CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Acute, Sustained, Intraocular Pressure increases following Anti-Vascular Endothelial Growth Factor Treatment for Retinal Conditions: A Review of Clinical Evidence and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	February 5, 2019
Report Length:	23 Pages

CADTH

Authors: D. Williams, Charlene Argáez

Cite As: Acute, Sustained, Intraocular Pressure increases following Anti-Vascular Endothelial Growth Factor Treatment for Retinal Conditions: A Review of Clinical Evidence and Guidelines. Ottawa: CADTH; 2018 Oct (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to Requests@CADTH.ca

Abbreviations

AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
CMT	Central macular thickness
CRVO	choroidal vein occlusion
CST	central subfield thickness
DEX	dexamethasone
DME	Diabetic macular edema
IOP	intraocular pressure
IVA	Intravitreal aflibercept
IVB	intravitreal bevacizumab
IVP	Intravitreal pegaptanib sodium
IVR	Intravitreal ranibizumab
IVTA	intravitreal triamcinolone acetonide
MGLA	macular grid laser photocoagulation augmentation
OHT	ocular hypertension
RCT	randomized controlled trials
VEGF	vascular endothelial growth factor

Context and Policy Issues

Vascular endothelial growth factor (VEGF) is a protein that is upregulated as a result of capillary dropout, hypoxia, and local inflammation secondary to increased intraluminal venous pressure from retinal vein compression and other forms of vascular occlusion such as branch retinal vein occlusion (BRVO) and choroidal retinal vein occlusion (CRVO).[1] VEGF is linked to the development of retinal diseases like age-related macular degeneration (AMD) and macular edema which are leading causes of vision loss.[2,3]

AMD and macular edema have been the target of several therapeutic developments including non-pharmaceutical options such as, macular grid laser photocoagulation augmentation (MGLA), laser-induced chorioretinal anastomosis, and surgery (e.g., pars plana vitrectomy).[1] Pharmaceutical options are primarily corticosteroids and anti-VEGF agents. Steroids such as, triamcinolone and dexamethasone (DEX) function by decreasing inflammation and edema through the modulation of vascular permeability and inflammatory agents like VEGF.[1] Common anti-VEGF agents are aflibercept , bevacizumab, pegaptanib sodium, and ranibizumab. Aflibercept (115 kDa) is a soluble recombinant decoy receptor fusion protein, bevacizumab (149 kDa) is a recombinant full-length humanized monoclonal immunoglobulin G1 antibody, pegaptanib sodium is a selective antagonist, while ranibizumab (48 kDa) is a recombinant humanized immunoglobulin G1 kappa isotype antibody fragment.[1,3] In the Health Canada drug product database, aflibercept and ranibizumab are listed as antineovascularization agents, bevacizumab is listed as an antineoplastic, and pegaptanib sodium is listed as an anti-VEGF agent for AMD.[4]

Anti-VEGF agents are linked to a number of adverse effects such as, sustained elevated intraocular pressure (IOP), endophthalmitis, cataract progression, vitreous hemorrhage, retinal tears and detachments, pain, vitreous floaters, and inflammation.[2,3] Patients may also experience non-ocular effects like hypertension, nasopharyngitis, and headache.[2] Sustained elevated IOP may self-resolve or may need to be controlled by additional anti-VEGF agents, IOP-lowering topical or oral medication (e.g., carbonic anhydrase inhibitor), or surgery (e.g., trabeculectomy, laser trabeculoplasty, laser peripheral iridotomy, or filtration surgery).[3]

The aim of this report is to summarize the evidence regarding risk factors that lead to acute, sustained IOP increases that require surgery following anti-VEGF intravitreal injection treatment for retinal disease, and to review the relevant evidence-based guidelines.

Research Questions

1. What is the evidence regarding risk factors that lead to acute sustained intraocular pressure increases requiring surgery following anti-VEGF intravitreal injection treatment for retinal disease?
2. What are the evidence-based guidelines regarding reducing the incidents of acute, sustained intraocular pressure increases following anti-VEGF intravitreal injection treatment for retinal disease?

Key Findings

Five relevant publications comprising one meta-analysis, two prospective randomized controlled trials, one retrospective non-randomized comparative study, and one retrospective non-comparative study were identified.

The evidence on the risk factors that lead to acute sustained intraocular pressure (IOP) increases (or sustained elevated IOP) requiring surgery following anti-vascular epithelial growth factor (VEGF) intravitreal injection treatment for retinal disease was inconclusive, primarily due to heterogeneity in the studies. Across the relevant studies, there was variation in the patient populations, the types of anti-VEGF agents used for treatment, compounding and administration of the agents, the comparators, and the length of follow-up. Importantly, studies reported on the incidence of elevated IOP that required any form of treatment as multiple management pathways are available for the condition. In addition to surgery, patients may be treated with medication, a combination of surgery and medication, or be put under observation.

Of the five relevant studies, one non-comparative study reported that surgical intervention (trabeculectomy) and medication were used together to control IOP in one patient with neovascular age-related macular degeneration, following treatment with single or combined doses of anti-VEGF agents. Given the low rate of elevated IOP that required surgery, the attendant risk factors could not be assessed.

No relevant evidence-based guidelines were identified.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and January 8, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients undergoing anti-VEGF therapy for the treatment of: • wet age related macular degeneration • diabetic macular edema • retinal vein occlusion
Intervention	bevacizumab, ranibizumab, aflibercept • delivered in prepared individual dose syringes (compounded); manufactured individual dose syringes; or drawn directly from vial immediately prior to use • using any syringe including diabetic insulin syringes, glass syringes • prepared immediately prior to use or stored prepared (up to 9 days) • delivered at intervals as per the product monograph, or at different intervals
Comparator	Any comparator, anti-VEGF vs anti-VEGF, different dosing or injection strategies of the same anti-VEGF, no comparator
Outcomes	Q1: acute sustained increase in intraocular pressure requiring surgical intervention post anti-VEGF intravitreal injection (risk factors could include: frequency of injection; total number of injections per patient; pre-existing glaucoma; retinal disease indication being treated; anti-VEGF drug being injected; storage process for syringes [freeze/thaw during delivery or length of time anti-VEGF drug stored in syringe];presence of silicone in the syringe; other) Q2: guidelines regarding reducing the incidents of acute sustained intraocular pressure post anti-VEGF intravitreal injection treatment of retinal disease [could include: early treatment of glaucoma with ocular anti-hypertensives; impact of thickness of central cornea on interpreting IOP and the decision for early IOP treatment; other]; regarding indications or contraindications for the injections based on those risk factors
Study Designs	Systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, guidelines

IOP = intraocular pressure; VEGF = vascular endothelial growth factor

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicates or if they were published prior to 2008. Relevant systematic reviews (SRs) were excluded if all of the primary studies were reported in one or more of the other relevant systematic reviews. Relevant randomized controlled trials (RCTs) were excluded if they were reported in an included systematic review.

Critical Appraisal of Individual Studies

All studies were critically appraised by one reviewer. The included systematic review was critically appraised using AMSTAR 2,[5] and the primary studies were critically appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 723 citations were identified in the literature search. Following screening of title and abstracts, 688 citations were excluded and 35 potentially relevant reports from the electronic search were retrieved for full-text review. Fifteen potentially relevant publications were retrieved from the grey literature search for full-text review. Of the 50 potentially relevant articles, 45 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[7] flowchart of the study selection. An additional reference of potential interest is provided in Appendix 5.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2, Table 2, Table 3, and Table 4.

Study Design

One meta-analysis,[8] two prospective randomized controlled trials (RCTs),[9,10] one retrospective non-randomized comparative study,[11] and one retrospective non-comparative study[12] were included in this review. The meta-analysis was published in 2018,[8] one of the RCTs[9] and the non-randomized study were published in 2015,[11] the second RCT was published in 2012,[10] and the non-comparative study was published in 2011.[12] The meta-analysis synthesized data from a systematic review that involved searches of PubMed, Embase, the Cochrane Library, and the clinicaltrials.gov database, from inception to August 2017.[8] The authors included four RCTs published between 2014 and 2017 with populations ranging in size from 20 to 363 patients.[8] They assessed the methodological quality of the included RCTs using the GRADE methodology.[8]

Country of Origin

The meta-analysis was published by authors in China,[8] the RCTs were published by authors in Kuwait[9] and in India,[10] and the two retrospective studies were published in the United States.[11,12]

Patient Population

The meta-analysis included 521 patients who had macular edema from BRVO or CRVO.[8] The mean ages of the study groups in three of the four RCTs that were included in the meta-analysis ranged between 61.2 to 65 years.[8] The mean age of patients enrolled in the fourth study that was included in the meta-analysis was not reported.[8] The authors of the meta-analysis did not specify where patients were treated.

One RCT enrolled 44 patients with DME[9] and the other enrolled 60 patients with diffuse DME.[10] In the first study, the mean age of the intervention group of 22 patients was 53.8 ± 5.57 years while that of the comparator group of 22 patients was 54 ± 4.33 years.[9] The mean age of all the patients in the second RCT was 53.7 ± 5.9 years.[10]

The retrospective comparative study included 740 eyes of 634 patients with neovascular AMD and a mean age of 78.6 years.[11] The retrospective non-comparative study included 155 eyes of 127 patients with neovascular AMD and a mean age was 81 ± 10 years.[12] All patients who were included in the primary studies were treated at specialist eye centres.[9-12]

Interventions and Comparators

In all of the included studies intravitreal anti-VEGF was administered to one or more groups of enrolled patients. The meta-analysis included data from 75 patients treated with intravitreal bevacizumab (IVB), 182 patients treated with intravitreal ranibizumab (IVR) and 264 patients who received the dexamethasone (DEX) implant[8]

In one RCT, patients in one group received three doses of 1.25 mg in 0.05 mL IVB, injected 30 days apart, while those in the comparator group had pars plana vitrectomy with induction of a posterior vitreous detachment followed by 0.5 mg in 1 mL indocyanine green (IC-Green Akorn, Inc., United States) assisted internal limiting membrane peeling.[9]

In the second RCT, patients were randomly assigned to receive 1.25 mg in 0.05 mL IVB, 4 mg in 0.1 mL intravitreal triamcinolone acetonide (IVTA) (Kenalog), or modified early treatment diabetic retinopathy study (ETDRS) MGLA.[10] For five days following treatment, all patients in the first two groups were prescribed topical moxifloxacin 0.5% four times daily.[10] Patients with a two line decrease in the best corrected visual acuity (BCVA) from the baseline, increasing leakage on fundus fluorescein angiography, or a 100 µ increase in the central macular thickness (CMT) on optical coherence tomography (OPT) were retreated.[10] A single experienced examiner performed MGLA on patients in the comparator group, with a spot size of 100 µ, a pulse of 100 ms, and at 50 to 100 mW, titrated to produce mild intensity burns in areas showing diffuse leakage.[10] On average, patients received 2.7 ± 0.4 IVB injections, 1.4 ± 0.2 IVTA injections, and 1.8 ± 0 (grid) laser treatments.[10]

In the comparative retrospective study, the authors recruited patients at two eye centres: at one centre, patients received prepackaged bevacizumab while at the other centre, bevacizumab was freshly prepared on-site.[11] In its prepackaged form, bevacizumab was compounded at an off-site pharmacy certified by the Pharmacy Compounding Accreditation Board with a Lo-Dose 3/10 mL U-100 insulin syringe (Becton-Dickinson, New jersey, United States) permanently attached to a 31-gauge and 5/16 inch needle.[11] The syringes were shipped overnight in an insulated, temperature-controlled container.[11] In its freshly prepared form, bevacizumab was compounded at the on-site hospital pharmacy and extracted from its original glass vial with a preassembled 25-gauge x 5/8 inch nonfiltered BD PrecisionGlide needle attached to 1 mL U-100 insulin syringes (Becton-Dickinson, Franklin Lakes, NJ).[11] The syringes were capped with a B Braun (Bethlehem, PA) red replacement cap, and stored in a refrigerator in the eye clinic for a maximum of 9 days.[11] Patients were injected monthly with 1.25 mg in 0.05 mL bevacizumab for three months using a 30-gauge and 5/16 inch BD PrecisionGlide needle.[11] Additional injections were administered as-needed based on response to treatment; on average patients received 8.8 IVB injections.[11] An aseptic technique was used with topical 0.5% proparacaine or subconjunctival 2% lidocaine and 5% povidone-iodine drops.[11]

In the second retrospective study,[12] patients received intravitreal injections of 0.5 mg in 0.1 mL ranibizumab, 1.25 mg in 0.1 mL bevacizumab, and/or 1.6 mg in 0.09 mL pegaptanib.[12] Anesthesia was administered through subconjunctival lidocaine injection or applied with a sterile cotton-tipped applicator soaked with topical 0.5% tetracaine over the intended injection site for three minutes.[12]

Outcomes

The outcomes of interest were the relative risk of elevated IOP,[8] incidence of high (i.e., elevated) IOP needing further treatment,[9] incidence of IOP increase (or rise) from baseline that required treatment,[10] incidence of sustained elevated IOP,[12] incidence of sustained

OHT,[11] and use of surgical intervention (with or without medication) to control sustained elevated IOP.[9-12]

IOP measurements were taken with a Goldmann applanation tonometer (Haag Streit USA and Reliance Medical Products, Mason, OH)[10] or a Reichert Tono-Pen XL (Reichert Inc, Depew, NY).[11,12] For IOP measurements greater than 25 mmHg, confirmatory Goldmann applanation tonometry measurements were taken in place of Tono-Pen measurements.[11,12]

For the authors of the meta-analysis, elevated IOP was reported when IOP measurements were greater than 21 mmHg, required glaucoma agents to control, or when IOP increased by at least 5 mmHg from baseline.[8] Although the authors did not describe elevated IOP as "sustained", the study was included in this review because patients were followed for six, seven, or 12 months after treatment.

Change in IOP from baseline was assessed two months after the last of three injections in one RCT[9] and at one, three, and six months following treatment in the second RCT.[10] In these studies, the authors did not report what threshold they used to determine when a patient had high IOP. These studies did not define their measurements as "sustained"; however, given the lengths of the follow-up periods, their results were considered relevant to the research questions.

In one retrospective study, sustained OHT was measured on average 29.4 months after treatment and was defined as an IOP measurement greater than 25 mmHg on two consecutive visits with an increase of at least 6 mmHg from baseline or a single IOP measurement greater than 25 mmHg with an increase from baseline of at least 6 mmHg and initiation of IOP-lowering therapy.[11] In the second retrospective study, IOP measurements were recorded at a median of 30.9 ± 16.3 months and sustained elevated IOP was indicated as IOP measurements greater than 25 mmHg on at least two separate visits or any IOP measurement greater than 25 mmHg that required glaucoma medication or glaucoma surgery.[12]

The risk factors for sustained OHT were assessed in the retrospective non-randomized study; however, none of the patients required surgery.[11]

Other outcomes related to vision (e.g., change in best-corrected visual acuity) and physical characteristics (e.g., change in central macular thickness) that were reported in the studies were not included in this report.

Summary of Critical Appraisal

A summary of the critical appraisal of the studies is summarized below and details are available in Appendix 3, Table 5, Table 6, and Table 7.

Systematic Review

The systematic review was critically appraised using the AMSTAR 2 checklist.[5] The review had numerous strengths such as following the Cochrane methodology, describing the patients, interventions, comparators, and outcomes, selecting studies and extracting data in duplicate and resolving disagreements by consensus, assessing the quality of individual studies, and accounting for risk of bias when discussing the results. In addition, the GRADE methodology was used to evaluate the quality of the evidence for each outcome. Following the Cochrane methodology implies that the authors developed a protocol *a priori* and as such reduced the risk of bias in conducting the review.[5] Duplicate study selection and data

extraction are considered best practices for conducting reviews as it limits propagating biases from a single reviewer.[5] Regarding the quality of the evidence on sustained elevated IOP, the review authors indicated that there was no serious inconsistency, no serious indirectness, and no serious imprecision across the four included RCTs but suggested that there was reporting bias due to small study sizes, industry sponsorship, or other conflicts of interest.[8]

In terms of limitations, the authors reported on the risk of sustained elevated IOP that in some cases required glaucoma agents, but they did not indicate whether surgical intervention was required.[8] The authors did not provide a list of excluded studies and sources of funding for the review and the included studies were not disclosed.

Randomized Controlled Trials

The RCTs[9,10] were appraised with the Downs and Black checklist.[6] Authors of both RCTs clearly described their objectives, inclusion and exclusion criteria, interventions being compared, and the main findings. Clear descriptions facilitated an unbiased assessment of the findings of the study.[6] They enrolled patients prospectively, used appropriate statistical tests to assess the main outcomes, and used similar follow-up periods for all enrolled patients. Enrolling patients prospectively and using similar follow-up periods reduce (though, they do not entirely eliminate) bias in the selection of study patients, while using appropriate statistical tests to assess the main outcomes helps in validating the significance of the comparisons between the study groups.[6] Both studies had more limitations than strengths. The lack of information on the location where patients were recruited, the proportion of the source population that was recruited, and whether patients who were included in the studies were representative of the entire population from which they were selected presented risks to external validity. There was insufficient[10] or no information[9] on blinding and compliance with the interventions and comparators. The process that was used to randomize patient enrollment was not described in either of the studies[9,10] and authors of one study did not discuss statistical power.[10] Without a discussion of statistical power, it is unclear whether the study was designed to adequately determine statistically relevant differences in outcomes between the intervention and the comparator groups.

Non-randomized Studies

The non-randomized studies[11,12] were also appraised with the Downs and Black checklist.[6] Strengths common to both studies were that the study objective, main outcomes, included patients' characteristics, interventions being compared, and the main findings were described clearly.[11,12] Patients were treated at specialist eye centres, strengthening external validity of the results.[11,12] Internal validity was enhanced as the period between the intervention and outcome was the same for each patient.[11,12] In one of the studies, risks to internal validity due to confounding were limited by recruiting patients for both the intervention and comparator groups from the same population.[12] The other study was powered to detect statistically relevant differences.[11]

The studies had comparable limitations.[11,12] Patients were retrospectively selected and it was unclear whether those who were included were representative of the entire population from which they were selected.[11,12] Patients were not randomly assigned to the intervention and comparators increasing the risk of internal validity due to confounding in the comparative study.[11]

Summary of Findings

Table 8, Table 9, and Table 10 of Appendix 4 present the main study findings and authors' conclusions.

Incidence of elevated IOP requiring treatment

Based on low quality data, the authors of the meta-analysis of results from four RCTs involving 521 patients indicated that the incidence of elevated IOP was higher in 264 patients treated with DEX (38.3%) than in 257 patients treated with IVB or IVR (7.8%).[8] The authors did not indicate whether medication was administered or surgery was conducted to control elevated IOP.[8] After treatment, patients were followed for six in two RCTs, seven in one, and 12 months in the fourth.[8]

In the RCTs, none (0%) of the patients (22 with DME refractory to laser photocoagulation[9] and 20 with diffuse DME[10]) who were treated with IVB (125 mg/0.05 mL), pars plana vitrectomy (22 patients)[9] or MGLA (20 patients)[9] experienced elevated absolute IOP[9] or an increase in IOP from baseline[10] that required any form of treatment. In comparison, 10 (50%) out of 20 patients who were treated with IVTA experienced a high increase in IOP from baseline and required IOP-lowering medication.[10] None of the patients with DME needed surgical intervention to control sustained elevated IOP following IVB treatment.[9,10] Patients were followed for approximately six months.[9,10]

Ten (2.9%) out of 339 patients with neovascular AMD who received prepackaged IVB (125 mg in 0.05 mL) experienced sustained OHT compared with four out of 401 (1%) of patients who received freshly prepared IVB (125 mg in 0.05 mL).[11] Of the 14 (1.9%) out of 740 patients who experienced sustained OHT following either prepackaged or freshly prepared IVB, none required surgery to control IOP.[11] These patients were enrolled at two different eye centres over the span of two years and were not randomly assigned to treatment groups.[11] Patients were followed for 29.4 months on average.[11]

In another group of 127 patients with neovascular AMD who were treated with single or combined doses of IVB, IVP, and IVR, eight (5.2%) out of 155 eyes had sustained elevated IOP that required treatment;[12] one (0.8%) required medication and surgical intervention (trabeculectomy) to control the sustained increase in IOP.[12] The authors of the study did not indicate which single anti-VEGF agents or combinations of anti-VEGF agents these patients received.[12] Patients were followed for a median of 30.9 ± 16.3 months.[12]

Risk factors for sustained OHT (not requiring surgery)

The authors of the non-randomized comparative study assessed the impact of preexisting glaucoma and the number of anti-VEGF injections on sustained OHT.[11] The incidence of sustained OHT was significantly higher in eyes with pre-existing glaucoma compared with eyes without pre-existing glaucoma In addition, the incidence of sustained OHT was significantly higher in eyes without pre-existing glaucoma that received 11 or more injections compared with eyes that received fewer injections.[11] For eyes with pre-existing glaucoma, the number of injections did not significantly affect the incidence of sustained OHT.[11] Incidence of sustained OHT was not linked to lens status or history of YAG capsulotomy.[11]

None of the studies reported on risk factors for sustained elevated IOP requiring surgery specifically.[8-12]

Guidelines

No relevant guidelines regarding reducing the incidents of acute sustained elevated IOP post anti-VEGF intravitreal injection treatment of retinal disease met the inclusion criteria.

Limitations

The body of evidence on the risk factors associated with the use of anti-VEGF in patients with retinal diseases with respect to sustained elevated IOP requiring surgery has limitations that warrant caution when interpreting the results of this report. A major limitation of this report is the indirectness of the outcomes of the studies and their relevance to the research questions. The primary outcomes pertained to clinical effectiveness measures such as best-corrected visual acuity and central macular thickness, while incidence of sustained elevated IOP requiring surgery following anti-VEGF intravitreal injection treatment for retinal disease and the risk factors linked to anti-VEGF agents were secondary outcomes. This means that the outcomes of interest in this report were not the primary focus of the included studies. The studies may not have been optimally designed to assess the outcomes of interest. Another major limitation is that none of the studies included aflibercept, as such, no comments can be made about its effect on sustained elevated IOP and its related risk factors.

Another limitation is the lack of common definitions or metrics across the studies. There was some heterogeneity in the definition of elevated IOP that required treatment: some studies referred to the absolute IOP value, others referred to the change in IOP from baseline, and some referred to both. Furthermore, two thresholds were used to diagnose IOP that required treatment: absolute IOP greater than 21 mmHg[8] or greater than 25 mmHg[11,12]; and change in IOP from baseline of at least 5 mmHg[8] or at least 6 mmHg[11]. Two of the studies did not provide thresholds for elevated IOP requiring treatment.[9,10] Finally, follow-up periods for ascertaining that the increase in IOP was *sustained* varied considerably from an average of approximately six months[9,10] to a median of 30.9 ± 16.3 months.[12] Given the wide range in follow-up periods different effects of treatment may have been measured.

Conclusions and Implications for Decision or Policy Making

Five relevant publications comprising one meta-analysis,[8] two prospective randomized controlled trials,[9,10] two non-randomized studies, one retrospective non-randomized comparative study,[11] and one retrospective non-comparative study[12] were identified. The findings from this review suggest that there is insufficient evidence to make firm, comprehensive conclusions about the risk factors that lead to acute sustained IOP increases (or sustained elevated IOP) requiring surgery following anti-VEGF intravitreal injection treatment of retinal disease. Caution should be taken in interpreting the evidence due to the limited quantity of studies available; their respective limitations; and the heterogeneity in the patient population, definitions of elevated IOP, follow-up periods, and outcomes reported.

The results from the meta-analysis suggest that patients treated with DEX implants are at a higher risk of sustained elevated IOP than patients treated with anti-VEGF agents, while one small randomized controlled study involving 60 patients indicated that more patients treated with IVTA experienced high changes in IOP from baseline than patients treated with IVB or with grid laser augmentation.

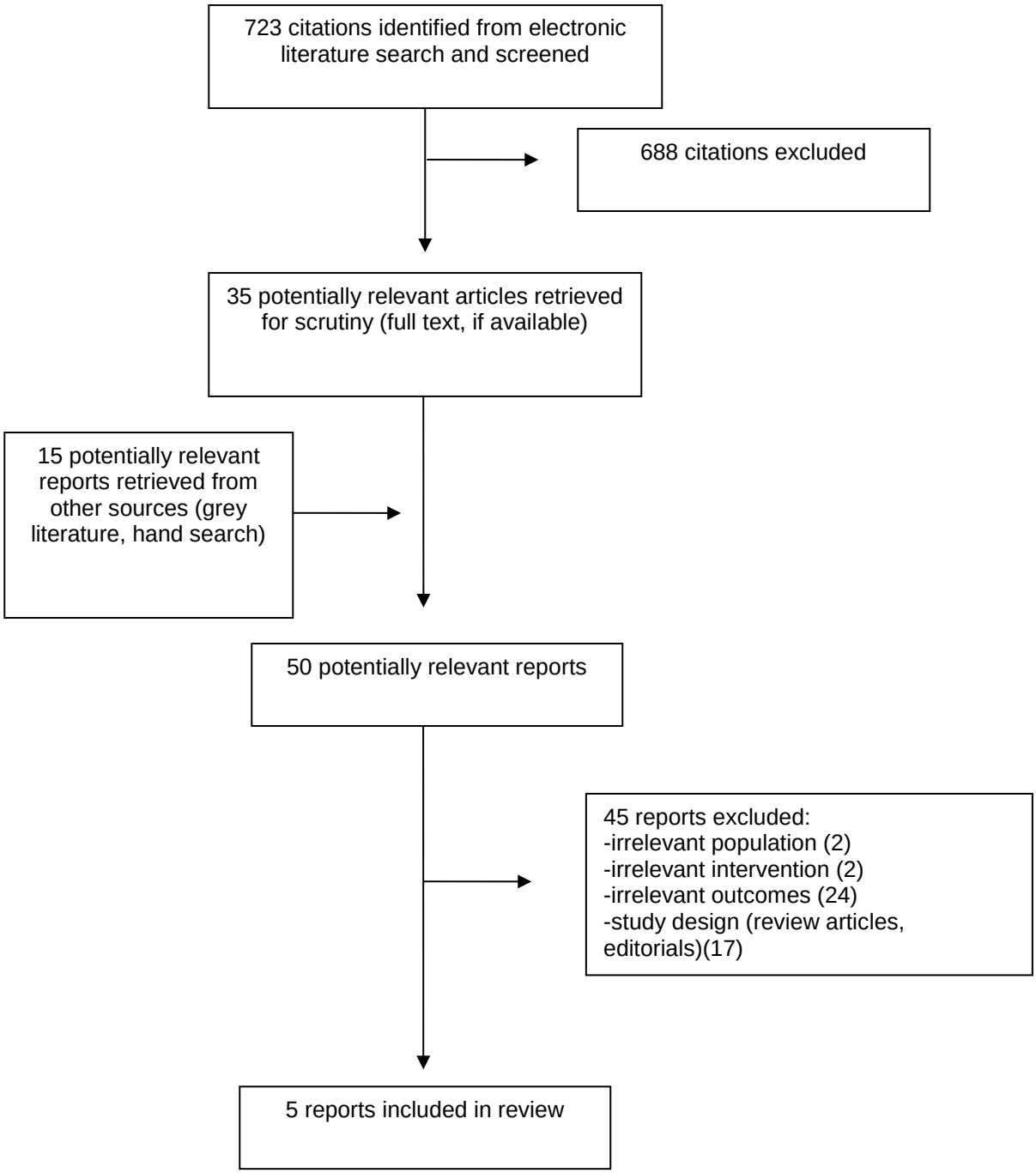
The use of surgical intervention to control sustained elevated IOP was negligible overall. Out of the five studies only one non-comparative study reported that surgical intervention (trabeculectomy) was used together with medication to control sustained elevated IOP in one patient (0.6%) out of 127 patients with neovascular AMD who were treated with single or combined doses of IVB, IVP, and IVR.[12] Across the included studies, the incidence of sustained elevated IOP requiring any form of treatment following anti-VEGF injections ranged from 0% in two studies involving 42 patients with DME treated with IVB,[9,10] to 5.2% (out of 155 eyes) in the group of 127 patients with neovascular AMD.[12] Given that only one patient across all of the studies was treated with surgery, it appears that other forms of treatment such as medication were used more frequently to control sustained elevated IOP in patients with DME and AMD following IVB, IVP, and IVR.

More research may be needed to understand when sustained elevated IOP following anti-VEGF treatment requires surgical intervention before related risk factors can be assessed.

References

1. Ehlers JP, Kim SJ, Yeh S, et al. Therapies for macular edema associated with branch retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2017;124(9):1412-1423.
2. Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, Giraldez J. Ranibizumab for neovascular age-related macular degeneration. *Am J Health Syst Pharm.* 2008;65(19):1805-1814.
3. Dedania VS, Bakri SJ. Sustained elevation of intraocular pressure after intravitreal anti-VEGF agents: what is the evidence? *Retina.* 2015;35(5):841-858.
4. Health Canada. Drug Product Database online query. 2018; https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Feb 5.
5. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
6. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
7. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
8. He Y, Ren XJ, Hu BJ, Lam WC, Li XR. A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema. *BMC Ophthalmol.* 2018;18(1):121.
9. Raizada S, Al Kandari J, Al Diab F, Al Sabah K, Kumar N, Mathew S. Pars plana vitrectomy versus three intravitreal injections of bevacizumab for nontractional diabetic macular edema. A prospective, randomized comparative study. *Indian J Ophthalmol.* 2015;63(6):504-510.
10. Azad R, Sain S, Sharma YR, Mahajan D. Comparison of intravitreal bevacizumab, intravitreal triamcinolone acetonide, and macular grid augmentation in refractory diffuse diabetic macular edema: A prospective, randomized study. *Oman J Ophthalmol.* 2012;5(3):166-170.
11. Storey PP, Ho V, Yeh S, et al. Incidence of sustained ocular hypertension using prepackaged versus freshly prepared intravitreal bevacizumab for neovascular age-related macular degeneration. *Retina.* 2015;35(10):1992-2000.
12. Choi DY, Ortube MC, McCannel CA, et al. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. *Retina.* 2011;31(6):1028-1035.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
He, 2018,[8] China	Systematic review and meta-analysis of RCTs published in PubMed, Embase, the Cochrane Library, and clinicaltrials.gov from inception to August 2017; included four RCTs	521 patients with macular edema due to BRVO and CRVO Age range: NR	Interventions (n = 257): any dose of IVB (n = 75), IVR (n = 182) Comparator (n = 264): DEX implant	Relative risk of elevated IOP (i.e., IOP > 21 mmHg, required glaucoma agents for IOP control, or IOP elevation by at least 5 mmHg from baseline) Measures of BCVA, change in BCVA, CST, changes in CST, CMT, incidence of serious adverse events, incidence of cataracts, number of injections Follow-up period: 6, 7, or 12 months

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CMT = central macular thickness; CRVO = Central retinal vein occlusion; CST = central subfield thickness; DEX = dexamethasone; DME = diabetic macular edema; IOP = intraocular pressure; IVB = intravitreal bevacizumab; IVR = ranibizumab; NR = not reported; RCT = randomized controlled trial

Table 3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Raizada, 2015[9] Kuwait	Prospective, randomized comparative study	44 patients diagnosed with diabetes mellitus, and with clinical and angiographic evidence of DME refractory to laser photocoagulation (last laser session ≥ 3 months before study enrollment) Mean age: 53.8 ± 5.57 years in the intervention group; 54 ± 4.33 years in the comparator group; % females NR	Intervention (n = 22 eyes): IVB (Avastin; Genetech; California, US) 1.25 mg/0.05 mL; three injections were administered 30 days apart Comparator (n = 22 eyes): Pars plana vitrectomy and enhanced internal limiting membrane peeling	Secondary outcomes: incidence of complications including high IOP requiring further treatment, use of surgical intervention to control IOP Measures of primary outcomes (BCVA, CMT) and adverse events are not included in this report Follow-up period: 2 months (after third injection) and reported as 5.81 ± 1.46 months in the intervention

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
				group and 5.36 ± 1.60 months in the comparator group
Azad, 2012,[10] India	Single-centre, prospective, randomized, comparative study	60 eyes of 60 patients with diffuse DME and CMT > 250 microns on time domain-optical coherence tomography without any evidence of vitreo-retinal traction and having good metabolic control (HbA1c < 7.0%) Mean age: 53.7 ± 5.9 years; 42% females	Intervention (n = 20): IVB (Avastin; Genetech; Illinois, US) 1.25 mg/0.05 mL Comparator 1 (n = 20): IVTA (Kenalog) 4 mg/0.1 mL Comparator 2 (n = 20): Modified macular grid laser photocoagulation augmentation.	Incidence of rise in IOP, surgical intervention to control IOP Measures of BCVA, presence of cataract, CMT, metabolic control, and adverse events are not included in this report Follow-up period: 1,3, and 6 months

BCVA = best corrected visual acuity; CMT = central macular thickness; DME = diabetic macular edema; IOP = intraocular pressure; IVB = intravitreal bevacizumab; IVTA = intravitreal triamcinolone acetonide; NR = not reported

Table 4: Characteristics of Included Non-Randomized Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Storey, 2015[11] United States	Dual-centre, retrospective, chart review	740 eyes of 634 patients with neovascular AMD treated with IVB between January 1, 2009 and December 31, 2011 at two centres Mean age: 78.6 years; 61.2% females	Intervention (n = 339 eyes): prepackaged IVB 1.25 mg/0.05 mL; 3 monthly injections with extended treatment as needed Comparator (n = 401 eyes): freshly prepared IVB 1.25 mg/0.05 mL; 3 monthly injections with extended treatment as needed	Incidence of sustained OHT; use of surgery to control IOP Assessment of risk factors (e.g., history of preexisting glaucoma, number of intravitreal injections, lens status, history of yttrium aluminum garnet capsulotomy, and history of intravitreal steroids) associated with sustained OHT is not included in this report because none of the patients required surgery to control elevated IOP Follow-up period (mean): 29.4 months

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Choi, 2011,[12] United States	Single-centre, retrospective, chart review	155 eyes of 127 patients with neovascular AMD treated with IVB, IVP, and/or IVR between 2005 and 2010 Mean age: 81 ± 10 years; 63% females	Interventions: IVB 1.25 mg/0.1 mL only (n = 61 eyes), IVP 1.6 mg/0.09 mL only (n = 6 eyes), IVR 0.5 mg/0.1 L only (n = 50 eyes), IVB + IVR (n = 28 eyes), IVP + IVR (n = 1 eye), IVB + IVP (n = 2 eyes), and IVB + IVP + IVR (n = 7 eyes) Comparator: None	Incidence of sustained elevated IOP that required treatment, use of medication + surgical intervention to control IOP Follow-up period (median): 30.9 ± 16.3 months for patients with elevated IOP measurements

AMD = age-related macular degeneration; IOP = intraocular pressure; IVB = intravitreal bevacizumab; IVP = intravitreal pegaptanib; IVR = ranibizumab; OHT = ocular hypertension

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Included Meta-Analysis using AMSTAR II[5]

Strengths	Limitations
He 2018,[8]	
• An explicit statement that the review methods were established *a priori* was not found. The study followed the Cochrane methodology. • The population, intervention, comparators, and outcomes were described • The review authors explained the process they used to select studies for inclusion. The review authors assessed all eligible studies independently and disagreements were resolved by consensus. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were RCTs. • The Cochrane Collaboration's tool was used to assess the quality (risk of bias) of the individual studies • The review authors accounted for risk of bias when discussing the results • The GRADE methodology was used to evaluate the quality of evidence on each outcome and the authors calculated heterogeneity in the data • The review authors declared that there were no conflicts of interest	• The authors reported on the incidence of sustained elevated IOP but did not indicate whether surgical intervention was required • A list of excluded studies was not provided (although reasons for exclusion were listed) • Sources of funding for the review and the included studies were not provided

IOP = intraocular pressure; RCT = randomized controlled trial

Table 6: Strengths and Limitations of Randomized Studies using the Downs and Black checklist[6]

Strengths	Limitations
Raizada et al., 2015[9]	
<u>Reporting</u> • The objective, inclusion and exclusion criteria, the interventions of interest, and the main findings of the study were clearly described <u>External validity</u> • Patients were prospectively enrolled <u>Internal validity - bias</u> • The statistical tests used to assess the main outcomes were appropriate • The period between the intervention and measurement of outcome was the same for each patient	<u>External validity</u> • The location where patients were recruited was not disclosed • The study did not report the proportion of the source population from which the patients were derived. • It is unclear whether the patients who were included in the study were representative of the entire population from which they were selected. <u>Internal validity - bias</u> • Blinding of patients and outcomes assessors were not discussed • Compliance with the intervention and comparator were not discussed

Strengths	Limitations
	Internal validity - confounding • The process used to randomize patient enrollment was not described Power • The study was not powered to assess systemic side-effects (according to the authors)
Azad et al., 2012[10]	
Reporting • The objective, inclusion and exclusion criteria, the interventions of interest, and the main findings of the study were clearly described External validity • Patients were prospectively enrolled Internal validity - bias • The statistical tests used to assess the main outcomes were appropriate • The period between the intervention and measurement of outcome was the same for each patient	External validity • The location where patients were recruited was not disclosed • The study did not report the proportion of the source population from which the patients were derived. • It is unclear whether the patients who were included in the study were representative of the entire population from which they were selected. Internal validity - bias • Although the reviewer was stated as being masked, no details were provided on blinding • Compliance with the intervention and comparator were not discussed Internal validity - confounding • The process used to randomize patient enrollment was not described Power • Statistical power was not discussed

Table 7: Strengths and Limitations of Non-Randomized Studies using the Downs and Black checklist[6]

Strengths	Limitations
Storey et al., 2015[11]	
Reporting • The objective, inclusion and exclusion criteria, the interventions of interest, and the main findings of the study were clearly described External validity • Patients were treated at two eye centres Internal validity - bias • The statistical tests used to assess the main outcomes were appropriate • The period between the intervention and measurement of outcome was the same for each patient	Reporting • Estimates of the random variability in the data were not reported for the outcomes of interest External validity • Patients were retrospectively selected. The study did not report the proportion of the source population from which the patients were derived. • It is unclear whether the patients who were included in the study were representative of the entire population from which they were selected. Internal validity - bias • Compliance with the intervention and comparator were not discussed

Strengths	Limitations
<u>Power</u> • The study was powered to detect differences with a statistical power of 80%	<u>Internal validity - confounding</u> • Patients were not randomized to intervention groups • Patients were recruited into the intervention group from a different city as patients recruited into the comparator group
Choi et al., 2011[12]	
<u>Reporting</u> • The objective, inclusion and exclusion criteria, the interventions of interest, and the main findings of the study were clearly described <u>External validity</u> • Patients were treated at one academic centre <u>Internal validity - bias</u> • The period between the intervention and measurement of the outcome of interest was the same for each patient	<u>Reporting</u> • Estimates of the random variability in the data were not reported for the outcomes of interest <u>External validity</u> • Patients were retrospectively selected. The study did not report the proportion of the source population from which the patients were derived. • It is unclear whether the patients who were included in the study were representative of the entire population from which they were selected. <u>Internal validity - bias</u> • No statistical tests were used to assess the outcome of interest • Compliance with the intervention was not discussed

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings of Included Meta-Analysis

Main Study Findings	Authors' Conclusion
He, 2018[8]	
DEX (n = 264) vs. Anti-VEGF (n = 257); 4 RCTs (heterogeneity I^2 = 43%, *P* = 0.15) Incidence of elevated IOP: 38.3% (101/264) vs. 7.8% (20/257) RR of elevated IOP: 4.14 (CI: 1.89 to 8.65; *P* = 0.0002); indicating that, compared with those treated with Anti-VEGF, patients treated with DEX had a statistically higher risk of elevated IOP	*"The groups receiving DEX had a higher risk of a rise in IOP and cataract progression than the anti-VEGF groups for DME. This suggests that the ophthalmologist should take care when using DEX implants in patients with high IOP or in young patients with a clear lens."* (p9)

CI = 95% confidence interval; DEX = dexamethasone; DME = diabetic macular edema; IOP = intraocular pressure; RCT = randomized controlled trial; RR = risk ratio; VEGF = vascular endothelial growth factor

Table 9: Summary of Findings of Included Randomized Controlled Trials

Main Study Findings	Authors' Conclusion
Raizada et al., 2015[9]	
1.25 mg/0.05 mL IVB (n = 22) vs. Pars plana vitrectomy and indocyanine green enhanced internal limiting membrane peeling (n = 22) Incidence of high IOP needing further treatment: 0 in both groups Use of surgical intervention to control elevated IOP: 0 in both groups as there was no incidence of high IOP that needed further treatment Measures of BCVA, CMT, and adverse events are not included in this report	*"Our study is limited by the small number of cases, and short follow-up period."*(p15)
Azad et al., 2012[10]	
1.25 mg/0.05 mL IVB (n = 20) vs. 4 mg/0.1 mL IVTA (n = 20) vs. grid laser augmentation (n = 20) Incidence of IOP increase from baseline that required treatment: 0% vs. 50% (10/20) vs. 0% Use of surgical intervention to control elevated IOP: 0 in all groups Measures of BCVA, presence of cataract, CMT, metabolic control, and adverse events are not included in this report	*"The effect of IVB lasts about 4-6 weeks and perhaps this would require a follow-up at second month postinjection as well for proper assessment of injection response. This along with a short follow-up duration of 6 months and limited sample size can be considered to be shortcomings of the study. The results of our study, however, revealed […] a benefit with both IVB and IVTA over grid laser augmentation for treatment of persistent refractory DME … in terms of both visual gain and reduction in central macular thickness. No significant ocular adverse events like IOP rise were noted in eyes injected with IVB. However, significant proportion of eyes treated with IVTA showed adverse ocular events. Hence, IVB may be a better alternative in treatment of refractory DME."*(p5)

BCVA = best corrected visual acuity; CMT = central macular thickness; DME = diabetic macular edema; IOP = intraocular pressure; IVB = intravitreal bevacizumab; IVTA = intravitreal triamcinolone acetonide

Table 10: Summary of Findings of Included Non-Randomized Studies

Main Study Findings	Authors' Conclusion
Storey et al., 2015[11]	
Prepackaged 125 mg/0.05 mL IVB (n = 339) vs. freshly prepared 125 mg/0.05 mL IVB (n = 401) Incidence of sustained OHT: 2.9% (10/339) vs. 1% (4/401; *P* = not significant) Use of surgery to control elevated IOP: 0 in both groups **Assessment of risk factors for sustained OHT (not requiring surgery)[a]** Incidence of sustained OHT was significantly higher for eyes with pre-existing glaucoma (4/81 eyes; 2.29% incidence per eye-year) compared with eyes without pre-existing glaucoma (10/659 eyes; 0.64% incidence per eye-year) (IRR = 3.58; CI, 1.09 to 11.81; *P* = 0.036). Incidence of sustained OHT was 0.66% (3 of 457) for eyes without pre-existing glaucoma receiving 1 to 10 injections compared with 3.5% (7 of 202) for eyes receiving 11+ injections (*P* = 0.011); indicating that there was a statistically significant difference between the groups. Incidence of sustained OHT was 4 of 65 (6.2%) for eyes with pre-existing glaucoma receiving 1 to 10 injections and 0 of 16 for eyes receiving 11+ injections (P = 0.58); indicating that there was no association between sustained OHT and number of intravitreal injections. Incidence of sustained OHT was not linked to lens status or history of YAG capsulotomy. Incidence of sustained OHT per eye-year, use of medication or observation to control IOP are not included in this report	*"previous studies have suggested that prepackaged bevacizumab may lead to higher rates of sustained OHT. Our study found a trend toward higher rates of sustained OHT in prepackaged bevacizumab compared with freshly prepared medication although the difference was not statistically or clinically significant. As a result, the method of preparation may not explain why some eyes develop sustained OHT after IVB injections. We believe that both preparations of bevacizumab can be safely used with similar low rates of ocular hypertensive effects in patients with neovascular AMD."*(p1999)
Choi et al., 2011[12]	
Various doses and combinations of IVB, IVP, and IVR Incidence of sustained elevated IOP that required treatment: 5.2% (8/155) Use of medication + surgical intervention (trabeculectomy) to control IOP: 1[b]	*"Our cases of sustained elevated IOP measurements certainly confirm the reports of others that sustained elevated IOP measurements can occur after anti-VEGFs."*(p1034) *"Limitations of this retrospective study include missing data and variability concerning treatment practices. Additionally, there are issues with variability with pressure measurements from the Tono-Pen…Clinicians should generally use at least two occasions of elevated IOP measurements before concluding that the pressure elevation is sustained and warrants ongoing therapy."*(p1035)

AMD = age-related macular degeneration; CI = 95% confidence interval; IOP = intraocular pressure; IRR = incidence risk ratio; IVB = intravitreal bevacizumab; IVP = intravitreal pegaptanib; IVR = ranibizumab; OHT = ocular hypertension

[a] Risk factors for sustained OHT requiring surgery were not reported in the study

[b] Intervention group was not indicated

CADTH

Appendix 5: Additional References of Potential Interest

Consensus-based guidelines

Grzybowski A, Told R., Sacu S., Bandello F., Moisseiev E., Loewenstein A., Schmidt-Erfurth U., on behalf of the Euretina Board. 2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations. 2018. Ophthalmologica 239: 181-193.