RETINAL VEIN OCCLUSIONS (RVO) PREFERRED PRACTICE PATTERNS (PPP) Philippines: 2016

The Retinal Vein Occlusions (RVO) Preferred Practice Patterns (PPP) Philippines: 2016 was prepared by the VitreoRetina Society of the Philippines (VRSP) for the Philippine Academy of Ophthalmology (PAO) Preferred Practice Patterns (PPP) of selected eye diseases.

The RVO PPP Philippines: 2016 was adapted from the American Academy of Ophthalmology (AAO) PPP for RVO 2015[1] and the Royal College of Ophthalmology Clinical Guidelines for Retinal Vein Occlusions July 2016[2]

The DR PPP Philippines: 2016 was reviewed and edited through correspondence by a Panel of Experts with interest in this condition. The panel then convened to draft the current manuscript.

This PPP will be updated on an ongoing basis.

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RETINAL VEIN OCCLUSIONS (RVO) PREFERRED PRACTICE PATTERNS (PPP) Philippines: 2016

Preferred Practice Patterns (PPP)

The Preferred Practice Patterns (PPP) for Retinal Vein Occlusions (RVO) were adapted from the American Academy of Ophthalmology (AAO) 2015[1] and the Royal College of Ophthalmology (RCO) Practice Guidelines for Retinal Vein Occlusions.[2] The practice patterns were assessed by a Panel of Experts composed of VitreoRetina Society (VRSP) members to be clinically relevant and specific enough to provide useful information to practitioners.

Preferred Practice Patterns (PPP) aim to provide guidance to practitioners for patient care. They do not aim to provide standards for the care of a particular individual. PPP cannot meet the needs of all patients. Adherence to this PPP will not ensure a successful outcome in every situation. It may be necessary to approach each patient's needs in different ways. The physician must make the ultimate decision about the propriety of care for every patient weighing all the presenting circumstances.

More complicated retinal vein occlusive diseases, are not covered by this PPP. It is recommended that other relevant sources of information should be referred to for guidance.

The PPP are not medical standards to be adhered to in all individual situations. The Philippine Academy of Ophthalmology and the Vitreo-Retina Society of the Philippines specifically disclaims any and all liability for injury or other damages of any kind resulting from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

It is essential to recognize that true medical excellence is achieved only when skills are applied in such a manner that patients' needs are the foremost consideration.

This PPP is designed to be a working document and will be updated on an ongoing basis.

PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades reported here have been adapted from the AAO PPP on RVO 2015[1] and the RCO Clinical Guidelines for RVO 2015.[2]

Details of these grading systems are reported in the Methods and Key to Ratings presented below.

Methods and Key to Ratings

Preferred Practice Patterns® should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[3] (SIGN) (I++; I+;I-;II++,II+; II-; III) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) . GRADE is a systematic approach to grading the strength of the total body of evidence (Good, Moderate, Insufficient) that is available to support recommendations on a specific clinical management issue (Strong, Discretionary)[4]. Organizations that have adopted GRADE include SIGN, the World Health Organization, and the Agency or Healthcare Research and Policy.[5]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.

- To rate individual studies, a scale based on SIGN[3] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or, RCTs with a very low risk of bias
I+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
II++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Non-analytic studies (e.g. case reports, case series)

- Recommendations for care are formed based on the body of evidence. The body of evidence quality ratings are defined by GRADE[4] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[4] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain-either because of low-quality evidence or because e evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points adapted from the AAO have been determined by the PPP Panel of Experts and VRSP Board of directors to be of particular importance to vision and quality of life outcomes

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE:[1]

The site of the occlusion, the extent and perfusion status (ischemic or non-ischemic) of the occlusion determine the prognosis of retinal vein occlusions (RVOs). Occlusions that are closer to the central vein have a worse prognosis.

Central retinal vein occlusions (CRVOs) are often associated with glaucoma. CRVOs have a higher risk of anterior segment neovascularization and neovascular glaucoma.

Branch retinal vein occlusions (BRVOs) and hemiretinal vein occlusions (HRVOs) have a visible arterio-venous crossing where the occlusion occurs. They are often associated with systemic hypertension, diabetes and lipid disorders. They are also more commonly associated with retinal neovascularization.

The common causes of decreased vision in both CRVOs and BRVOs are ischemia, macular edema and late complications such as vitreous hemorrhage, neovascular glaucoma (NVG) and traction retinal detachment.

At present, the preferred treatment for macular edema from venous occlusions is treatment with intravitreal anti-vascular endothelial growth factor medications (anti-VEGFs). Another possible agent which has also shown efficacy, is intravitreal dexamethasone implant. Low dose (1 mg) intravitreal triamcinolone is an option for macular edema secondary to Central Retinal Vein Occlusion. However, dexamethasone and triamcinolone have potential risks of glaucoma and cataract formation. Intravitreal triamcinolone acetonide was not found to be beneficial for macular edema secondary to Branch Retinal Vein Occlusion.

Pan Retinal Photocoagulation and Sectoral Retinal Photocoagulation still have roles in the treatment of ischemic CRVO and BRVO, respectively. Grid Macular Laser Photocoagulation has benefits for macular edema in BRVO for patients unsuitable or not willing to receive anti-VEGF therapy. However, focal/grid laser photocoagulation for Macular Edema due to CRVO is not beneficial for visual gain.

The Optical Coherence Tomography (OCT) makes it possible to quantify macular changes over time. In clinical practice, OCT measurements are often used as the basis for clinical decisions. The decision to repeat anti-VEGF injections, to change therapeutic agents, to initiate laser treatment or even to perform vitrectomy surgery is frequently based on both visual acuity and OCT findings.

Age is the strongest risk factor associated with retinal venous occlusions. The systemic risk factors include: arterial hypertension, diabetes, lipid and coagulation disorders. Other associated conditions include hyperhomocysteinemia, systemic inflammatory diseases and retrobulbar and/or external compression.

The management of the patient's systemic condition is equally important. Systemic arterial hypertension, diabetes, lipid and coagulation problems should be optimally controlled. Communication and coordination with the patient's primary care physician is essential for holistic care.

OVERVIEW: EVALUATION AND THERAPY

Initial Therapy (Key elements)

- Ocular history (e.g. glaucoma, other ophthalmologic disorders, ocular injections, surgery, including laser treatment, cataract surgery, refractive surgery)
- Onset, location, and duration of visual loss
- Current medications
- Systemic history (e.g. systemic hypertension, diabetes, dyslipidemia, cardiovascular disease, sleep apnea, coagulopathies, thrombotic/embolic disorders, connective tissue disorders, hyperhomocysteinemia, systemic inflammatory diseases and retrobulbar and/or external compression).

Physical Exam (Key elements)

Medical Investigation at the Eye Clinic[2]

- Medical History
- Blood pressure measurement
- Serum glucose
- CBC and ESR when indicated

Ophthalmologic Examination

- Visual acuity
- Pupil exam to detect presence of Relative Afferent Pupillary Defect (RAPD)
- Measurement of IOP
- Slit-lamp biomicroscopy to detect fine abnormal new iris vessels
- Gonioscopy prior to pupil dilation; especially in cases of an ischemic CRVO, when IOP is elevated, or when iris neovascularization risk is high
- Dilated examination of the entire retina with indirect ophthalmoscopy
- Slit lamp biomicroscopic evaluation of the posterior pole

Diagnostic Tests

- Color fundus photography to document retinal findings
- Fluorescein angiography to evaluate the degree of vascular occlusion and ischemia
- Optical coherence tomography to detect macular disease
- Ultrasonography (e.g., when vitreous hemorrhage is present)

Care Management

- Best prevention is to manage risk factors aggressively by optimizing control of diabetes mellitus, hypertension and hyperlipidemia *(I+ Good Quality, Strong Recommendation)*
- Multiple studies have demonstrated the efficacy of intravitreal anti-VEGF agents in the treatment of macular edema related to BRVO and CRVO *(I++, Good Quality, Strong Recommendation)*
- Betadine antiseptic drops and a lid speculum are recommended during all intravitreal injections *(III, Moderate Quality, Discretionary Recommendation)*
- Intravitreal triamcinolone, dexamethasone, and other corticosteroids have been shown to be efficacious for macular edema associated with CRVO, yet there are known associated risks of cataract and glaucoma *(I+, Good Quality, Strong Recommendation)*
- When indicated, grid/focal laser treatment for macular edema, sector photocoagulation for retinal neovascularization remain viable treatment options in eyes with BRVO, even if the duration of the disease is greater than 12 months *(I+, Good Quality, Strong Recommendation)*
- Sectoral pan-retinal photocoagulation is still recommended for neovascularization related to Branch Retinal Vein Occlusions with vitreous hemorrhage. *(I+, Good Quality, Strong Recommendation)*
- Ophthalmologists caring for patients with retinal vascular occlusions should be familiar with specific recommendations of relevant clinical trials due to the complexity of diagnosis and treatment *(II++, Good Quality, Strong Recommendation)*
- Attending ophthalmologists who treat RVOs should 1) initiate treatment within 1-2 weeks after diagnosis and should 2) be associated with facilities equipped for diagnosis, treatment, and monitoring. *(Good Quality, Strong Recommendation)*
- Careful cardiovascular assessment and treatment of cardiovascular risk factors by a qualified physician are advocated in patients with RVO. *(Good Quality, Strong Recommendation)*

Patient Follow-up

- Ophthalmologists should refer patients with RVO to a qualified physician for appropriate management of their systemic condition *(Good Quality, Strong Recommendation)*
- Risk to the fellow eye should be communicated to the patient and the patient's health care provider(s) *(I+, Moderate Quality, Strong Recommendation)*
- Patients whose conditions fail to respond to therapy and when further treatment is unavailable should be provided with professional support and offered a referral for counseling, vision rehabilitation or social service as appropriate (*I++, Good Quality, Strong Recommendation)*

RETINAL VENOUS OCCLUSION (RVO)

DISEASE DEFINITION

After diabetic retinopathy, retinal vein occlusion (RVO) is the second most common retinal vascular disorder and is likewise often associated with vision loss.[6] Retinal vein occlusion results from a partial or complete obstruction of a retinal vein. It is classified by the location of the occlusion.

A central retinal vein occlusion (CRVO) is an obstruction, usually as a result of thrombosis, of the retinal vein at or posterior to the optic nerve head.

A branch retinal vein occlusion (BRVO) is a complete or partial obstruction of a branch or tributary of the central retinal vein.

Hemi-retinal vein occlusion (HRVO) affects either the superior or inferior hemisphere/hemi-retina.

A RVO will result in a complete or partial decrease in venous outflow within the area of retina drained by the vein. This leads to retinal vascular leakage, leading to macular edema and an increase of intravenous pressure that results in multiple intraretinal hemorrhages.[6] Branch retinal vein occlusions often occur at the crossing points of the arteries and veins where the two vessels share a common adventitial sheath. They are often found in the superior temporal quadrant of the retina.[7] The major risk factors for BRVO include systemic arterial hypertension, arteriosclerosis and diabetes.[8]

Retinal vein occlusions can lead to loss of central vision due to macular ischemia and/or macular edema. More diffuse vision loss is caused by vitreous hemorrhage, epiretinal membrane formation, rubeosis iridis and neovascular glaucoma.[6]

Macular Edema (ME) is the most common cause of decreased visual acuity in RVO, followed by macular ischemia. ME results from retinal capillary leakage of fluid into the extracellular spaces around the fovea caused by increased capillary permeability as a result of the thrombosis of the retinal veins. Macular ischemia further increases capillary permeability and leakage due to the production of vascular endothelial growth factor (VEGF).[2]

Retinal ischemia and retinal neovascularization: New vessel formation (neovascularization) is a result of increased production of VEGFs and other cytokines due to ischemia. In CRVO, neovascularization usually forms at the iris (NVI) and which can lead to neovascular glaucoma (NVG). In BRVO, neovascularization usually forms in the retina which can lead to vitreous hemorrhage and traction retinal detachment.[2]

Ischemic versus non-ischemic RVO: RVOs are classified into ischemic and non-ischemic types based on the extent of capillary non-perfusion. This classification is useful in management. Based on the Central Retinal Vein Occlusion Study (CVOS),[9] ischemic CRVO is defined by fluorescein angiographic evidence of more than 10 disc areas of capillary non-perfusion in seven retinal fields. Moreover, *foveal ischemia* refers to non-perfusion at the central macula while *ischemic CRVO/BRVO* refers to non-perfusion in the other retinal areas (global retinal ischemia). Foveal ischemia results in visual impairment which is non-responsive to treatment. Peripheral/global ischemia results in retinal neovascularization and neovascular glaucoma usually seen in CRVO. It is significant to note that 1/3 of non-ischemic CRVO can degenerate to the ischemic type which results into further decrease in vision and possible neovascular glaucoma.[2,10-13]

PATIENT POPULATION

The most common age range where RVOs occur is from the 6th to the 7th decade.[9,14] Retinal vein occlusions are less common in individuals less than 40 years of age.

CLINICAL OBJECTIVES

- Identify patients at risk of developing RVO
- Optimize Control of systemic blood pressure, diabetes, control of glaucoma and ocular hypertension all of which are potential risk factors for CRVO and BRVO
- Increase awareness among health care providers of the occurrence of systemic conditions in patients with RVO. These conditions include *diabetes, hypertension, stroke, cardiovascular disease, peripheral arterial disease, peripheral venous disease.[2]
- Monitor for signs of posterior or anterior segment neovascularization at the iris (NVI) and at the angle (NVA) and neovascular glaucoma (NVG) following all RVOs
- Treat patients with RVO who are at risk for vision loss or who have developed vision loss
- Minimize side effects from treatment that might adversely impact vision or vision related quality of life
- Advise patients about and refer them for visual rehabilitation services when permanent visual impairment results.

BACKGROUND

PREVALENCE AND INCIDENCE

It is estimated that more than 16 million people worldwide are affected by RVOs.[14,15] The prevalence in the United States and in East Asia appears to be similar. The best estimate for the prevalence of RVO is 4.4 per 1000 adults in USA, Asia and Australia. [14,16] Branch retinal vein occlusions occur 6-7 times more often than central vein occlusions.[17] RVO usually occurs in only one eye. 10% of fellow eyes may also become involved over time.[2]

RISK FACTORS

Older age is the main risk factor for both CRVO and BRVO. A prior RVO is a risk factor for developing an RVO in the fellow eye.[14,15] In a patient who has developed CRVO, the chance of the fellow eye developing CRVO is 1% per year.[17] Patients have a 10% risk of developing an RVO of either type in the fellow eye over 3 years if one eye has a BRVO.[11,12,14] Risk factors for BRVO include arterial hypertension, hyperlipidemia, diabetes mellitus and coronary artery disease.[13,18,21]

The most common ocular condition related to the development of CRVO is glaucoma.[19] Systemic factors which may be more likely to contribute to the development of CRVO include hematologic factors, (e.g., hyperhomocysteinemia), carotid occlusive disease and sleep apnea.[22,23] Other systemic risk factors include systemic hypertension, diabetes, hyperlipidemia, cardiovascular disease, sleep apnea, coagulopathies, thrombotic/embolic disorders, connective tissue disorders, hyperhomocysteinemia, systemic inflammatory diseases and retrobulbar and/or external compression.

Individuals below 50 years who develop retinal vein occlusions, warrant evaluation for other hematologic risk factors; however, the cost-effectiveness of such an extensive work-up is controversial.[21,22] Systemic lupus erythematosus has been found to have an incidence of CRVO 3.5 times higher than in a control population.[23]

NATURAL HISTORY

Patients with RVOs typically present acute visual symptoms in one eye which could be due to macular edema and/or macular ischemia. Other fundus changes include vascular tortuosity, venous dilation of the affected

veins, retinal edema, intraretinal hemorrhages, cotton-wool spots, occasionally hard exudates or rarely retinal detachment in the affected area.[24,25] In time, the hemorrhages and cotton wool spots may resolve. Typically, the macular edema remains a significant cause of visual impairment unless appropriately treated. However, even with treatment, macular edema may persist despite resolving peripheral changes but will as well resolve over time, leaving secondary retinal pigment epithelial atrophy and decreased visual acuity.

Branch Retinal Vein Occlusion:

If a BRVO does not involve one of the major temporal branch veins or macular veins, the patient may remain asymptomatic and the BRVO is usually detected on routine eye examination. When the BRVO involves the macula, patients suddenly notice a decrease in central vision and/or a corresponding visual field defect. Although vision improvement is more common in BRVO compared to CRVO, few studies report improvement better than 6/12.[13] The patient may also consult when vitreous hemorrhage occurs due to retinal neovascularization related to significant peripheral capillary non-perfusion.

As a general rule eyes with BRVOs are less likely to develop neovascular glaucoma when compared to eyes with CRVO or hemi-CRVO.

In BRVO, collateral vessels may be seen between the superior and inferior retinal veins crossing the horizontal.

Recovery of lost vision due to BRVO depends on the degree of perfusion and the location of the occlusion.[26] Important prognostic factors for the final visual acuity depends on the severity of the occlusion and the extent of the ischemia.[27]

In the long term, the retinal findings in BRVO show minimal intraretinal hemorrhages and resolution of cotton wool spots with mild residual venous tortuosity and collateral vessels adjacent to the affected area. Other changes may include sheathed or ghost vessels, peripheral RPE atrophic changes over the involved area and the fovea. Complications of fibrovascular formation such as traction and/or rhegmatogenous retinal detachment may also occur.

Central Retinal Vein Occlusion (CRVO)

Non-ischemic CRVO may spontaneously improve without need for any treatment and without occurrence of complications. It is recommended that these patients be followed up for at least 2 years. Non-ischemic CRVO may however, deteriorate to the ischemic type as seen by an increase of areas of non-perfusion.[2]

In CRVO, collateral vessels may develop between the retinal venules and the choroidal circulation at the disc.

Macular edema is a likely occurrence in CRVO. Iris neovascularization will develop in approximately 25% of patients with CRVO. Once diagnosed with a CRVO, follow-up evaluations every 4-6 weeks for around 6 months is recommended. This may be done by a slit-lamp biomicroscopic exam, undilated gonioscopy (to detect iris or angle neovascularization that can lead to neovascular glaucoma), and dilated binocular funduscopic slit lamp exam or indirect ophthalmoscopy. Patients should likewise be evaluated for cystoid macular edema (CME).

Long term clinical findings of CRVO include optic atrophy, formation of disc collaterals, vascular attenuation and/or diffuse RPE atrophic changes.

RATIONALE FOR TREATMENT

The use of either anti-VEGF and/or intraocular corticosteroid agents should be strongly considered in patients with BRVO and CRVO as primary treatment for decreased vision related to macular edema. The rationale for their use is that anti-VEGFs reduce leakage from retinal capillaries and inhibit the action of VEGF.

Anti-vascular endothelial growth factor (anti-VEGF) agents may be used as an adjunctive treatment when PRP has been completed and appears unable to control angiogenesis.[28,29] Anti-VEGF agents are commonly used to treat macular edema, reduce the severity of anterior segment neovascularization and to lower the risk of ocular angiogenesis.[29] Pre-operative intravitreal injection with anti-VEGFs may also be used in selected patients to reduce the risk of intra-operative bleeding and facilitate membrane dissection. [30,31]

Initial treatment with an anti-VEGF agent may be helpful for an immediate benefit and may also improve the ability to deliver a more complete focal and/or grid laser treatment for macular edema of BRVO and sectoral or pan-retinal photocoagulation for global ischemia in BRVO and CRVO.

CARE PROCESS

In general, the management of patients with a new RVO should involve a primary care physician, internist or a physician capable of managing systemic conditions associated with RVO to optimize control of systemic risk factors, such as diabetes hypertension and hyperlipidemia.[32] *(II++, Good Quality, Strong Recommendation)*

PATIENT OUTCOME CRITERIA

Patient outcome criteria include the following:

- Improvement or stabilization of visual function
- Improvement or stabilization of vision-related quality of life
- Detection and treatment of all neovascular complications
- Detection and treatment of macular edema
- Optimal control of hypertension, diabetes, and other systemic risk factors through direct communication and coordination of care with the patient's health care providers

DIAGNOSIS

A comprehensive medical evaluation is performed in a patient with RVO with particular attention to systemic conditions related to retinal vascular disease.[33]

History

The history should include the following:

- The onset, location, and duration of vision loss
- Current medications
- Medical history: The following systemic conditions may be associated with RVOs
    - Systemic hypertension
    - Diabetes
    - Hyperlipidemia
    - Cardiovascular disease
    - Sleep apnea
    - Coagulopathies: high plasma viscosity e.g. leukemia, myeloma, Waldenstroms's macroglogulinemia, myelofibrosis, changes in protein C pathway
    - Thrombotic and embolic disorders

- Systemic inflammatory disorders (Behcets disease, polyarteritis nodosa, sarcoidosis, Wegener's Granulomatosis and Goodpasture's syndrome) [2]
- Ocular history
  - Glaucoma
  - Shorter axial length
  - Ocular injections
  - Surgery (e.g., retinal laser treatment, cataract and refractive surgery)
  - Retrobulbar and/or external compression

Physical Examination

An initial examination should include the following:

- Visual acuity
- Pupillary assessment for a relative afferent pupillary defect which corresponds to the level of ischemia and also predicts eyes at risk for neovascularization
- Slit-lamp biomicroscopy, looking carefully for fine, abnormal new vessels at the iris
- Intraocular pressure (IOP)
- Gonioscopy prior to dilation. This is important to perform, especially in cases of ischemic CRVO, when iris and/or angle neovascularization is suspected
- Examination of the retina and vitreous through a dilated pupil should be performed. It is recommended that slit-lamp biomicroscopy with the appropriate lenses be conducted to evaluate the macula, posterior pole, and midperiphery. An indirect ophthalmoscopic examination is needed to examine the mid to far peripheral retina. The risk of vision loss can be effectively reduced by detailed examination and consideration of the following features:
  - Macular edema which can be detected during the eye examination and confirmed using optical coherence tomography (OCT)
  - Signs of ischemia, which include neovascularization of the disc or elsewhere, extensive hemorrhages, venous dilation and tortuosity and cotton wool spots, as well as presence of a RAPD
  - Optic nerve head neovascularization and/or neovascularization elsewhere
  - Vitreous or preretinal hemorrhage

Diagnostic Tests

Optimizing patient care and confirming the clinical exam may be enhanced by the following imaging tests. All must be used judiciously.

- Color and red-free fundus photography
- Optical coherence tomography (OCT)
- Fluorescein angiography (FA)
- Ultrasonography

  - **Color and Red-free Fundus Photography**
    The severity of the retinal findings and the response to treatment may be documented by fundus photography:
    - the presence of new vessels elsewhere in the retina (NVE),
    - new vessels on or near the optic disc (NVD)
    - the extent of intraretinal hemorrhages

  - **Optical Coherence Tomography (OCT)**
    The presence and extent of macular edema, vitreomacular interface changes, neurosensory retinal detachment, subretinal fluid, as well as other macular diseases may be documented

by optical coherence tomography (OCT). This imaging test provides high-resolution imaging of the fovea. The OCT makes it possible to quantify macular changes over time. For example, the decision to repeat anti-VEGF injections, to change therapeutic agents, to initiate laser treatment or even to perform vitrectomy surgery is frequently based on both visual acuity and OCT findings. However, visual acuity is not consistently related to retinal thickness as measured by OCT.[34] In clinical practice, OCT measurements are often used as the basis for clinical decisions. It is the preferred modality for monitoring the response to treatment of macular edema.

- **Fluorescein Angiography (FA)**

  The severity of peripheral and macular ischemia as well as the co-existence of macular edema can be documented with the use of FA. Images taken by FA are used:
  - to localize leaking microaneurysms or areas of capillary non-perfusion
  - to distinguish collateral vessels
  - to confirm the presence of suspicious neovascularization seen on clinical exam.

  In small BRVOs, FA may help confirm the diagnosis. FAs are helpful in determining the extent of peripheral capillary non-perfusion.

  FA can identify macular capillary non-perfusion. In selected cases, it may be used to monitor response to therapy and give the etiology for associated vision loss. The FA may also be used to detect areas of untreated retinal capillary non-perfusion that may explain persistent retinal or disc neovascularization despite peripheral, scatter laser retinal photocoagulation.

  Wide-field FA has recently become available to evaluate peripheral non-perfusion.

  Informed consent must be obtained by an ophthalmologist who orders an FA. The patient must be made aware of both common and rare potential risks associated with the procedure, including death which can occur in 1/200,000 patients.[35] *(Good Quality, Strong Recommendation)* Each angiography facility should have an emergency care plan and a clear protocol to manage known risks and complications *(Good Quality, Strong Recommendation).*

  Fluorescein dye can cross the placenta and enter the fetal circulation, [36] but adverse effects of the dye on the fetus are not documented. The FA should be requested only when absolutely necessary. *(Good Quality, Strong Recommendation)*

  B-Scan Ultrasonography (UTZ)
  If the media is clear, OCT is more appropriate to assess the status of the macula. In the presence of a vitreous hemorrhage or other causes of media opacity, ultrasonography is a useful diagnostic tool that enables assessment of the anatomic status of the posterior segment.

- **Systemic Evaluation**
  The patient with RVO should be co-managed with the primary care physician or internist. There are no clear guidelines on systemic testing. The extent of systemic testing is left to the discretion of the primary care physician or internist. In young patients; however, careful cardiovascular workup and treatment of risk factors by the patient's primary care physician or internist is recommended.[2] In females within the child bearing age, the use of oral contraceptive hormonal medication should be elicited.

MANAGEMENT

Prevention and Early Detection

The occurrence of BRVO has shown a strong relationship with systemic vascular disorders such as arterial hypertension and peripheral vascular disease. Older age and systemic vascular disorders are the more significant risk factors for RVO.[37] A meta-analysis suggests that 48% of RVO is attributable to hypertension, 20% to hyperlipidemia, and 5% to diabetes.[32] Fundus changes associated with increased risk of developing a BRVO include arteriovenous nicking, ocular perfusion pressure, and focal arteriolar narrowing. The best prevention is to manage risk factors by optimizing control of diabetes mellitus, hypertension and hyperlipidemia.[32] *(I+, Good Quality, Strong Recommendation)*

Medical and Surgical Management

1. Laser Photocoagulation

1.1. BRVO-Macular Edema (ME): The target of BRVO treatment is to address the sequelae of the venous occlusion which include: CME and NVD/NVE. Treatment does not target the site of the occlusion itself. Laser photocoagulation remains a treatment option in eyes with BRVO, even if the duration of the disease is greater than 12 months.[26] *(I++, Good Quality, Strong Recommendation)* Grid and/or focal laser treatment can help reduce vision loss from BRVO related macular edema by reducing the leakage from foveal capillaries.

1.2. CRVO-Macular Edema (ME): The Central Vein Occlusion Study: CVOS found no evidence to support grid treatment or focal laser for CME in patients with CRVO-ME.[10]

1.3. BRVO: Branch Vein Occlusion Study (BVOS): In 1984, BVOS reported on the natural history and the effect of laser treatment in BRVO. The study showed that after 36 months, 63% of laser-treated eyes had improved vision by $\geq$2 lines compared to 13% of untreated eyes.[26] If laser treatment is to be used, it should be performed in eyes with BRVO-ME with visual acuity of $\leq$6/12 without macular hemorrhage or in eyes with BRVO-ME of at least three to six months' duration to allow for the possibility of spontaneous resolution. The procedure should be guided by a fluorescein angiogram to show the areas of capillary non-perfusion.[26] FA will identify the leaking capillaries and the degree of macular ischemia. If macular ischemia is present, improvement in visual acuity despite treatment is limited. FA will also identify collateral vessels which should not receive laser treatment. Thus, the BVOS demonstrated the benefit of grid laser treatment to improve visual acuity outcomes in eyes with macular edema from BRVO.[26] This was the standard of care until recently when the results of intravitreal injections of anti-VEGF and corticosteroids were reported.[27] The BVOS also demonstrated that laser treatment of ischemic BRVO is of benefit in reducing the complications related to retinal neovascularization.

1.4. Ischemic CRVO: Currently, Ischemic CRVO is defined as the presence of RAPD and by the presence of 10 disc areas (DA) or more of capillary non-perfusion on seven-field fluorescein angiography.

1.4.1. Management of ischemic central retinal vein occlusion and anterior segment neovascularization : Eyes with ischemic CRVO should ideally be evaluated on a monthly basis to monitor the development of iris new vessels (NVI) or angle new vessels (NVA).[65] The risk for iris

and angle neovascularization (NVI and NVA) is higher in ischemic CRVO with >10 disc areas of capillary non-perfusion as seen on Fluorescein Angiography. [64,65]

Dense scatter pan-retinal photocoagulation should be applied once NVI or NVA are noted. The Central Vein Occlusion Study (CVOS) recommended pan-retinal photocoagulation to help cause the regression of NVI and/or NVA. Pan-retinal photocoagulation ablates areas of retinal non-perfusion thereby decreasing the risk of neovascularization which results from the release of VEGFs. If regular monthly follow-up is not possible, prophylactic PRP may be appropriate even if NVI, NVA and NVG are not yet present. Prophylactic PRP should be guided by ischemic fluorescein angiographic findings of ≥10DA of capillary non-perfusion and/or the presence of RAPD.[10,28] PRP will not improve visual acuity. Intravitreal injection with anti-VEGF agents, such as on-label ranibizumab, aflibercept and off-label bevacizumab may be used as adjunctive treatment for PRP. [2] (See Section 3.2 below: Intravitreal Anti-VEGFs)

1.4.2. Management of posterior segment neovascularization: Panretinal photocoagulation of the retina applied to the periphery in all ischemic areas may help in preventing vitreous hemorrhage.

1.4.3. Pan-retinal Photocoagulation Technique: The aim of retinal laser treatment for CRVO with NVI or NVA is to cause their regression over time. To achieve this, an adequate amount and appropriate distribution of the laser shots should be delivered to cover the ischemic retina. Additional laser and/or adjunctive treatments with intraocular anti-VEGFs may be needed in some eyes if the neovascularization fails to regress. (See Section 3.2 below: Intravitreal Anti-VEGFs)

1.4.4. Management of established neovascular glaucoma: Topical corticosteroids and atropine are prescribed to keep the patient pain free even if vision is No Light Perception (NLP). Elevated intraocular pressures should be controlled with topical agents or cyclo-ablative procedures. Neovascular glaucoma also warrants dense peripheral, scatter PRP. In addition, intravitreal and intracameral anti-VEGF agents can cause regression of NVI and NVA and thus decrease angle obstruction. Adjunctive Bevacizumab treatments have been shown to cause iris new vessels to regress faster compared with PRP alone and may reduce the need for surgical procedures. Bevacizumab may also be used as an adjunct to filtering surgery.[66,67] (See Section 3.2 below: Intravitreal Anti-VEGFs)

1.4.5. Recommendations for Further Follow-up: Follow-up evaluations of eyes with ischemic CRVO should be done between 1-3 months in the first year. Patients with non-ischemic CRVO may be monitored every 3 months. The development of disc collaterals with or without the resolution of the CRVO indicates a good outcome. However, the available studies indicate that macular edema tends to recur for many years and treatment of macular edema may be required in a patient on a long term basis to ensure maintenance of visual acuity gains before RPE changes ensue.

2. Intravitreal Steroids

2.1. CRVO and BRVO: The GENEVA study evaluated the use of an injected intravitreal dexamethasone implant in two doses compared with sham injection in eyes with either a CRVO or a BRVO.[38] The study included pooled data from 1131 patients, 34% with CRVO and 66% with BRVO. There was a significant gain in visual acuity at 90 days which was however lost at 6 months. Results from an open-label extension beyond 6 months were similar to the initial study, showing visual acuity gains up to 90 days, then loss of treatment effect at 1 year.[39] Cataract formation and elevated IOP was seen more frequently at 1 year. The dexamethasone implant which is administered via injection into the vitreous

was US and Philippine FDA-approved in 2009 for the treatment of macular edema due to CRVO and BRVO.

2.2. BRVO : Intravitreal triamcinolone acetonide (IVTA): The Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study (SCORE) evaluated the long-term safety and efficacy of preservative-free triamcinolone and found that this treatment is not beneficial for this condition.[40,41] The GENEVA study [38,39] evaluated the safety and efficacy of an intravitreal implant of dexamethasone in eyes with macular edema secondary to BRVO and CRVO. The percentage of eyes with ≥15 letter gain in BCVA was significantly higher in the dexamethasone groups compared with sham at days 30 and 90. The peak effect occurred at 60 days. Intraocular pressure increased at month two with an IOP>35 mmHg, but declined by month three. However, pressure lowering medications and surgical procedures were needed in 19% and 0.7% of patients respectively. The progression of cataracts is also a significant complication of dexamethasone implant therapy.[38,39,40,41]

2.3. CRVO: The SCORE (Standard Care Versus Corticosteroid for RVO) study indicates that CRVO-ME may benefit anatomically from intravitreal triamcinolone. The SCORE study showed that in perfused CRVO, 27% of patients who received a low-dose 1 mg IVTA had a visual gain of 3 lines in contrast to only 7% of patients in the observation group. Currently, IVTA with a low-dose 1 mg triamcinolone remains an option for patients with perfused CRVO-ME.[41]

Intravitreal dexamethasone to treat CRVO-ME was analysed in the GENEVA STUDY.[38,39] In this study, an intravitreal injection of a biodegradeable implant containing 0.7 mg dexamethasone was compared to sham injections in patients with CRVO and BRVO. The primary outcome measure for all patients was time to achieve a ≥ 15 letter gain. The percentage of eyes with ≥ 15 letter gain in BCVA was significantly higher in both CRVO and BRVO groups compared with sham at days 30 to 90 with a peak at 60 days. Intraocular pressure increased and peaked at month two but declined significantly by month three and was close to 0% by month 6. Cataract progression was seen in both groups. The results also showed instituting treatment earlier gave a better chance to improve visual acuity compared to eyes that were treated later.

The use of intravitreal triamcinolone and dexamethasone are however, associated with risks of cataracts and glaucoma.[40,41]

3. Intravitreal Anti-VEGF : Anti-VEGF agents have been shown to be safe and effective in treating macular edema because VEGF A is a key cytokine that mediates capillary leakage that causes macular edema for BRVO and CRVO. These agents have also been shown to limit neovascularization associated with BRVO.[42] Currently, there are three anti-VEGF agents for intravitreal injection. Two are Philippine FDA approved namely: ranibizumab and aflibercept. Bevacizumab; however, remains off-label for ophthalmic conditions.

1) off label use of bevacizumab (1.25mg(
2) on label use of ranibizumab (0.5mg)
3) on label use of aflibercept (2mg)

3.1. BRVO

3.1.1. Ranibizumab. Studies have demonstrated the efficacy of anti-VEGF agents in the treatment of macular edema associated with BRVO.[37,43-47] *(I++, Good Quality,Strong Recommendation)* BRAVO (Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety) was a double-masked multicenter randomized phase 3 clinical trial that demonstrated efficacy of monthly intravitreal injection of 0.3 or 0.5 mg ranibizumab compared with sham injection in 397 eyes followed for 6 months. In this trial, monthly intravitreal ranibizumab injections resulted in a gain of 16 (0.3mg) to 18 letters (0.5 mg) compared with a gain of 7.3 letters in the sham group at month 6; 55% (0.3 mg) to 61% (0.5 mg)

of ranibizumab-treated eyes gained at least 15 letters from baseline compared with 29% in the sham group.[44] After 6 months, all eyes received injections of ranibizumab 0.5 mg on a PRN basis until month 12.[45]

The HORIZON[44] trial included all patients who completed the BRAVO trial and entered an open-label multicenter extension trial. Patients were followed quarterly for 12 months with repeat injections of 0.5 mg ranibizumab at the investigator's discretion.[43] About half of the eyes in HORIZON achieved resolution of edema and 80% had visual acuity of better than or equal to 20/40. However, about half of the eyes enrolled in the HORIZON extension study received grid laser photocoagulation at some point during the study period. The long term administration of ranibizumab in a PRN regimen was well tolerated and efficacious in patients with BRVO-ME. These studies used ranibizumab, whereas other smaller, level 2 studies have demonstrated the efficacy of bevacizumab for macular edema associated with BRVO.[37,46,47]

The RETAIN Study showed that the long term effects of intravitreal injections with ranibizumab of macular edema in BRVO was favorable although 50% of eyes needed continuing injections at 4 years. The study followed 34 patients with BRVO for a total of 49 months after treatment with ranibizumab. 17/34 (50%) of eyes had resolved macular edema for 6 months after the last injection. The mean number of injections in unresolved macular edema was 3.2 in year four. The mean improvement in BCVA was 25.9 letters in eyes with resolved macular edema compared to 17.1 letters (p=0.09) in eyes with unresolved edema.[48]

3.1.2. Aflibercept . The VIBRANT trial was a randomized double-masked phase 3 trial that demonstrated the efficacy of aflibercept over grid treatment for macular edema in BRVO.[49]

3.1.3. Bevacizumab. The off-label use of intravitreal bevacizumab to reduce BRVO-ME is currently supported by increasing data. Bevacizumab may be used even in those eyes where ME has not responded to previous laser treatment. However, randomized, controlled trials are needed to assess long-term safety and efficacy of intravitreal bevacizumab.[50,51]

3.2. CRVO

3.2.1. Ranibizumab. There are several randomized controlled trials that have shown the efficacy of anti-VEGF agents in the treatment of macular edema due to CRVO.[39,52-54] *(I++, Good Quality, Strong Recommendation)*. The CRUISE (Ranibizumab for the treatment of Macular Edema after Central Retinal Vein OcclusIon Study: Evaluation of Efficacy and Safety; showed a doubling of the number of letters read following intravitreal ranibizumab compared with sham injections. A decrease in retinal thickness was likewise documented by OCT imaging.[52] Patients who completed the 12 month CRUISE trial were followed up for 24 months in the HORIZON extension study. The patients receivee 0.5 mg ranibizumab on a PRN basis. A key finding from the HORIZON was that ranibizumab is well tolerated in the long term. In the second year of treatment, results showed worse visual and anatomical outcomes due to a reduced number of injections. The study also showed differences in the outcomes of BRVO and CRVO patients. CRVO patients required more frequent follow-up and continued ranibizumab therapy to control edema.[55]

3.2.2. Aflibercept. In the Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (COPERNICUS) study, intravitreal aflibercept was compared with sham injections. The primary endpoint was a 15-letter gain in 56% of the treated eyes compared with 12% of sham injections from baseline to week 24.[53] Between weeks 24 and 100, patients received injections on a PRN basis. At week 100, patients in the aflibercept treatment group showed a mean gain of 13.0 ETDRS letters, compared to sham-treated eyes which gained 1.5 letters (P<0.001). This study also showed that treatment has to be started

early to achieve optimal visual results, otherwise there is likely to be a degree of irrecoverable visual loss.[55] Ocular neovascularization in the first 52 weeks was 0% in the aflibercept treated patients versus 6.8% in the sham treatment group (P=0.0006). The neovascularization occurred in the anterior segment. Between week 24 and 100, the study showed that once macular edema was stable over several months of anti-VEGF injections, the frequency of injections could be decreased. Similar findings were found in GALILEO: General Assessment Limiting Infiltration of Exudates in Central Retinal Vein Occlusion with VEGF Trap-Eye study.[54] Intravitreal bevacizumab was compared with sham injections in a randomized trial that found a 15-letter gain at week 72 in 57% of the treated eyes compared with 20% for sham injections.[56] However, by week 76, the sham and aflibercept group showed similar OCT changes.[57,58]

3.2.3. Bevacizumab. The use of multiple intravitreal injections with bevacizumab to reduce CRVO-ME is supported by increasing data. However, additional randomized, controlled trials are required to assess long-term safety and efficacy of intravitreal bevacizumab.[59,60]

Ranibizumab, Aflibercept, Bevacizumab or Pegaptanib Sodium. *A Cochrane meta-analysis on anti-VEGF agents for the treatment of Macular Edema secondary to CRVO included high-quality data from 937 participants in six RCTs, who were either treated with intravitreal anti-VEGF (aflibercept, bevacizumab, ranibizumab or pegaptanib sodium) or sham injection.*[61] *It found that participants receiving anti-VEGF therapy were 2.71 (95% confidence interval for risk ratio 2.10 to 3.49) times more likely to gain at least 15 letters of visual acuity at six months compared to participants treated with sham. High-quality evidence from five trials suggested anti-VEGF treatment was associated with an 80% lower risk of losing at least 15 letters of visual acuity at six months compared to sham injection (RR 0.20; 95% CI 0.12 to 0.34). Moderate-quality evidence from three trials (481 participants) revealed that the mean reduction from baseline to six months in central retinal thickness was 267.4 microns (95% CI 211.4 microns to 323.4 microns) greater in participants treated with anti-VEGF than in participants treated with sham. In addition, high-quality evidence from six trials suggested that anti-VEGF treatment was associated with an 82% lower risk of developing iris neovascularization at six months compared to sham injection (RR 0.18; 95% CI 0.09 to 0.36).*[2]

For all intravitreal injections, it is recommended that betadine antiseptic drops and a sterile lid speculum be used. Routine antibiotic eye drops is not necessary. *(III, Moderate Quality, Discretionary Recommendation)* Intravitreal injections are rarely associated with severe adverse effects such as infectious endophthalmitis, cataract formation, retinal detachment and elevated IOP. Increased IOP is common with the use of intravitreal corticosteroids and corticosteroid implants.

TRANSLATION OF CLINICAL TRIALS ON ANTI-VEGF THERAPY IN CLINICAL PRACTICE[2]

1. Branch Retinal Vein Occlusion (BRVO): Macular Edema (ME)

1.1 **Natural History of BRVO-ME.** The BRAVO study evaluated the natural history of macular edema due to BRVO. The study found that macular edema may resolve over time with a

mean gain of 7.3 ETDRS letters at six months. However, treatment of the macular edema at 6 months resulted in an inferior visual outcome compared to prompt treatment at diagnosis. Therefore, prolonged delay in instituting anti-VEGF treatment after diagnosis is established for macular edema should be avoided unless it is the decision of the patient to delay treatment

1.2 **Macular Laser.** The BVOS study reported that 40% of patients who underwent laser photocoagulation as first-line treatment for macular edema had a final visual acuity of 6/12 at 36 months. Although, laser treatment of the macula was the treatment of choice for the past 20 years, it is currently used only for patients who are unsuitable or unwilling to receive anti-VEGF treatment. Currently, intravitreal injection with anti-VEGF is the first line of treatment for macular edema due to BRVO. Therefore, intravitreal injection with anti-VEGF should be performed as soon as possible after the diagnosis is established.

1.3 **Ranibizumab and Aflibercept for BRVO-ME.** Intravitreal injections with the anti-VEGFs (ranibizumab and aflibercept) show visual gains in the treatment of BRVO-ME. The BRAVO study followed by the HORIZON and RETAIN showed the need for initiation of treatment as soon after diagnosis. The intravitreal injections are continued on a monthly basis until stable vision is achieved. The BRAVO, HORIZON and RETAIN studies demonstrated that shifting to the PRN schedule after maximal visual acuity has been gained will need close monitoring at monthly intervals followed by 3-4 month visits. The BRAVO, HORIZON and RETAIN showed that the long term outcome in BRVO eyes treated and monitored adequately are favorable.

1.4 **Dexamethasone for BRVO-ME.** The GENEVA study results showed favorable results for the use of intravitreal dexamethasone injections. Real-life experience shows that in order to produce optimal results, more frequent injections than the six-monthly dosing schedule used in the GENEVA study is needed. Side effects of treatment with this agent include the higher rate of cataract progression and increase in intra-ocular pressures. Currently, there are no head to head comparisons of dexamethasone implants with the anti-VEGF agents.

1.5 **Intravitreal triamcinolone for BRVO-ME.** Current trials do not support the use of intravitreal triamcinolone injection for BRVO-ME.

RECOMMENDATION FOR BRVO-ME

Because of the favorable risk-to-benefit profile, the use of anti-VEGF agents is the preferred initial therapy for treatment of macular edema related to BRVO given as soon as possible after diagnosis. Either corticosteroids and/or FA guided focal laser should be considered when there is a failure to respond or an inadequate response to treatment with anti-VEGF agents. Injection of a dexamethasone implant may be the better drug of choice for patients who do not wish for monthly injections and for patients with recent cardiovascular events.

2. BRVO: Neovascularization

2.1 Monitoring with follow-up retinal examinations at 3-4 month intervals is recommended in patients with one quadrant of capillary non-perfusion because these eyes are at risk for retinal neovascularization. Slit-lamp biomicroscope contact lens exams and/or fundus color photos can help confirm the areas of retinal ischemia and new vessel growth. Fluorescein Angiography (FA) is not always needed since the areas of ischemia can be seen clinically or with peripheral fundus photos. It is recommended that sector retinal laser treatment be performed to the areas of retinal ischemia for disc and/or retinal neovascularization.

2.2 Laser photocoagulation of the retina still has a place in the treatment of BRVO. Sectoral laser treatment in the non-perfused area helps to decrease the risk of a vitreous hemorrhage in patients with a BRVO and neovascularization of the retina.[62] In sectoral PRP, laser treatment is applied to the sector of retinal capillary non-perfusion. Sectoral PRP is still recommended for neovascularization when complications such as vitreous hemorrhage or iris neovascularization are already present.[62] *(I+, Good Quality, Strong Recommendation)* Laser shots which produce a grey-white spot should be applied one-spot-width apart in the affected sector.

RECOMMENDATION FOR ISCHEMIC BRVO

With the presence of at least one-quadrant of ischemia, detected clinically or by fluorescein angiography, with or without evidence of neovascularization, sectoral laser photocoagulation is recommended.

3. CRVO:

3.1 Duration of CRVO: The CRUISE, COPERNICUS and GALILEO studies evaluated the effects of intravitreal anti-VEGFs for CRVO-ME in patients diagnosed in the previous 12 months (CRUISE) and in the previous 9 months (COPERNICUS and GALILEO).[55,57,63] The effects of treatment with intravitreal anti-VEGFs and/or dexamethasone beyond this time is not fully studied. Therefore, the effects of treatment on vision after three loading doses at monthly intervals may help the ophthalmologist decide if additional treatment is necessary.

3.2 Duration of ME and VA outcome: The anti-VEGF trials indicate that visual outcome is best when CRVO eyes are treated promptly. 71.2% of participants in the CRUISE trial and 55% in the aflibercept trials had a duration of macular edema of less than three months and less than two months duration respectively.

3.3 Early referral and prompt treatment: The studies also show that fewer vision gains are achieved when treatment is initiated six months after diagnosis. Therefore, intravitreal injections soon after diagnosis is recommended. Anatomical and functional response after the three loading doses at monthly intervals may help the ophthalmologist decide if further treatment will be of benefit in patients with delayed presentation.

3.4 Presenting VA: Participants in the CRUISE, GALILEO AND COPERNICUS trials had vision of 24 ETDRS letters (Snellen 6/96) vision at entry. Therefore, the effects of anti-VEGF treatment on visual outcome in patients with less than 24 letters vision, needs further study. The Royal College of Ophthalmologists guidelines for RVO 2015 [2] report anecdotal clinical experience that shows slight vision gains in eyes with Snellen VA<6/96 as long as there is no afferent pupillary defect. The anatomical and functional response after the three loading doses at monthly intervals may help the ophthalmologist decide if further treatment will be of benefit.

3.5 Poor VA at presentation and VA outcome: The CRUISE, GALILEO and COPERNICUS trials report that 20% of the participants had visual acuity of Snellen 6/60 to 6/96 at enrollment. The final visual acuity and quality of vision of the patients in this category is not clear. Therefore, factors such as degree of macular ischemia, histologic damage at the fovea should be considered in the decision whether to continue treatment after initial therapy.

3.6 ischaemic CRVO: Currently, Ischemic CRVO is defined as the presence of RAPD and by the presence of 10DA or more of capillary non-perfusion on seven-field fluorescein angiography. The CRUISE study excluded patients with positive RAPDs, whereas the COPERNICUS and GALILEO trials did not. It is thought that this accounts for the higher proportion of eyes with retinal capillary-non-perfusion in the COPERNICUS (15.5%) and GALILEO (14%) compared to the CRUISE (1.5%). In clinical practice, after careful consideration, patients who present with ischemic CRVO may receive treatment with intravitreal anti-VEGFs. Therefore, the decision to continue intravitreal injections should be guided by changes in visual acuity or OCT central subfield thickness after three loading injections at monthly intervals.

3.7 Monitoring intervals: The CRUISE, GALILEO and COERNICUS trials monitored their participants on a monthly basis for 52 weeks. In the second year, the HORIZON and GALILEO trials reported that the visual gain obtained in the first year will most likely not be sustained if patients are monitored every 3 months. The COPERNICUS trial reported that the visual gain in the first year will likewise not be sustained with an 8 week interval of follow up. Therefore, patients receiving treatment should be monitored at least monthly to maintain visual gains especially if a PRN treatment regimen is to be followed.

3.8 Ocular neovascularization: The GALILEO and COPERNICUS trials reported a low incidence of ocular neovascularization: 2.9% of eyes treated with aflibercept by 24 weeks and 5% by 52 weeks. All the eyes had CRVO of less than two months and included both ischemic and non-ischemic types at baseline. Neovascularization was noted 240 days from baseline. Therefore, although the incidence of ocular neovascularization is low, and the time to its development prolonged in aflibercept treated eyes, patients should

continue to be monitored for ocular neovascularization and for signs of conversion from the non-ischemic to ischemic type of CRVO.

3.9 Previous treatment: The COPERNICUS and GALILEO trials excluded patients with previous anti-vegf treatments. The COPERNICUS trial, however, included patients who had previous intraocular or periocular corticosteroids up to three months prior to randomization and the GALILEO trial included eyes previously treated with macular laser or panretinal photocoagulation. The CRUISE trial included patients who had received anti-VEGF 3 months prior to the study. Currently, there is no conclusive data regarding outcomes of switching from corticosteroids to anti-VEGF agents, switching between anti-VEGF agents or combining corticosteroids with anti-VEGFs in the treatment of CRVO-ME. Therefore, an informed decision should be made by the patient if another agent is to be used for injection.

3.10 Anatomical outcomes: The Optical Coherence Tomography (OCT) central subfield thickness (CST) is used to monitor anatomical outcomes of treatment. The maximum reduction in central macular thickness occurs four weeks after the first injection whether the treatment was started promptly or after a delay. The OCT CST thickness remains unchanged for up to 24 weeks in the CRUISE, GALILEO and COPERNICUS trials for up to 24 weeks. However, the mean retinal thickness increases with increased intervals between follow-up. Therefore, since functional benefits depend on anatomical integrity, this implies that changes in macular anatomy warrants additional treatment and at least monthly visits, in order to sustain maximal visual benefit.

3.11 Injection frequency*:* The treatment protocols of all the anti-VEGF trials called for monthly injections for the first six months. This initial schedule showed maximal visual gain. The effects of less frequent dosing from baseline needs further evaluation. However, patients in whom a PRN dosing regimen of anti-VEGF injections were instituted six to twelve months from baseline showed a mean gain of five letters. This small visual gain is attributed to the chronic edema and/or the PRN schedule. Therefore, injections at monthly intervals may be followed until maximum visual gain is achieved and visual acuity is stable before changing to another treatment schedule. The increased risk of endophthalmitis (1:1000) with repeated injections should be explained to patients who are in need of repeated injections.

3.12 PRN dosing: In the COPERNICUS study, after 6 monthly injections, the patients were switched to a PRN schedule. The mean time to a repeat aflibercept injection, following the PRN schedule was 68 days. This suggests that an eight-weekly dosing schedule may be sufficient after the initial 6 monthly injections. Only 7.3% of patients in the aflibercept group of the COPERNICUS study no longer needed additional injections from week 24 to week 52. Whereas, 50% needed three to five more injections during this period. All anti-VEGF trials to date show that macular edema persists or recurs up to 52 weeks, thus, patients will require more injections up to week 52 to sustain the visual benefit obtained at 24 weeks. The RETAIN study results showed that 56% of eyes required frequent ranibizumab injections to maintain good visual outcomes at 4 years, whereas 44% of eyes showed resolution of edema. Thus, if a PRN schedule is to be followed, patients should be followed-up on a monthly basis. The alternative is to follow a treat and extend regimen at eight weekly fixed dosing. However, it is thought that this eight weekly fixed regimen may result in under-dosing since 40% of patients in the COPERNICUS study required more than three injections after 24 weeks.

3.13 Re-treatment criteria: The criteria for re-treatment included increase in central subfield thickness of >50um compared to the lowest previous measurement, new or persistent

cystic retinal changes or subretinal fluid, persistent diffuse edema >250um in the central subfield or loss of $\geq$ 5 letters from the best prior measurement. In the CRUISE study, the criteria for repeat injections were BCVA $\leq$20/40 or center subfield thickness of >250um. Therefore, using the criteria for re-treatment in clinical practice is thought to be the optimum way to achieve similar results to ensure that the macula remains dry and vision remains within 5 letters of best achieved visual acuity.

3.14 Long-term treatment of CRVO: The RETAIN study followed-up 32 of the 392 patients with CRVO-ME who were initially enrolled in the CRUISE study. The patients were evaluated every three months and received injections on a PRN dosing schedule for 48 months. 53.1% gained 15 letters or more and 43.8% had a final BCVA of 20/40 or better. Fourteen of the patients had chronic unresolving edema and poorer visual outcome despite being on treatment. Thirteen patients had resolution of macular edema for at least six months.

RECOMMENDATION FOR CRVO-ME

The preferred first line of treatment for CRVO-ME is intravitreal anti-VEGF injection monthly for 6 months to be started as soon as possible for maximal visual benefit. The effects of treatment on vision after three loading doses at monthly intervals may help the ophthalmologist decide if additional treatment is necessary. The alternative treatment options are injection with a dexamethasone implant or low-dose (1 mg) intravitreal triamcinolone. Injection with an intravitreal dexamethasone implant may be the better drug of choice for patients who do not wish for monthly injections and for patients with recent cardiovascular events. Intravitreal triamcinolone is associated with a higher rate of increased intra-ocular pressure and cataracts when compared to dexamethasone and anti-VEGF injections.

On follow-up visits, visual acuity, gonioscopic exams, IOP measurements and macular thickness maps are taken. The patient is likewise examined for the presence of NVI and/or NVA. If there is no improvement in visual acuity after a regimen of 3-6 monthly injections, treatment with anti-VEGF may be discontinued. Treatment intervals between two consecutive doses should not be shorter than 4 weeks.

Anti-VEGF injections may be stopped if visual acuity has not improved by at least five letters on the ETDRS chart or central foveal thickness has not decreased from baseline after three consecutive monthly doses. The injections may likewise be discontinued if visual acuity is stable or if the OCT shows a resolved macular edema even if vision has no improvement i.e. a "sub-optimal" outcome is reached.

Intraocular injections of a dexamethasone implant and a low (1 mg) dose intravitreal triamcinolone remain options for the treatment of CRVO-ME. If a steroid is the first line of treatment, the patients should be examined for changes in intraocular pressure and the formation or progression of cataracts during their follow-up visits. Repeat injections with a dexamethasone implant may be required at four to six monthly intervals until visual acuity is stable. More frequent injections of either steroid will increase the risk of increased IOP and/or cataract formation. The risks are greater with the use of a low dose (1 mg) intravitreal triamcinolone when compared to the dexamethasone implant.

RECOMMENDATION FOR ISCHEMIC CRVO

Dense scatter pan-retinal photocoagulation should be applied once NVI or NVA are noted.

If regular monthly follow-up is not possible, PRP may be appropriate even if NVI, NVA and NVG are not yet present. PRP should be guided by ischemic fluorescein angiographic findings of $\geq$10 DA of capillary non-perfusion and/or the presence of RAPD.

Follow-up

Evaluation

The follow-up evaluation includes a history and ocular examination.

History

A follow-up history should include changes in the following:

- Symptoms
- Systemic status (pregnancy, blood pressure, serum cholesterol, blood glucose)

Examination

- Visual acuity
- Undilated slit-lamp biomicroscopy and gonioscopy with careful iris examination for early iris or angle neovascularization [52]
- Pupillary assessment for a relative afferent pupillary defect
- Intraocular pressure (IOP
- Stereoscopic assessment of the posterior pole after dilation of the pupils
- OCT imaging
- Peripheral retina and vitreous examination

PROVIDER AND SETTING

The ophthalmologist should perform most of the examination and any associated surgery. The ophthalmologist may supervise trained individuals with certain aspects of data collection. The ophthalmologist should review and monitor the data collected. The ophthalmologist must moreover be familiar with the specific recommendations of relevant clinical trials which address the complexities of the diagnosis and treatment for retinal vascular occlusive diseases. *(I++, Good Quality, Strong Recommendation).*

The Philippine Academy of Ophthalmology has made a consensus statement regarding the role of the ophthalmologist in the delivery of intravitreal agents. (See Appendix 3)

COUNSELING AND REFERRAL

The ophthalmologist should co-manage a patient with RVO together with a primary care physician for holistic care of the systemic condition and should communicate examination results to the physician.[31] *(II++, Good Quality, Strong Recommendation)* The risk to the fellow eye should also be communicated to both the primary care provider and the patient. [9,15] *(I+, Moderate Quality, Strong Recommendation)* Vision may be lost despite being treated according to the recommendations in this document. Patients whose conditions fail to respond to therapy and those for whom further treatment is unavailable should be provided with proper professional support and offered referral for counseling, vision rehabilitation, or social service as appropriate.[68] *(I++, Good Quality, Strong Recommendation)* Vision rehabilitation helps to restore some functional ability, [69] and patients with functionally limiting postoperative visual impairment should be referred for vision rehabilitation and social services.[68]

SOCIOECONOMIC CONSIDERATIONS

The AAO has calculated lines-saved values for anti-VEGF agents. When looking at the US dollars per quality-adjusted life years (QALY), this was US$824 (PhP45:US$1 = PhP37,080) for bevacizumab versus US$1572 (PhP45:US$1 = PhP70,740) for grid laser, US$5536 (PhP45:US$1 = PhP249,120) for dexamethasone intravitreal implant, and US$25,566 (PhP45: US$1 = PhP1,150,470) for ranibizumab. [70]

APPENDIX 1. PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades reported here have been adapted from the AAO PPP on Diabetic Retinopathy 2016.
Details of these grading systems are reported in the Methods and Key to Ratings presented below.

Methods and Key to Ratings

Preferred Practice patterns® should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) (I++; I+;I-;II++,II+; II-; III) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) . GRADE is a systematic approach to grading the strength of the total body of evidence (Good, Moderate, Insufficient) that is available to support recommendations on a specific clinical management issue (Strong, Discretionary). Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency or Healthcare Research and Policy, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or, RCTs with a very low risk of bias
I+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
II++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g. case reports, case series)

- Recommendations for care are formed based on the body of evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very unlikely to have an important impact on our confidence in the estimate of effect is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain-either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

APPENDIX 2: Consensus on Intravitreal Injection Technique: VitreoRetina Society of the Philippines

Vascular endothelial growth factor (VEGF) has been shown to play a central role in the pathophysiologic process underlying neovascular eye diseases. As such, anti-VEGF based pharmacologic agents have emerged as a highly effective treatment modality for various visually debilitating retinal and choroidal vascular pathologies. The introduction of these pharmacologic agents directly into the vitreous cavity by means of an injection through the pars plana has become a widely performed ophthalmic procedure both locally and overseas.

As the sole physician organization of vitreoretinal specialists in the country, the VitreoRetina Society of the Philippines (VRSP), in coordination with the Philippine Academy of Ophthalmology (PAO), through a review of current evidence and a consensus among its members has developed guidelines for the performance of intravitreal injections in the Philippine setting to ensure patient safety and to maximize the benefits Filipino patients may obtain from this highly valuable treatment modality.

I. All intravitreal injections should be performed by a Philippine Board of Ophthalmology certified ophthalmologist who is knowledgeable, skilled and comfortable in the diagnosis and comprehensive management of retinal diseases for which anti-VEGF treatment is indicated, and adept at minimizing the risks and managing the potential complications associated with trans pars plana delivery of these medications.

II. Clinical Setting of Care:

- It is suggested that the procedure be performed in an operating theater or in a room/facility specifically dedicated for intravitreal injections.[1,2]

III. Preprocedural Issues

- Informed Consent [3]
    i. An informed consent has to be signed by the patient prior to the procedure.
    ii. The consent form should include the name of the drug to be injected, the indication for injection, the potential risks and benefits of the use of anti-VEGF agents and of the procedure itself.
    iii. Information must be fully explained to the patient.
    iv. A consent form specific for an individual drug is recommended.

- Currently, there is no data that indicates anticoagulant use will affect visual outcomes after intravitreal injection. However, there is an increased likelihood of subconjunctival hemorrhage at the site of injection.
- Medical Clearance
    i. The benefits, risks and indications of anti-VEGF injections should be carefully reconsidered in the following situations:
        1. Patients with a history of myocardial infarction, any cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within the past 4 months [4]
        2. Major surgery within 28 days
        3. Uncontrolled hypertension
        4. Pregnancy
    ii. Necessity for medical clearance is at the discretion of the attending ophthalmologist. While arteriothromboembolic events have been reported, the direct causative relation between stroke and intravitreal anti-VEGF injection use has not been established.

IV. Surgical Site Preparation

- Intravitreal injections are intraocular procedures that merit equal attention to adherence to principles of asepsis and sterile technique as for conventional intraocular surgeries.
- As part of the World Health Organization Surgical Safety Checklist,[5] "time-out" or surgical site marking is recommended.

- Pre-operative dilation is performed at the discretion of the attending ophthalmologist
- There is no evidence to support that the instillation of a topical antibiotic solution prior to injection reduces the risk of subsequent intraocular infection. Pre-operative antibiotics may be administered at the discretion of the attending ophthalmologist.
- Preoperative disinfection of the *periocular skin* with 10% povidone iodine and a minimum exposure time of 3 minutes is suggested. 10% aqueous chlorhexidine may be used as an alternative in patients with hypersensitivity to povidone iodine. [6]
- The use of a newly opened bottle of topical anesthetic is recommended.
- 5% povidone iodine should be applied onto the *conjunctival cul-de-sac* or *lower fornix* with a minimum contact time of 30 seconds. [6,7,8,9,10,11]
- The use of a sterile solid-blade lid speculum[9, 10] or any type of occlusive dressing is recommended to isolate the lashes from the site of injection.

V. Injection Procedure

- As part of good surgical practice, the use of a sterile eye sheet or equivalent drapes,[11] the donning of sterile surgical gloves and the wearing of a surgical mask [11, 12] are advised. The surgical assist is advised to wear a surgical cap and mask.
- The injection site should be 3 to 3.5 mm from the corneoscleral limbus for aphakic and pseudophakic eyes, and 3.5 to 4 mm for phakic eyes.
- The use of a sterile 30-gauge needle is recommended for intravitreal injection of anti-VEGF drugs.
- Once the needle is withdrawn, the ophthalmologist may apply a sterile cotton applicator to prevent reflux of liquid vitreous.
- The ophthalmologist should assess central retinal artery perfusion by checking for gross vision *or* venous pulsation via indirect ophthalmoscopy.
- Anterior chamber paracentesis may be performed in cases with evidence of a sustained rise in intraocular pressure.
- Bilateral Same Day Injections [13]
    i. Each eye should be prepared with povidone-iodine separately.
    ii. A completely new and different surgical set of sterile eye sheet, lid speculum, instruments, 30-gauge needle and syringe should be utilized.
    iii. Whenever feasible, separate vials of medication with different lot numbers should be used for each eye.
- There is no evidence to suggest that the instillation of post-injection antibiotics confers additional benefit in reducing the risk of endophthalmitis following intravitreal injections. Post injection antibiotics may be administered at the discretion of the attending ophthalmologist.

VI. Post-Injection Management

- Post-injection follow-up is recommended within 7 days.
- Patient should be instructed to return sooner if with symptoms of inflammation or infection.

This consensus statement is subject to re-evaluation and revision as new evidence-based studies on intravitreal anti-VEGF injections become published and new practice patterns evolve.

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