% CI         0.42 (0.15, 1.16)           0.67 (0.14, 3.17)         2.03 (0.17, 1.69)           0.67 (0.14, 3.17)         2.03 (0.17, 1.69)           0.69 (0.35, 1.33)         2.00 (0.66, 1.16)           0.54 (0.32, 0.300)         %           75         Risk Ratio           H.Rk Ratio         0.44 (0.24, 0.83)           0.69 (0.35, 1.33)         2.026 (0.06, 1.16)           0.44 (0.24, 0.83)         %	0.01 Year 2013 2014 2016 2017 2013 2013 2014 2015 2013 2014 2015 2014 2015 2014 2015 2014 2015 2014 2015 2014 2015 2014 2015 2014 2015	0.1 10 propranolol control M-H, Random, 95% Cl 0.1 00 M-H, Random, 95% Cl 0.1 00 M-H, Random, 95% Cl M-H, Random, 95% Cl 0.1 00 propranolol control 0.1 00 M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiqing 2018 Total (95% CO) Total events Hetrogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D. Removing</b> Study or Subgroup Study or Subgroup Subgroup Subgroup Subgroup Subgroup Subgroup Subgroup Subgroup Subgroup Subgroup Subgroup Total events Huiqing 2018 Total (95% CO) Total events Huiqing 2018 Cotal (95% CO) Total events Huiqing 2018 Cotal (95% CO) Total events Huiqing 2018	$\begin{array}{c} I \ Injectic \\ flow quiz \\ Propranolol \\ Events \ Total \\ 2 \ 51 \\ 2 \ 51 \\ 5 \ 41 \\ 5 \ 41 \\ 5 \ 41 \\ 5 \ 41 \\ 5 \ 41 \\ 5 \ 41 \\ 5 \ 41 \\ 5 \ 41 \\ 5 \ 41 \\ 6 \ 51 \\ 6 \ 51 \\ 5 \ 51 \ 51$	on of Anti- ality studie. Control Events Total Wei Events Total Wei 2 90 c 2 90 c 2 90 c 3 51 24 8 43 52 120 100 12, df = 2 (P = 0.57); .04) Events Total Wei Events Total Wei E	Vascular Er. S mit H-H, Random, 95 2.% 0.42 (0.09, 0.42 (0.09, 0.42 (0.09, 0.42 (0.09, 0.42 (0.09, 0.42 (0.09, 0.42 (0.09, 0.42 (0.09, 0.46 (0.22, 0) 1° = 0% dics Risk Ratio 0.53 (0.24, 1° = 0%	% CI         Year           1.951         2013           3.701         2014           3.801         2016           1.121         2017           1.841         2018           3.958         50           3% CI         Year           1.951         2013           3.001         2016           1.121         2017           1.141         2018	ial Growth н. к.	Factor sk Ratio ndom, 95% CI lol control sk Ratio k Ratio	10
ierogeneity: Chi <sup>2</sup> = it for overall effect Laser Photo Removin yor Subgroup pi 2013 houl 2014 timaz 2016 piv 2017 Huileing 2018 al 405% Cl) el events toro averall effect: Removin dyor Subgroup pi 2013 houl 2014 el events al 405% Cl) el events al 405% Cl) el events for overall effect: Fictor ove	$\begin{array}{c} 0.39,  \mathrm{Min}^{-1}  \mathrm{eff} = 0.00\\ \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	$\begin{array}{c} 10, (1-3/2)\\ 10, (1-3/2)$	Risk Ratio           1-H, Barkon, 55% CI           0.47 [01:13, 116]           0.47 [01:14, 317]           0.33 [01:7, 169]           0.33 [01:7, 169]           0.42 [01:05, 116]           0.42 [01:05, 116]           0.54 [0.32, 0.90]           %           Risk Ratio           1-H, Bandrom, 55% CI           0.42 [01:5, 116]           0.44 [01:35, 116]           0.42 [01:5, 116]           0.44 [02:4, 0.83]           %           Risk Ratio           M-H, Fined 95% CI           0.42 [01:5, 116]           0.44 [02:4, 0.83]		0.1 10 propranolol control M-H, Random, 95% Cl 0.1 10 propranolol control M-H, Random, 95% Cl 0.1 10 M-H, Random, 95% Cl 0.1 10 Risk Ratio M-H, Random, 95% Cl 0.1 10 M-H, Random, 95% Cl	100	D Intravitreau a. Removing Filippi 2013 Mahoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiqing 2018 Total (95% C) Total event: Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>Discussion Status</b> Sunghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2014 Makhoul 2014 Korkmaz 2016 Sanghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sanghvi 2018 Sanghvi 2019 Sanghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2014 Sanghvi 2015 Sanghvi 2014 Sanghvi 2014 Sanghvi 2015 Sanghvi 2014 Sanghvi 2015 Sanghvi 2014 Sanghvi 2	I Injectia           Clow qua           Propranolo           Events Total           2           0           117           9           0.00; Chi <sup>2</sup> = 1.1           2           117           9           0.00; Chi <sup>2</sup> = 1.1           2           0.00; Chi <sup>2</sup> = 1.1           2           0.10           2           0.00; Chi <sup>2</sup> = 0.6           2           2           0.00; Chi <sup>2</sup> = 0.6           2           2           12           13           14           15           160           8           100           100           100           100           100           100           100           110           110           12           13           14           15           160           100           100           100           100           100	on of Anti- ality studie. Control Events Total Wei 2 00 c 2 00 c 2 00 c 2 30 c 2 2 0 c 2 2 c 2 2 c 2 c	Vascular Er. S mix Ratio mix H-H, Random, 95 2.% 0.42 (0.07), 0.05 0.20 (0.01, 0.05 0.22, 0.02, 1.% 0.66 (0.23, 0.05), 0.66 (0.23, 0.05), 0.65 (0.23, 0.05), 0.65 (0.23, 0.05), 0.65 (0.23, 0.05), 0.65 (0.23, 0.05), 0.65 (0.23, 0.05), 0.65 (0.24, 0.05), 0.65 (0.25, 0.05), 0.65 (0.25, 0.05),	% CI         Year           1.951         2013           3.701         2014           3.801         2016           1.121         2017           3.801         2018           3.9881         2013           3.9881         2013           3.9982         0           3.9983         0           3.9983         0           3.9983         0           3.9983         0           3.9983         0           3.9983         0           3.9984         2016           1.121         2017           1.122         2017           1.141         1           5.012         2013	ial Growth м.н. ка .01 01 .01 01 ргоргало .01 01 .01 01 гор лот .01 01 .01 01 .01 .01 .01 .01 .01 .01 .01	Factor	10
terogeneity: Chi <sup>2</sup> = st for overall effect Laser Photo Removin 49 or Subgroup 19 2013 40 or Subgroup 19 2013 40 or Subgroup 19 2013 41 0954 C1) 10 or overall effect Removin 40 or Subgroup 10 pt 2013 10 or overall effect 10 or	2 = 3/72 (P = 0.00 to coagula g low quai Propranolo 4 = 25 4 = 25 4 = 25 117 1000 Chi <sup>2</sup> = 1.70, 4 2 = 3.55 (P = 0.02) g the first Propranolol 2 = 2.55 (P = 0.01) 159 1000 Chi <sup>2</sup> = 0.85, 5 2 = 2.55 (P = 0.01) Cect model Propranolol Cech = 0.85, 6 4 = 25 4 = 25 159 1000 Chi <sup>2</sup> = 0.85, 7 1000 Chi <sup>2</sup>	$\begin{array}{c} 10), (1-3), (2-3$	Risk Ratio           1-H, Random, 955 C1           0.47 [01:14, 117]           0.47 [01:14, 117]           0.33 [01:17, 169]           0.33 [01:17, 169]           0.48 [01:36, 1:16]           0.48 [00:36, 1:16]           0.48 [00:36, 1:16]           0.48 [00:36, 1:16]           0.44 [01:3, 1:16]           0.44 [02:4, 0.83]           %           Risk Ratio           M-H, Fixed, 95% C1           0.44 [02:4, 0.83]           %	0.01  Vear  0013 0014 0014 0015 0015 0015 0017 0018 0014 001 0015 0015 0016 0017 0018 0014 0017 0018 001 001 001 001 001 001 001 001 00	0.1 10 propranolol control M-H, Random, 95% Cl 0.1 propranolol control 0.1 propranolol control	100	D Intravitreau a. Removing Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hulqing 2018 Total eventive Tau <sup>2</sup> = Test for overall effect: b. Removing Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hulqing 2018 Total (95% C) Total eventive Tau <sup>2</sup> = Test for overall effect: c. Fixed effect Study or Subgroup Filippi 2013 Makhoul 2016 Study or Subgroup Filippi 2013	L Injectia L Injectia Propraolol <u>Verters Total</u> 2 25 0 10 2 0 10 2 2 25 0 10 2 5 41 10 9 0.00; Ch <sup>2</sup> = 1.1 2 - 2.01 (# -0.0) <b>Propraolol</b> <u>Verters Total</u> 2 2 5 0 10 2 <b>Verters Total</b> 160 8 Propraolol <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Propraolol</u> <u>Pr</u>	on of Anti- ality studie. Control Events Total Wei Sents Total Wei Peents Total Wei Sents Total Wei Control Events Total Wei Sents Total Wei	Vascular Er. S Isk Ratio M -H, Random, 53 2.26 0.42 [0.09, 42 0.25 [0.02, 1] 3.06 0.25 [0.02, 1] 3.06 0.46 [0.22, 0] 1 <sup>2</sup> = 0% dicas Misk Ratio ght M-H, Random, 93 4.46 0.42 [0.09, 1] 1.16 0.42 [0.09, 1] 1	Sci         Year           1,951         2013           1,952         2013           1,952         2013           1,952         2013           1,952         2017           1,841         2013           1,841         2018           1,121         2013           1,841         2018           1,141         \$           1,142         \$	ial Growth М.Н. ка 0.01 0.1 м.Н. ка угоргало М.Н. ка м.Н. ка угоргало ка м.Н. ка угоргало ка м.Н. ка и м.Н. ка и м.	Factor	10
teropeneity: Chi <sup>2</sup> et for overall effect Laser Photo Account of the second of the second of the second dy of subgroup pp 2013 the second of the second of the second of the second dy of subgroup the second of the second of the second of the second of the second dy of subgroup of the second of the seco	$\begin{array}{c} 0.38,  \mathrm{min}^{-4}  \mathrm{Ge}^{-0}  $	$\begin{array}{c} 10); (1-3/2) \\ (10); (2); (2); (2); (2); (2); (2); (2); (2$	Risk Ratio           1-H, Random, 95% C1           0.42 (0.13, 1.16)           0.53 (0.17, 1.66)           0.53 (0.17, 1.66)           0.53 (0.17, 1.66)           0.53 (0.17, 1.66)           0.53 (0.17, 1.66)           0.53 (0.17, 1.66)           0.54 (0.32, 0.90)           %           ZS           Risk Ratio           1-H, Random, 95% C1           0.54 (0.05, 1.16)           0.56 (0.06, 1.16)           0.56 (0.06, 1.16)           0.57 (0.14, 3.17)           0.58 (0.05, 1.16)           0.58 (0.05,	0.01  Year  2013 2013 2013 2014 2013 2017 2018  0.01  Year  0.01  Vear  2013 2014 0.01  2017 2018  201 201 201 201 201 201 201 201 201 20	0.1 10 propranolol control M-H, Random, 95% Cl 0.1 10 propranolol control M-H, Random, 95% Cl 0.1 10 propranolol control Risk Ratio M-H, Random, 95% Cl 0.1 10 propranolol control Risk Ratio M-H, Random, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hudging 2018 Total (195K CD) Total (195K CD) Total events Heterogenetiy: Tau' = Test for overall effect: B. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hudging 2018 Total (195K CD) Total events Heterogenetiy: Tau' = Test for overall effect: C. Effect effect Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 opt 2018	Injectia           Propranoloj           vents Total           2           0           117           0.00. Cnif = 1.1           5           117           0.01. Cnif = 1.1           5           10           2           0.02. Cnif = 0.0           2           0.03. Cnif = 0.0           2           0.04. Cnif = 0.0           0.05. Cnif = 0.0           0.08. Chif = 0.0           2           10           10           10           117           118           2           118           2           118           2           118           2           2           118           2           2           118           2           2           118           2           2           118           2           2           118           2           2           2	on of Anti- ality studie Control Events Total Wei Events Total Wei Events Total Wei Events Total Wei 12, df = 2 ( $P = 0.57$ ; .0.4) <i>i j hase stu</i> Control Events Total Wei Forts Total Wei Control Events Total Wei Events Tot	Vascular Elt.           S           Risk Radom, 95           2.2%         0.42 [0.09, 10.00, 10	% CI         Year           1.951         2013           1.701         2014           1.701         2014           1.951         2013           1.121         2017           1.841         2018           3.701         2014           1.951         2013           3.701         2014           1.981         2015           3.701         2014           1.841         2015           1.841         2018           1.141         5           CI         Year           951         2013           701         2014           121         2017           121         2016           121         2016	ial Growth н, ка м.н., ка о.01 0.1 ргоргало 0.01 0.1 ргоргало ка м.н., ка м.н., ка м.	Factor sk Ratio ndom, 95% Cl lol control sk Ratio lol control lol control	10
tereignenity: Chi <sup>2</sup> = st for overall effect st for overall effect Laser Photo Account of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of the state of the state of the state state of the state of th	$\begin{array}{c} 0.38, \mbox{ in - 4} \mbox{ (i - 6, 0)} \\ 0.38, \mbox{ in - 4} \mbox{ (i - 6, 0)} \\ 0.38, \mbox$	$\begin{array}{c} 10); 1 = 3.7\% \\ 0(2) = 3.7\% \\ \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Risk Ratio           -H, Random, 95% CI           0.42 (0.13, 1.16)           0.47 (0.14, 1.17)           0.46 (0.13, 1.16)           0.47 (0.14, 1.17)           0.46 (0.05, 1.16)           0.47 (0.14, 1.17)           0.48 (0.05, 1.16)           0.48 (0.05, 1.16)           0.48 (0.05, 1.16)           0.44 (0.15, 1.16)           0.46 (0.05, 1.16)           0.46 (0.05, 1.16)           0.44 (0.24, 0.43)           %           Risk Ratio           H+Fined 95% CI           0.44 (0.24, 0.43)           0.45 (0.05, 1.16)           0.47 (0.14, 3.17)           0.48 (0.24, 0.43)           0.49 (0.51, 1.16)           0.41 (0.24, 0.43)           0.42 (0.51, 1.16)           0.43 (0.24, 0.15, 1.16)           0.44 (0.24, 0.15, 1.16)           0.47 (0.14, 3.17)           0.53 (0.17, 1.69)           0.47 (0.14, 3.17)           0.54 (0.05, 1.13)           0.59 (0.51, 1.31)           0.59 (0.51, 1.31)           0.46 (0.66, 1.16)	0.01           Year           2013           2014           2017           2018           0.01           Year           2013           0.01           Year           2013           0.01           Year           2013           2014           2015           2014           2013           2014           2013           2014           2015           2017           2018	0.1 10 propranolol control M-H, Random, 95% Cl 0.1 10 propranolol control Risk Ratio M-H, Random, 95% Cl 0.1 10 propranolol control Risk Ratio M-H, Fixed, 95% Cl	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hulging 2018 Total (95% C) Total events Heterogeneity: Tau' = Test for overall effect: b. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hulging 2018 Total (95% C) Total events Heterogeneity: Tau' = Test for overall effect: c. Fixed effect Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Hulging 2018	$\begin{array}{c} I \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ $	on of Anti- alicy studie Control Events Total Wei Points Total Wei 2 00 2 2 00 2 2 00 2 2 00 2 2 00 2 2 00 2 2 120 100 12, df = 2 ( $P = 0.57$ ); .04) 12 df = 2 ( $P = 0.57$ ); .04) 15 20 2 2 0 10 2 2 0 10 2 16 9 100 16 9 100 16 9 100 16 9 100 16 9 100 16 9 100 16 9 100 17 2 0 10 2 0 10 2 0 10 2 0 10 2 0 10 3 8 43 3 3 8 43 3 8 43 3 8 43 3 3 8 43 3 3 8 43 3 3 8 43 3 3 8 43 3 3 7 20 20 20 20 20 20 20 20 20 20 20 20 20	Vascular Elt           S           Risk Ration           MH-H, Random, 95           2.2%         0.42 [0.09, 0.00]           0.8         0.20 [0.01, 1.00]           0.8         0.20 [0.01, 1.00]           0.8         0.20 [0.01, 1.00]           0.8         0.20 [0.01, 1.00]           0.8         0.42 [0.00, 1.00]           12         0.66 [0.22, 1.00]           12         0.46 [0.22, 1.00]           14 <sup>2</sup> 0.46 [0.22, 1.00]           15         0.46 [0.22, 1.00]           15         0.46 [0.23, 1.00]           15         0.20 [0.01, 1.3]           15         0.54 [0.05, 1.00]           15         0.54 [0.05, 1.00]           16         0.42 [0.00, 1.3]           17         0.54 [0.05, 1.00]           16         0.42 [0.00, 1.3]           17         0.54 [0.05, 1.1]           18         0.25 [0.06, 1.1]           1.11%         0.42 [0.00, 1.2]	% CI         Year           1,951         2013           1,701         2014           1,801         2017           1,801         2017           1,801         2017           1,801         2017           1,801         2017           1,801         2017           1,801         2018           5,801         2016           1,121         2017           1,412         2018           951         2013           701         2014           801         2016           121         2017           801         2016           121         2017           801         2016           121         2017           801         2016           121         2017	0.01 0.1 MH, R 0.01 0.1 proprano MH, R 0.01 0.1 proprano	Factor sk Ratio ndom, 95% Cl lol control sk Ratio control sk Ratio lol control lol control sk Ratio lol control sk Ratio lol control sk Ratio lol control lol c	10
teropeneity: Chi <sup>2</sup> = st for overall effect Laser Photo Agent Shares Photo Agent Sh	$\begin{array}{c} 0.38, 0.14 + 0 = 0.0\\ 0.38, 0.14 + 0 = 0.0\\ 0.38, 0.2$	$\begin{array}{c} 10,  -2  > 3/8\\ (2) = 3/8\\$	Risk Ratio           1-H, Random, 95% Cl         3           0.42 (0.15, 1.16)         2           0.53 (0.17, 1.69)         2           0.54 (0.32, 0.90)         3           %         25           Risk Ratio	0.01           Year           2013           2014           2016           2017           2018           2013           2014           2015           2017           2013           2014           2015           2017           2018           ear           2013           2014           2015           2017           2018	0.1 10 propranolol control M-H, Random, 95% Cl 0.1 0 propranolol control M-H, Random, 95% Cl M-H, Random, 95% Cl Risk Ratio M-H, Random, 95% Cl Risk Ratio	100	D Intravitreau a. Removing Study or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiging 2018 Total 095% CD Total events Hetrogeneity: Tau' = Test for overall effect: B. Removing Suby or Subgroup Filippi 2013 Korkmaz 2016 Sanghvi 2017 Sun Huiging 2018 Total events Hetrogeneity: Tau' = Test for overall effect: C. Fixed effe Suby or Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2015 Sun Huiging 2018 Total 095% CD Total events	$\begin{array}{c} I \ Injectic \\ flow quize \\ Propranolol \\ Events \ Total \\ 2 \ 5 \ 41 \\ 3 \ 5 \ 41 \\ 5 \ 5 \ 41 \\ 5 \ 5 \ 41 \\ 2 \ 5 \ 41 \ 41 \\ 2 \ 5 \ 41 \ 41 \\ 2 \ 5 \ 41 \ 41 \ 41 \ 41 \ 41 \ 41 \ 41 $	on of Anti- ality studie Control Events Total Wei Sents Total Wei Sents Total Wei Sents Total Wei Sents Total Wei Control Events Total Wei Events Total Wei Events Total Wei Sents Total Wei	Vascular Er.           S           (NH-H, Random, 95           2.2%         0.42 [0.03]           0.3%         0.20 [0.01]           0.42 [0.03]         0.3%           0.5 0 [0.02]         0.20 [0.01]           0.66 [0.23]         0.66 [0.23]           0.7%         0.45 [0.02]           12"         0.5%           0.45 [0.03]         0.45 [0.02]           14"         0.46 [0.02]           14"         0.42 [0.03]           15%         0.42 [0.03]           15%         0.42 [0.03]           15%         0.42 [0.03]           15%         0.42 [0.03]           15%         0.42 [0.03]           15%         0.42 [0.03]           16%         0.52 [0.06]           16%         0.52 [0.06]           17%         0.52 [0.06]           100%         0.53 [0.24]           113%         0.66 [0.23]           113%         0.66 [0.23]           113%         0.66 [0.23]           113%         0.66 [0.23]	% CI         Year           1.951         2013           7.01         2014           8.601         2015           8.602         2016           1.951         2013           3.701         2014           3.701         2014           5.801         2013           5.801         2016           1.121         2017           8.41         2018           1.141         C           92         2013           1.121         2017           1.121         2017           1.121         2017           1.121         2017           1.121         2017           1.121         2017           1.121         2017           1.141         C           1.141         C           11         2016           11         2016           11         2016           11         2016           11         2016           11         2016           11         2016           11         2016           11         2016           11         <	0.01 O,1 Proprano 0.01 O,1 Proprano M-H, R, M-H, R,	Factor	10
tereogeneity: Chi <sup>2</sup> = st for overall effect st for overall effect <b>Laser Photo</b> <b>Age 5 Ubytomy</b> ph2013 Ph012017 Huding 2018 <b>a 105%</b> CDI <b>a levents</b> <b>a 105%</b> CDI <b>a levents</b> <b>a 105%</b> CDI <b>a levents</b> <b>b constantion</b> <b>b constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>constantion</b> <b>consta</b>	$\begin{array}{c} 0.36, \mathrm{M}, \mathrm{H} + \mathrm{Q} = 0.0\\ 2 = 3.72  (\mathrm{P} = 0.30  \mathrm{C})\\ \text{propranoid}\\ \mathbf{g} \ [low quark]\\ \mathrm{Propranoid}\\ \mathrm{Yeropranoid}\\ \mathrm{Yeropranoid\\ \mathrm{Yeropranoid}\\ Yero$	$\begin{array}{c} 10), (1-3/8)\\ (2), (2), (2), (2), (2), (2), (2), (2),$	Risk Ratio           1-H, Ration, 055 CI           0.47 (01.4, 3.17)           0.33 (0.7), 1.43 (2.7)           0.33 (0.7), 1.43 (2.7)           0.42 (01.5), 1.16 (2.7)           0.54 (0.32, 0.90)           %           25           Risk Ratio           1-H, Rankon, 055 CI           0.42 (01.5, 1.16) (2.0)           0.44 (0.24, 0.83)           %           Risk Ratio           1-H, Rankon, 055 CI           0.44 (0.24, 0.83)           %           Risk Ratio           M-H, Fined, 05% CI           0.42 (0.15, 1.16) (2.0)           0.44 (0.24, 0.83)           %           Risk Ratio           0.42 (0.15, 1.16) (2.0)           0.42 (0.15, 1.16) (2.0)           0.42 (0.15, 1.16) (2.0)           0.44 (0.24, 0.83)           %           Risk Ratio           0.42 (0.45, 1.16) (2.0)           0.43 (0.17, 1.16) (2.0)           0.43 (0.15, 1.16) (2.0)           0.44 (0.24, 0.83)           0.42 (0.51, 1.16) (2.0)           0.42 (0.51, 1.16) (2.0)           0.44 (0.24, 0.83)           0.42 (0.51, 1.16) (2.0)           0.44 (0.43, 0.82) </td <td>0.01           Year           2013           2014           2016           2017           2013           2014           2015           2017           2013           2014           2015           2014           2015           2014           2015           2014           2015           2014           2015           2014           2015           2014           2015           2017           2018           0.01</td> <td>C.1 to propranolol control Risk Ratio M-H, Random, 95% Cl C.1 propranolol control 10 M-H, Random, 95% Cl M-H, Random, 95% Cl Risk Ratio M-H, Fixed, 95% Cl Risk Ratio</td> <td>100</td> <td>D Intravitreau a. Removing Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiqing 2018 Total (95% C) Total events Heterogeneity: Tau' = Test for overall effect: <b>D. Removing</b> Study of Subgroup Filippi 2013 Makhoul 2014 Sanghvi 2017 Sun Huiqing 2018 Total (95% C) Total events Heterogeneity: Tau' = Test for overall effect: <b>C. Fixed effe</b> Study of Subgroup Filippi 2013 Makhoul 2014 Korkmaz 2016 Sanghvi 2017 Sun Huiqing 2018 Total events Heterogeneity: Chi' = Test for overall effect: Sun Huiqing 2018</td> <td><math display="block">\begin{array}{c} I \ Injectic \\ flow quiz \\ Propranolol \\ Events \ Total \\ 2 \ 25 \\ 0 \ 10 \\ 117 \\ 5 \ 41 \\ 15 \ 41 \\ 117 \\ 5 \ 41 \\ 117 \\ 100 \ Chi^2 = 1.1 \\ 2 \ 2.01 \ (\theta = 0.0 \\ 100 \ Chi^2 = 1.1 \\ 100 \ Chi^2 = 0.0 \\ 2 \ 1.0 \ (\theta = 0.0 \\ 100 \ Chi^2 = 0.0 \\ 2 \ 1.0 \ (\theta = 0.0 \\ 100 \ Chi^2 =</math></td> <td>on of Anti- ality studie Control Events Total Wei Control 2 90 c 2 00 c 2 90 c 2 120 100 12, df = 2 (<math>P = 0.57</math>); .04) <b>Events Total Wei Events Total Wei Events Total Wei Control Events Total Wei S 169 100 17 169 100 19 df = 3 (<math>P = 0.87</math>); .11) <b>Control</b> <b>Events Total Wei S 169 100</b> 17 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10</b></td> <td>Vascular Er. 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these conclusions. We recommend that additional multicenter, high-quality randomized controlled studies are needed.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s

# **AUTHOR CONTRIBUTIONS**

HK and QZ designed the research subject. HK and GZ conducted literature retrieval and screening, and BH and YZ provided

guidance in statistical analysis. HK wrote the manuscript. QZ critically revised the manuscript. All authors read and approved the final manuscript.

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# SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped. 2021.631673/full#supplementary-material

## REFERENCES

- Chen M, Citil A, McCabe F, Leicht KM, Fiascone J, Dammann CE, et al. Infection, oxygen, and immaturity: interacting risk factors for retinopathy of prematurity. *Neonatology*. (2011) 99:125–32. doi: 10.1159/000 312821
- Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Pretermassociated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. *Pediatr Res.* (2013) 74(Suppl. 1):35–49. doi: 10.1038/pr.2013.205
- Fielder A, Blencowe H, O'Connor A, Gilbert C. Impact of retinopathy of prematurity on ocular structures and visual functions. *Arch Dis Child Fetal Neonatal Ed.* (2015) 100:F179–84. doi: 10.1136/archdischild-2014-3 06207
- Petricli IS, Kara C, Demirel N, Ulubas Isik D, Bas AY. Retinopathy of prematurity in extremely premature infants: multiple births versus single births. *Turk J Med Sci.* (2018) 48:131–5. doi: 10.3906/sag-17 06-52
- Hellgren G, Löfqvist C, Hård A-L, Hansen-Pupp I, Gram M, Ley D, et al. Serum concentrations of vascular endothelial growth factor in relation to retinopathy of prematurity. *Pediatric Res.* (2016) 79):70–5. doi: 10.1038/pr.2015.181
- Chan-Ling T, Gole GA, Quinn GE, Adamson SJ, Darlow BA. Pathophysiology, screening and treatment of ROP: a multi-disciplinary perspective. *Prog Retin Eye Res.* (2018) 62:77–119. doi: 10.1016/j.preteyeres.2017. 09.002
- Wallace DK, Wu KY. Current and future trends in treatment of severe retinopathy of prematurity. *Clin Perinatol.* (2013) 40:297–310. doi: 10.1016/j.clp.2013.02.005
- Jamrozy-Witkowska A, Kowalska K, Jankowska-Lech I, Terelak-Borys B, Nowosielska A, Grabska-Liberek I. [Complications of intravitreal injectionsown experience]. *Klin Oczna*. (2011) 113:127–31.
- Morrison D, Shaffer J, Ying GS, Binenbaum G, Group G-Rop Study. Ocular complications following treatment in the postnatal growth and retinopathy of prematurity (G-ROP) study. J AAPOS. (2018) 22:128–33. doi: 10.1016/j.jaapos.2017.12.005
- Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med.* (2008) 358:2649–51. doi: 10.1056/NEJMc0708819
- Filippi L, Cavallaro G, Fiorini P, Daniotti M, Benedetti V, Cristofori G, et al. Study protocol: safety and efficacy of propranolol in newborns with Retinopathy of Prematurity (PROP-ROP): ISRCTN18523491. *BMC Pediatr.* (2010) 10:83. doi: 10.1186/1471-2431-10-83
- Buhrer C, Bassler D. Oral Propranolol: A New Treatment for Infants with Retinopathy of Prematurity? Neonatology. (2015) 108:49–52. doi: 10.1159/000381659
- International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol. (2005) 123:991–9. doi: 10.1001/archopht.123. 7.991
- Zhao J-G, Zeng X-T, Wang J, Liu L. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA*. (2017) 318:2466–82. doi: 10.1001/jama.2017.19344
- Ozturk MA, Korkmaz L. The efficacy of propranolol in very preterm infants at the risk of retinopathy of prematurity: which newborn and when? *Int Ophthalmol.* (2018) 39:1921–30. doi: 10.1007/s10792-018-1 018-8
- Korkmaz L, Bastug O, Ozdemir A, Korkut S, Karaca C, Akin MA, et al. The efficacy of propranolol in retinopathy of prematurity and its correlation with the platelet mass index. *Curr Eye Res.* (2016) 42:88–97. doi: 10.3109/02713683.2016.1158272
- Filippi L, Cavallaro G, Bagnoli P, Dal Monte M, Fiorini P, Donzelli G, et al. Oral propranolol for retinopathy of prematurity: risks, safety concerns, and perspectives. J Pediatr. (2013) 163:1570–7.e6. doi: 10.1016/j.jpeds.2013.07.049
- Makhoul IR, Peleg O, Miller B, Bar-Oz B, Kochavi O, Mechoulam H, et al. Oral propranolol versus placebo for retinopathy of prematurity: a pilot,

randomised, double-blind prospective study. *Arch Dis Child*. (2014) 98:565–7. doi: 10.1136/archdischild-2013-303951

- Sanghvi KP, Kabra NS, Padhi P, Singh U, Dash SK, Avasthi BS. Prophylactic propranolol for prevention of ROP and visual outcome at 1 year (PreROP trial). Archives of disease in childhood Fetal and neonatal edition. (2017) 102:F389-94. doi: 10.1136/archdischild-2016-3 11548
- Sun H, Li M, Yu Z, Xing S, Yuan M, Cheng P. The efficacy and safety of oral propranolol in the treatment of retinopathy of prematurity. *Chin J Neonatol.* (2018) 033:P.266–70. doi: 10.3760/cma.j.issn.2096-2932.2018.04.007
- Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. *Lancet*. (2013) 382:1445–57. doi: 10.1016/S0140-6736(13)60178-6
- Miller JW, Le Couter J, Strauss EC, Ferrara N. Vascular endothelial growth factor a in intraocular vascular disease. *Ophthalmology*. (2013) 120:106–14. doi: 10.1016/j.ophtha.2012.07.038
- Dorrell MI, Aguilar E, Scheppke L, Barnett FH, Friedlander M. Combination angiostatic therapy completely inhibits ocular and tumor angiogenesis. *Proc Natl Acad Sci USA*. (2007) 104:967–72. doi: 10.1073/pnas.0607542104
- 24. Dal Monte M, Filippi L, Bagnoli P. Beta3-adrenergic receptors modulate vascular endothelial growth factor release in response to hypoxia through the nitric oxide pathway in mouse retinal explants. *Naunyn Schmiedebergs Arch Pharmacol.* (2013) 386:269–78. doi: 10.1007/s00210-012-0828-x
- Ristori C, Filippi L, Dal Monte M, Martini D, Cammalleri M, Fortunato P, et al. Role of the adrenergic system in a mouse model of oxygen-induced retinopathy: antiangiogenic effects of beta-adrenoreceptor blockade. *Invest Ophthalmol Vis Sci.* (2011) 52:155–70. doi: 10.1167/iovs.10-5536
- 26. Martini D, Monte MD, Ristori C, Cupisti E, Mei S, Fiorini P, et al. Antiangiogenic effects of  $\beta 2$  -adrenergic receptor blockade in a mouse model of oxygen-induced retinopathy. *J Neurochem.* (2011) 119:1317–29. doi: 10.1111/j.1471-4159.2011.07530.x
- Filippi L, Cavallaro G, Berti E, Padrini L, Araimo G, Regiroli G, et al. Propranolol 0.2% eye micro-drops for retinopathy of prematurity: a prospective phase IIB study. *Front Pediatr.* (2019) 7:180. doi: 10.3389/fped.2019.00180
- Sidbury R. Update on vascular tumors of infancy. *Curr Opin Pediatr.* (2010) 22:432–7. doi: 10.1097/MOP.0b013e32833bb764
- Filippi L, Gozzini E, Daniotti M, Pagliai F, Catarzi S, Fiorini P. Rescue treatment with terlipressin in different scenarios of refractory hypotension in newborns and infants. *Pediatr Crit Care Med.* (2011) 12:e237–41. doi: 10.1097/PCC.0b013e3181fe304c
- Harbison AL, Votava-Smith JK, Del Castillo S, Kumar SR, Lee V, Schmithorst V, et al. Clinical factors associated with cerebral metabolism in term neonates with congenital heart disease. *J Pediatr.* (2017) 183:67–73.e1. doi: 10.1016/j.jpeds.2016.12.061
- Kaempfen S, Neumann RP, Jost K, Schulzke SM. Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants. *Cochrane Database Syst Rev.* (2018) 3:CD011893. doi: 10.1002/14651858.CD011893.pub2
- 32. Stritzke A, Kabra N, Kaur S, Robertson HL, Lodha A. Oral propranolol in prevention of severe retinopathy of prematurity: a systematic review and meta-analysis. *J Perinatol.* (2019) 39:1584–94. doi: 10.1038/s41372-019-0503-x
- Bancalari A, Schade R, Lazcano C, Muñoz T, Sepúlveda G. Treatment of retinopathy of prematurity with propranolol: randomized control trial. *E-PAS*. (2018) 2665.
- Gibbs ME, Hutchinson DS, Summers RJ. Noradrenaline release in the locus coeruleus modulates memory formation and consolidation; roles for alpha- and beta-adrenergic receptors. *Neuroscience*. (2010) 170:1209–22. doi: 10.1016/j.neuroscience.2010.07.052
- Romano MR, Biagioni F, Besozzi G, Carrizzo A, Vecchione C, Fornai F, et al. Effects of bevacizumab on neuronal viability of retinal ganglion cells in rats. *Brain Res.* (2012) 1478:55–63. doi: 10.1016/j.brainres.2012.08.014
- Padrini L, Isacchi B, Bilia AR, Pini A, Lanzi C, Masini E, et al. Pharmacokinetics and local safety profile of propranolol eye drops in rabbits. *Pediatr Res.* (2014) 76:378–85. doi: 10.1038/pr.2014.108
- 37. Filippi L, Cavallaro G, Bagnoli P, Dal Monte M, Fiorini P, Berti E, et al. Propranolol 0.1% eye micro-drops in newborns with retinopathy

of prematurity: a pilot clinical trial. *Pediatr Res.* (2017) 81:307–14. doi: 10.1038/pr.2016.230

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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