International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 192-203 www.ijdmsrjournal.com ISSN: 2582-6018

Neovascular Glaucoma in Central Retinal Vein Occlusion (CRVO): A Contemporary Assessment Strategies and Therapeutic Approach

Author: Dr. Siddharth Mishra
Co-Author: Prof. Dr. Prasanta Kumar Nanda

Date of Submission: 05-12-2025 Date of Acceptance: 15-12-2025

SUMMARY
Neovascular glaucoma (NVG) represents one of the most severe and vision-threatening complications arising from central retinal vein occlusion, with the potential to precipitate irreversible blindness when inadequately managed. This comprehensive review synthesizes current knowledge regarding diagnostic differentiation between ischemic and non-ischemic presentations, delineates emerging assessment methodologies, and critically evaluates therapeutic interventions including pan-retinal photocoagulation (PRP) and anti-vascular endothelial growth factor (anti-VEGF) treatment modalities. Contemporary evidence suggests that multimodal diagnostic approaches incorporating both functional and structural imaging yield superior classification accuracy compared to isolated assessment techniques. Furthermore, combined therapeutic strategies may optimize long-term outcomes while mitigating adverse effects inherent to monotherapy approaches.

I. INTRODUCTION

Clinical Significance and Disease Burden

Central retinal vein occlusion represents a substantial cause of retinal vascular pathology, with variable clinical consequences ranging from relatively benign outcomes to catastrophic vision loss. The development of neovascular glaucoma constitutes the most severe complication trajectory, transforming what might initially appear as manageable retinal pathology into a relentless glaucomatous process culminating in permanent blindness. The temporal relationship between retinal vein occlusion and neovascular sequelae underscores the critical importance of early recognition and timely intervention.

Historical Context and Evolving Understanding

Earlier ophthalmological literature emphasized corticosteroid therapy and general supportive measures for retinal vein occlusion complications. Contemporary practice has substantially evolved, incorporating mechanistic insights into angiogenesis regulation, refined diagnostic capabilities through advanced imaging technologies, and increasingly sophisticated pharmaceutical interventions. Yet significant controversies persist regarding optimal timing of therapeutic interventions, appropriate patient selection criteria, and the relative merits of various treatment modalities.

Scope and Organization

This review systematically addresses four interconnected clinical domains:
(1) Pathophysiological mechanisms underlying neovascular glaucoma development;
(2) contemporary diagnostic strategies for differentiation between ischemic and non-ischemic disease presentations;
(3) critical appraisal of prophylactic and therapeutic interventions; and
(4) synthesis of evidence regarding combination treatment approaches. The overarching objective involves facilitating clinical decision-making through evidence-based recommendations while acknowledging persistent knowledge gaps requiring future investigation.

Pathophysiological Foundations of Neovascular Glaucoma

Fundamental Mechanism: Hypoxia-Driven Angiogenesis

The development of anterior segment neovascularization in response to retinal vein occlusion represents a consequence of tissue hypoxia rather than direct infectious or inflammatory processes. When venous drainage becomes obstructed, the retinal tissue transitions into an oxygen-deprived microenvironment triggering compensatory vascular proliferation. This adaptive response, while potentially beneficial in other physiological contexts, becomes pathological when neovascularization encroaches upon the anterior chamber angle and trabecular meshwork.

Role of Vascular Endothelial Growth Factor

The discovery of vascular endothelial growth factor (VEGF) fundamentally transformed understanding of ocular neovascular diseases. VEGF functions as a potent secreted signaling molecule that orchestrates endothelial cell proliferation, migration, and enhanced vascular permeability. Experimental investigations in primate models definitively established that VEGF alone suffices to induce iris neovascularization and subsequent glaucoma formation. Conversely, selective VEGF antagonism substantially suppresses neovascular development in comparable animal models.

Significantly, aqueous humor VEGF concentrations substantially exceed those in non-ischemic presentations, supporting the mechanistic rationale for anti-VEGF therapeutic strategies specifically in ischemic variants. The temporal dynamics of VEGF expression appear closely coupled to the severity and extent of retinal hypoxia, explaining the variable neovascular progression patterns observed across the clinical spectrum.

Counterbalance: Angiogenic Inhibitory Pathways

Beyond VEGF, physiological homeostasis depends upon endogenous angiogenesis suppressors maintaining equilibrium. Pigment epithelium-derived factor (PEDF) represents a particularly significant endogenous inhibitor, with compromised production or activity contributing to pathological neovascularization. The pathophysiological framework conceptualizes neovascular glaucoma as resulting from disruption of this delicate equilibrium between pro-angiogenic and anti-angiogenic factors, with hypoxic stress systematically favoring neovascular signaling pathways.

Anatomical Consequences

The proliferation of fibrovascular tissue at the iris root and anterior chamber angle initiates a cascade of structural changes. Initial iris surface neovascularization may progress to angle involvement, ultimately leading to trabecular meshwork obstruction through fibrovascular tissue proliferation. This mechanical obstruction of aqueous humor outflow mechanisms generates the dramatically elevated intraocular pressures characteristic of neovascular glaucoma. The pathological process transforms the anterior chamber into a zone of progressive fibrotic remodeling, with iris neovascularization occasionally regressing even as angle involvement progresses, creating a dissociation between anterior segment and functional glaucomatous severity.

Classification and Risk Stratification of Central Retinal Vein Occlusion

Dichotomization: Ischemic Versus Non-Ischemic Presentations

Contemporary nosology distinguishes central retinal vein occlusion into ischemic (iCRVO) and non-ischemic (niCRVO) phenotypes, a classification with profound prognostic and therapeutic implications. This distinction fundamentally reflects the extent of retinal capillary dropout and tissue perfusion adequacy rather than merely the anatomical location of venous obstruction.

Ischemic CRVO encompasses presentations with extensive retinal capillary occlusion and widespread tissue hypoxia, establishing the pathophysiological substrate for neovascular complications. Non-ischemic CRVO conversely demonstrates preserved capillary perfusion with central retinal thickness preservation and more favorable visual prognosis, though transformation toward ischemic phenotypes occurs with sufficient frequency to warrant careful monitoring.

Clinical Risk Spectrum

Natural history studies demonstrate that approximately half of ischemic CRVO patients will experience iris neovascularization development within six months of acute onset, with subsequent anterior chamber angle involvement occurring in roughly 40 percent of cases and frank neovascular glaucoma supervening in approximately 30 percent. Critically, between 55 and 65 percent of ischemic presentations never progress to clinically apparent neovascular glaucoma, highlighting the substantial heterogeneity in disease trajectory and the risk of unnecessarily aggressive prophylactic intervention.

Distinction from Branch Retinal Vein Occlusion (BRVO)

Branch retinal vein occlusion (BRVO) warrants separate consideration given its markedly different natural history. Neovascular glaucoma remains an exceptionally rare complication of branch occlusion, occurring in fewer than 1% of cases. This striking difference reflects the limited spatial extent of retinal ischemia in BRVO, as the obstructed vascular territory constitutes a minority of total retinal perfusion. The requirement for approximately 50 percent or greater capillary non-perfusion to trigger significant neovascular pathology explains the divergent disease trajectories between CRVO and BRVO, with BRVO predominantly manifesting retinal rather than anterior segment neovascularization, neither of which typically progresses to glaucomatous disease.

Diagnostic Classification: Contemporary Assessment Approaches
DIAGNOSTIC ALGORITHM
Classification of Ischemic vs Non-Ischemic CRVO

■ STEP 1 — INITIAL CLINICAL ASSESSMENT
• Measure visual acuity
• Check for RAPD (≥0.7 log units suggests ischemia)
• Dilated fundus examination (hemorrhage, disc edema, cotton wool spots)

■ STEP 2 — FUNCTIONAL TESTING
• Electroretinography (ERG): b-wave amplitude ↓ ≥40%
• Visual field testing: central scotoma ± peripheral loss
• Functional findings collectively strengthen ischemic suspicion

---

■ STEP 3 — MORPHOLOGICAL IMAGING
• Fluorescein angiography (FA) to evaluate:
– Capillary non-perfusion zones
– FA leakage
• Non-perfusion continuum reference:
<30 DD = low risk
30–75 DD = moderate risk
>75 DD = high ischemic risk

■ STEP 4 — ADVANCED IMAGING
• OCT Angiography (OCTA):
– Deep capillary plexus dropout
– FAZ enlargement
– Presence of p-MLM sign (outer plexiform hyperreflectivity)
• Ultra-widefield FA:
– Quantifies global non-perfusion
– Enables ischemic index calculation

■ STEP 5 — QUANTITATIVE RISK ASSESSMENT (ISCHEMIC INDEX)
• Ischemic Index = Proportion of retina with non-perfusion
• Key thresholds:
>35% → Strong predictor of ischemic CRVO
>45% → Strong association with anterior segment neovascularisation
• Predictive value:
– >35% predicts ischemic conversion in ~75% of early non-ischemic cases

---

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 192-203 www.ijdmsrjournal.com ISSN: 2582-6018

■ STEP 6 — FINAL CLASSIFICATION
- Integrate functional + FA + OCTA + ischemic index findings
- Classify as:
  – Non-Ischemic CRVO
  – Ischemic CRVO (high risk for NVG; requires tight surveillance)

Clinical Monitoring and Prediction of Neovascular Glaucoma Development

Temporal Dynamics of Neovascular Manifestation

Longitudinal studies tracking natural disease progression reveal critical temporal patterns: anterior segment neovascularization predominantly emerges within the first 6-7 months following acute ischemic CRVO onset, with cumulative incidence reaching plateau beyond this interval. Approximately 80 percent of patients who will develop neovascular glaucoma experience disease onset within 6-8 months, supporting the designation of NVG as "100-day glaucoma" in recognition of its characteristically early manifestation.

This temporal pattern has profound implications for surveillance frequency and intervention timing: weekly or biweekly examination intervals appear warranted during the first 6-month high-risk period, with subsequent examination frequency potentially reduced based on absence of neovascular developments. Extended follow-up exceeding 12 months appears unnecessary in the absence of documented neovascular progression.

Imaging Parameters Predicting Neovascular Risk

Recent investigations have identified specific imaging metrics correlating with neovascular development probability. Central retinal thickness (CRT) elevation on optical coherence tomography at follow-up encounters associates with increased NVG risk, suggesting that macular edema severity may reflect underlying retinal hypoxia intensity. Anterior segment OCTA (AS-OCTA) provides non-invasive quantification of iris vasculature distribution and intensity, with quantitative measurements demonstrating superior correlation to neovascularization severity compared to qualitative slit-lamp assessments.

Demographic and Systemic Risk Factors

Patient age significantly influences neovascular transformation probability: individuals aged 65 years or older demonstrate substantially higher propensity for non-ischemic CRVO conversion toward ischemic phenotypes compared to younger cohorts. The presence of co-existing primary open-angle glaucoma substantially increases NVG development risk and independently predicts worse visual outcomes, likely reflecting decreased optic nerve reserve and enhanced susceptibility to glaucomatous damage.

Multi-Parameter Risk Integration

Optimal clinical practice integrates demographic factors (age, glaucoma history), baseline imaging parameters (ischemic index, non-perfused areas, CRT), functional metrics (RAPD, visual acuity), and temporal evolution patterns to establish individualized risk assessment and surveillance protocols. Eyes demonstrating low peripheral ischemic index values with absence of posterior pole non-perfusion appear to warrant less intensive surveillance than those with extensive central ischemia or rapidly progressing non-perfusion.

Pan-Retinal Photocoagulation: Mechanism, Efficacy, and Controversy

Historical Context and Current Role

Pan-retinal photocoagulation has occupied a central role in retinal vascular disease management for over five decades, with initial enthusiastic adoption predicated upon observation that scattered laser treatment appeared to suppress neovascular development. However, subsequent prospective investigations revealed substantially more nuanced efficacy patterns than early reports suggested, generating persistent clinical controversy regarding appropriate indications, optimal timing, and patient selection criteria.

Proposed Mechanisms of Action

Photocoagulation effects operate through at least two distinct biological mechanisms. Oxygen tension modification: Laser application destroys the metabolically active photoreceptor-pigment epithelium complex, which represents the retina's primary oxygen consumer. Simultaneously, photocoagulation-induced physical disruption of tissue barriers enhances oxygen diffusion from the choroid into photocoagulated retinal regions. This creates a microenvironment of relative hyperoxia, which through autoregulatory mechanisms induces

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 192-203 www.ijdmsrjournal.com ISSN: 2582-6018

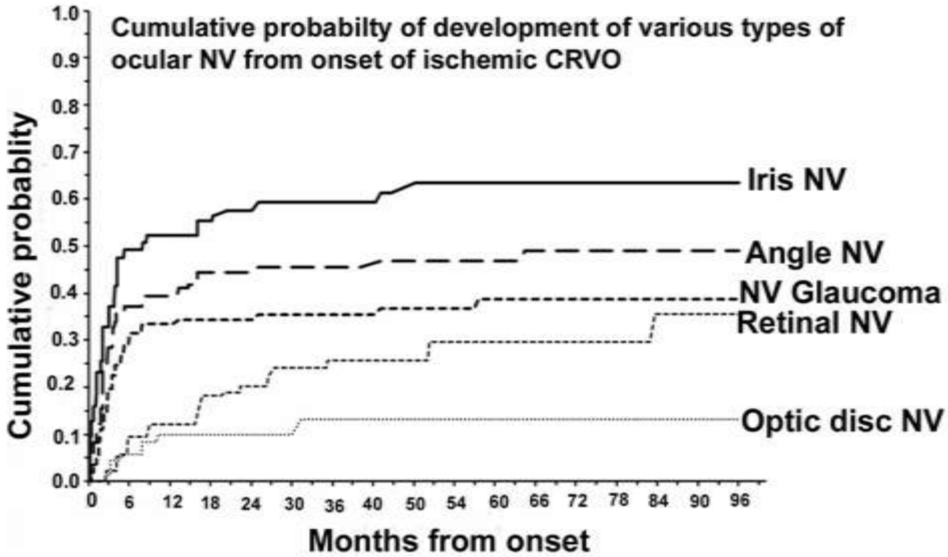
vasoconstriction and suppresses oxygen-driven hypoxic signaling.

Growth factor modulation: PRP produces complex effects on angiogenic signaling. VEGF levels demonstrate both decreased expression in some studies (reflecting destruction of VEGF-producing retinal cells) and increased expression in others (reflecting recruitment of hypoxic-response cells to treatment boundaries). Conversely, endogenous angiogenic inhibitors including PEDF and transforming growth factor-beta demonstrate relatively consistent upregulation following photocoagulation, potentially contributing to neovascularization suppression.

Efficacy in Preventing Iris Neovascularization

The definitive Central Vein Occlusion Study Group investigation demonstrated that prophylactic PRP prior to iris neovascularization manifestation fails to substantially reduce iris neovascularization incidence. Instead, the most robust PRP efficacy emerges when iris neovascularization has already become clinically apparent, at which point photocoagulation substantially reduces both iris neovascularization progression and angle neovascularization development probability.

However, Hayreh's extensive longitudinal studies paradoxically suggested that early prophylactic PRP (within 3 months of iCRVO onset) modestly reduced iris neovascularization incidence compared to untreated controls, though this reduction did not translate into reduced neovascular glaucoma development. This apparent disconnect between iris neovascularization suppression and glaucoma prevention reflects the multifactorial nature of NVG pathogenesis: iris involvement does not invariably precede or predict angle involvement, and trabecular meshwork obstruction occurs through fibrovascular tissue mechanisms partially independent of iris surface neovascularization status.



Adverse Effects and Visual Field Consequences

Among the most concerning PRP complications is peripheral visual field constriction resulting from excessive laser spot density or treatment extension into peripheral retina. This adverse effect particularly impacts patients with CRVO-associated central visual field losses (scotomas), where loss of peripheral field compounds existing central vision restriction, potentially exacerbating patient disability. Studies indicate that 40-55 percent of photocoagulated eyes demonstrate measurable peripheral field constriction.

Yet the natural history of untreated CRVO includes substantial visual field deterioration from inherent disease mechanisms: approximately 55 percent of ischemic CRVO patients develop central scotomas within 3 months of onset, while 17 percent present with peripheral defects at diagnosis. The critical clinical dilemma emerges from the fact that PRP-induced field loss may cause visual disability equivalent to untreated disease progression, yet prophylactic PRP fails to prevent neovascular glaucoma development in the majority of cases.

Optimal Timing: Reconciling Prevention and Harm

European Society of Retina Specialists guidelines recommend reserving PRP for circumstances where iris or angle neovascularization has become clinically evident, combined with weekly to biweekly patient monitoring to detect neovascular developments requiring intervention. As a practical compromise acknowledging the challenge of maintaining intensive surveillance, early prophylactic PRP within 90 days of iCRVO onset is suggested as an alternative when close follow-up cannot be reliably achieved.

This staged approach reflects contemporary understanding that prophylactic PRP provides modest neovascularization suppression at the cost of visual field damage, while reactive PRP (after neovascularization manifestation) provides superior neovascularization control. The optimal individual strategy depends upon baseline disease severity, patient demographics, physician-patient communication regarding uncertainties, and feasibility of surveillance.

Intravitreal Anti-VEGF Therapy: Promise and Limitations

Mechanistic Rationale and Pilot Experience

Selective VEGF antagonism represents an intuitively appealing therapeutic approach given the well-established role of VEGF in neovascular glaucoma pathogenesis. Multiple pharmaceutical agents have entered clinical practice for intravitreal administration, including bevacizumab (humanized monoclonal anti-VEGF antibody), ranibizumab (anti-VEGF antibody fragment), and aflibercept (VEGF receptor fusion protein). Early case reports and small series documented dramatic regression of iris neovascularization within 1-4 weeks following intravitreal anti-VEGF injection, seemingly validating the mechanistic approach.

Efficacy and Duration Limitations

More rigorous investigation revealed substantial complexity. While anti-VEGF therapy effectively reduces iris neovascularization and produces short-term intraocular pressure reduction, these beneficial effects prove temporally limited. Prospective studies demonstrate that intraocular pressure reduction becomes evident within 1 month but lacks durability during extended follow-up, with pressure re-elevation occurring in substantial patient proportions after 6 months despite continued therapy.

Critically, neovascular glaucoma recurrence develops approximately 7 months after final anti-VEGF injection in the majority of cases, essentially replicating the untreated disease trajectory with temporal delay. Monthly ranibizumab injections modestly reduce retinal non-perfusion area expansion during active treatment but this benefit reverses when transition to pro re nata (as-needed) dosing occurs. These observations suggest that anti-VEGF therapy functions as a temporizing measure rather than achieving durable disease modification.

Mechanistic Explanations for Limited Efficacy

Several biological factors explain anti-VEGF therapy's insufficient long-term efficacy. Short pharmacokinetic half-life: Most anti-VEGF agents demonstrate intraocular half-lives measured in days, requiring frequent re-dosing to maintain therapeutic concentrations. Patient compliance challenges, practical limitations on injection frequency, and cost considerations necessitate dosing intervals that allow VEGF re-accumulation between treatments.

Polyvalent angiogenic pathway activation: Retinal ischemia stimulates multiple angiogenic pathways beyond VEGF, including angiopoietin, fibroblast growth factor, and other cytokines. VEGF inhibition alone insufficiently suppresses the totality of pro-angiogenic signaling, permitting neovascular progression through alternative pathways.

VEGF-independent hypoxic signaling: The profound hypoxia characterizing ischemic CRVO activates cellular stress responses through hypoxia-inducible factors and related pathways operating independently of VEGF availability. Continuing hypoxic signaling perpetuates neovascular stimulus despite VEGF blockade.

Anti-VEGF Cannot Replace Photocoagulation

Current evidence establishes that anti-VEGF monotherapy does not provide sufficient durable neovascularization suppression to substitute for photocoagulation. Eyes receiving anti-VEGF therapy alone demonstrate equivalent long-term intraocular pressure elevation and neovascular glaucoma development probability compared to untreated controls, confirming anti-VEGF's role as adjunctive therapy rather than primary intervention.

Combination Therapeutic Approaches: Synergistic Potential

Rationale for Integration

Sequential or concurrent application of anti-VEGF therapy followed by photocoagulation theoretically offers several potential advantages. Anti-VEGF's rapid neovascularization regression (within 1-4 weeks) extends the therapeutic window for photocoagulation effectiveness, since laser treatment typically requires several weeks to produce observable neovascularization suppression. Additionally, rapid anterior segment neovascularization reduction prior to photocoagulation reduces inflammation, VEGF concentrations, and operative complexity during subsequent laser treatment.

Clinical Benefits of Combination Strategy

Multiple retrospective and small prospective investigations have documented superior neovascular glaucoma control with combination PRP plus anti-VEGF compared to photocoagulation alone. Combination-treated patients demonstrate faster intraocular pressure reduction (2-3 weeks versus 4-6 weeks), more sustained pressure control during extended follow-up, and reduced hyphema and post-operative complications in patients subsequently requiring vitrectomy.

Specifically, pre-operative anti-VEGF injection 5-14 days prior to vitrectomy substantially reduces post-operative vitreous hemorrhage probability and neovascular glaucoma recurrence. The elevated aqueous and vitreous VEGF concentrations during peri-operative periods appear to predict post-operative complications; VEGF reduction prior to surgery mitigates these risks.

Limitations and Unresolved Questions

Despite potential advantages, combination therapy does not produce dramatic superiority to photocoagulation monotherapy in all outcome domains. Long-term intraocular pressure reduction does not exceed that achieved with optimized photocoagulation alone. Visual acuity outcomes demonstrate minimal difference between combination-treated and photocoagulation-alone patients, suggesting that neither modality substantially preserves vision in advanced presentations.

Furthermore, emerging evidence suggests that anti-VEGF therapy may impair photoreceptor function, as measured by full-field electroretinography, indicating potential for unanticipated retinal toxicity at higher exposure levels. The optimal duration of anti-VEGF combination therapy, ideal injection frequencies, and specific clinical scenarios justifying combination versus sequential approaches remain incompletely defined.

Emerging Intracameral Administration

Recent investigations have proposed direct intracameral anti-VEGF injection rather than intravitreal administration, theoretically achieving higher target tissue concentrations while minimizing systemic exposure. Intracameral injection appears particularly appealing for silicone oil-filled eyes, where ensuring adequate vitreous drug concentration proves problematic. These novel administration approaches remain in early investigation phases with limited clinical data.

Management of Established Neovascular Glaucoma

Disease Staging and Treatment Pathways

Clinically apparent neovascular glaucoma is conceptually divided into three stages reflecting progressive pathological changes. Pre-glaucomatous phase (Phase I) encompasses iris neovascularization with normal intraocular pressure, during which anti-neovascularization therapy aims to prevent glaucoma development. Open-angle neovascular glaucoma (Phase II) involves iris and angle neovascularization with elevated intraocular pressure but gonioscopic evidence of angle patency. Angle-closure neovascular glaucoma (Phase III) demonstrates complete or near-complete angle synechiae with refractory pressure elevation.

Pharmacological IOP Management

Standard glaucoma medications addressing aqueous humor dynamics include topical β-adrenergic antagonists reducing aqueous production, α-2-adrenergic agonists with dual aqueous suppression and uveoscleral outflow facilitation mechanisms, and carbonic anhydrase inhibitors (both topical and systemic) that suppress aqueous secretion by the ciliary epithelium. These conventional approaches frequently prove inadequate monotherapy given the severe IOP elevation characteristic of neovascular glaucoma, often requiring multiple agent combinations or surgical intervention.

Surgical Options for Refractory Pressure

When pharmacological therapy fails to achieve target pressures, multiple surgical approaches address aqueous humor dynamics. Trabeculectomy remains a foundational procedure though fibrosis frequently compromises filtration bleb function in neovascular glaucoma given the heightened inflammatory state. Glaucoma drainage devices (Ahmed, Baerveldt implants) bypass trabecular pathways entirely through artificial drainage to episcleral space or orbital compartments.

Cyclophotocoagulation and cyclocryotherapy reduce aqueous production by destructing ciliary epithelium, providing options when drainage-based approaches prove inadequate.

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 192-203 www.ijdmsrjournal.com ISSN: 2582-6018

These destructive procedures carry risks of chronic hypotony and accelerated cataract formation but remain necessary for advanced refractory disease.

Emerging and Future Therapeutic Possibilities

Endogenous Angiogenic Inhibitors

Beyond direct VEGF antagonism, research increasingly focuses on enhancing endogenous angiogenic suppression. PEDF restoration through gene therapy approaches, transforming growth factor-beta modulation, and interleukin-6 pathway antagonism represent promising preclinical developments. These strategies theoretically address the fundamental pathophysiology (disturbed pro/anti-angiogenic balance) rather than merely blocking single mediators.

Gene Therapy Approaches

Innovative gene therapy modalities deliver DNA or RNA sequences promoting sustained expression of angiogenic inhibitors. Plasminogen kringle 5, prolyl hydroxylase domain inhibitors, and recombinant adeno-associated virus delivery platforms demonstrate experimental efficacy in animal models. Clinical translation faces regulatory and technical hurdles, but these approaches represent potential alternatives for patients with inadequate response to conventional therapy.

Novel Insulin Receptor Substrate Inhibition

Recent development of topical antisense oligonucleotide formulations targeting insulin receptor substrate-1 has demonstrated impressive pre-clinical and phase II/III trial results in neovascularization prevention. This emerging therapy exploits intracellular signaling mechanisms distinct from VEGF pathways, potentially providing clinical benefit to patients with anti-VEGF-resistant disease.

Synthesis: Unified Approach to NVG Management

Diagnostic Strategy

Comprehensive diagnostic assessment incorporating functional parameters (RAPD, visual fields, ERG, acuity), morphological imaging (ophthalmoscopy, fluorescein angiography), and advanced imaging (OCTA, ultra-widefield angiography) enables confident ischemic/non-ischemic differentiation and risk stratification. Multimodal approaches substantially surpass isolated modality reliability, justifying increased diagnostic complexity in clinical practice.

Risk Assessment and Surveillance Protocol

Following iCRVO diagnosis, patients warrant monthly examination intervals during the critical 6-month post-onset period, with weekly or biweekly surveillance if extensive ischemia or rising ischemic indices are documented. Baseline ischemic indices exceeding 35 percent, posterior pole non-perfusion exceeding 10 disk areas, elevated RAPD, and severe baseline vision reduction identify highest-risk subsets. Low peripheral ischemia without posterior involvement and ischemic indices below 20 percent predict minimal neovascular glaucoma risk permitting more conservative surveillance.

Therapeutic Algorithm

Table 1: Staged Management of Neovascular Glaucoma

Disease Phase	Management Approach
Phase I (Iris neovascularization, normal IOP)	• Initiate intravitreal anti-VEGF injection. • Intensive surveillance for angle involvement. • PRP timing depends on followup reliability and baseline ischemia severity. • AntiVEGF alone is inadequate longterm; PRP within 4–8 weeks improves outcomes.
Phase II (Open- angle NVG)	• Immediate antiVEGF plus comprehensive PRP (same session or within 1–2 weeks). • Start topical IOPlowering medications targeting aqueous suppression and outflow. • Monthly antiVEGF injections for the first 3–4 months.
Phase III (Closed- angle NVG with high IOP)	• Emergency antiVEGF injection. • Maximal topical therapy + systemic carbonic anhydrase inhibitors. • Cyclophotocoagulation or cyclocryotherapy reserved for refractory cases or failed drainage procedures.

Long-term Perspective

The fundamental challenge in neovascular glaucoma management remains the absence of truly curative therapy producing durable disease arrest. Current approaches optimize damage prevention through early intervention, but the underlying pathophysiology—extensive retinal ischemia driving relentless hypoxic neovascular signaling—resists complete pharmacological suppression. Future progress likely requires multi-targeted approaches simultaneously addressing VEGF signaling, alternative angiogenic pathways, and fundamental hypoxic cellular responses through gene therapy or novel molecular interventions.

II. CONCLUSIONS AND FUTURE DIRECTIONS

Neovascular glaucoma secondary to ischemic central retinal vein occlusion represents an ophthalmological emergency demanding rapid diagnosis, risk stratification, and appropriately timed intervention. Current practice evidence supports the following evidence-based recommendations:

Diagnostic Practice: Integrated multimodal assessment combining functional testing, conventional imaging, and advanced technologies provides superior classification accuracy and risk identification compared to isolated modality reliance.

Surveillance Intensity: High-risk presentations warrant intensive monitoring during the initial 6-month period when neovascular development probability peaks, with subsequent intervals adjusted based on observed disease progression.

Therapeutic Approach: Contemporary evidence does not support photocoagulation monotherapy prior to neovascular manifestation for most patients. Instead, intensive surveillance permitting reactive photocoagulation upon neovascular appearance, combined with immediate anti-VEGF therapy when neovascular developments are documented, appears optimal. Combination PRP plus anti-VEGF provides superior short-term outcomes compared to either monotherapy.

Acknowledged Limitations: Persistent uncertainties regarding optimal anti-VEGF dosing intervals, ideal photocoagulation timing and extent, and patient selection criteria for prophylactic versus reactive approaches necessitate continued investigation. Substantial heterogeneity in individual disease trajectories complicates unified management recommendations.

Future Research Priorities: Large-scale prospective randomized controlled trials comparing monotherapy versus combination approaches, evaluation of emerging anti-ischemic and angiogenesis-inhibitor technologies, and development of improved risk prediction models incorporating genetic and biomarker parameters represent essential research frontiers. Additionally, investigation of novel molecular targets distinct from VEGF pathways may overcome therapeutic resistance observed in current regimens.

The management paradigm for neovascular glaucoma continues evolution, with modern approaches offering substantially improved outcomes compared to earlier eras while remaining inherently limited by the fundamental challenge of arresting hypoxia-driven pathological angiogenesis. Enhanced understanding of ischemic disease biology, coupled with advancing diagnostic capabilities and evolving therapeutic armamentarium, provides optimism for continued clinical progress while acknowledging that prevention of high-risk ischemic retinal vein occlusions remains the most effective strategy for neovascular glaucoma elimination.

Critical Perspectives and Controversies

Prophylactic Photocoagulation Debate

The medical literature contains substantive disagreement regarding prophylactic PRP indications. Conservative approaches emphasize that majority of ischemic CRVO patients never develop neovascular glaucoma, cautioning against treating the substantial cohort destined to experience natural disease arrest with prophylactic intervention causing visual field damage. More aggressive approaches counter that NVG development, when it occurs, causes irreversible blindness, making prophylactic treatment justifiable despite modest efficacy uncertainty.

This controversy reflects genuine uncertainty regarding individual patient neovascularization risk and incomplete understanding of PRP's mechanisms. Resolution requires better risk prediction tools enabling selective prophylactic intervention in highest-risk patients while sparing others unnecessary treatment.

Anti-VEGF Efficacy Reassessment

Early enthusiasm for anti-VEGF therapy has given way to more sober assessment recognizing the temporizing rather than curative nature of such treatment. The observation that anti-VEGF primarily delays rather than prevents NVG development reframes therapeutic expectations. Practitioners must communicate these limitations clearly to patients, explaining that anti-VEGF provides valuable time potentially allowing spontaneous disease resolution in susceptible individuals while preventing acute vision-threatening pressure elevation.

Imaging Technology Integration

The rapid proliferation of advanced imaging modalities (OCTA, ultra-widefield fluorescein angiography) creates new diagnostic possibilities yet establishes new practice complexities. Different imaging modalities sometimes yield discordant results regarding non-perfusion extent and location, requiring clinician judgment synthesizing multiple perspectives. Standardization of imaging protocols and quantitative metrics remains incomplete, potentially limiting practice uniformity.

Table 2. Key Clinical Domains and Essential Points in the Management of Neovascular Glaucoma

Clinical Domain	Essential Points
Risk Stratification	• Baseline ischemic index, age, glaucoma history, and extent of posterior pole non-perfusion identify the highest-risk patients.
Diagnostic Certainty	• Multimodal assessment (functional + morphological + advanced imaging) yields superior accuracy compared with single-modality evaluation. • Early acute presentations may require re-evaluation as ischemic features evolve.
Surveillance Intensity	• Intensive follow-up is warranted during the first 6 months post-CRVO, the peak risk window for NVG. • Follow-up intervals can be reduced once no neovascularisation is present beyond this period.
Therapeutic Timing	• Prophylactic PRP is generally not recommended. • Reactive PRP initiated at the onset of iris/angle neovascularisation provides a more favorable risk–benefit profile.
Combination Strategy	• Anti-VEGF combined with PRP results in faster neovascular regression and better short-term IOP control compared with monotherapy. • Long-term superiority remains uncertain.
Anti-VEGF Expectations	• Anti-VEGF agents offer rapid but temporary suppression of neovascularisation. • Patients should be counseled that anti-VEGF delays—but does not prevent—NVG progression.
Patient Communication	• Discuss the severity and variable natural history of NVG. • Emphasize uncertainties regarding prevention strategies and the importance of close follow-up.

REFERENCES

[1]. Hayreh S. Neovascular glaucoma. Prog Retinal Eye Res. (2007) 26:470–485. doi: 10.1016/j.preteyeres.2007.06.001

[2]. Nishinaka A, Tanaka M, Aoshima K, Kuriyama A, Sasaki T, Otsu W, et al. The pathological association between the anterior eye segment and the retina in a murine model of neovascular glaucoma. FASEB J. (2022) 36:e22323. doi: 10.1096/fj. 202101917R

[3]. HayrehS.Photocoagulationforretinalveinocclusion.ProgRetinalEyeRes.(2021) 85:100964. doi: 10.1016/j.preteyeres.2021.100964

[4]. Nicholson L, Vazquez-Alfageme C, Patrao N, Triantafyllopolou I, Bainbridge J, Hykin P, et al. Retinal nonperfusion in the posterior pole is associated with increased risk of neovascularization in central retinal vein occlusion. Am J Ophthalmol. (2017) 182:118–25. doi: 10.1016/j.ajo.2017.07.015

[5]. The Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. . Arch

Ophthalmol. (1997) 115:486–91. doi: 10.1001/archopht.1997.01100150488006
[6]. Schmidt-Erfurth U, Garcia-Arumi J, Gerendas B, Midena E, Sivaprasad S, Tadayoni R, et al. Guidelines for the management of retinal vein occlusion by the European Society of Retina Specialists (EURETINA). Ophthalmologica. (2019) 242:123–62. doi: 10.1159/000502041
[7]. BrownD,WykoffC,WongT,MarianiA,CroftD,SchuetzleK,etal.Ranibizumab in preproliferative (ischemic) central retinal vein occlusion: the rubeosis anti-VEGF (RAVE) trial. Retina. (2014) 34:1728–35. doi: 10.1097/IAE.0000000000000191
[8]. Lee Y, Kim Y. Central retinal thickness changes and risk of neovascular glaucoma after intravitreal bevacizumab injection in patients with central retinal vein occlusion. Sci Rep. (2022) 12:2051. doi: 10.1038/s41598-022-06121-x
[9]. Ehlers J, Spirn M, Lam A, Sivalingam A, Samuel M, Tasman W. Combination intravitreal bevacizumab/panretinal photocoagulation versus panretinal photocoagulation alone in the treatment of neovascular glaucoma. Retina. (2008) 28:696–702. doi: 10.1097/IAE.0b013e3181679c0b
[10]. Mannina A, Olivier M, Patrianakos T. Neovascular glaucoma. Dis Mon. (2021) 67:101137. doi: 10.1016/j.disamonth.2021.101137
[11]. Havens S, Gulati V. Neovascular glaucoma. Dev Ophthalmol. (2016) 55:196–204. doi: 10.1159/000431196
[12]. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature. (1992) 359:843–5. doi: 10.1038/359843a0
[13]. SengerD,GalliS,DvorakA,PerruzziC,HarveyV,DvorakH.Tumorcellssecrete a vascular permeability factor that promotes accumulation of ascites fluid. Science. (1983) 219:983–5. doi: 10.1126/science.6823562
[14]. Leung D, Cachianes G, Kuang W, Goeddel D, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science. (1989) 246:1306–9. doi: 10. 1126/science.2479986
[15]. KeckP,HauserS,KriviG,SanzoK,WarrenT, FederJ,etal.Vascularpermeability factor, an endothelial cell mitogen related to PDGF. Science. (1989) 246:1309–12. doi: 10.1126/science.2479987
[16]. Plate K, Breier G, Weich H, Risau W. Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. Nature. (1992) 359:845–8. doi: 10.1038/359845a0
[17]. Tang Y, Cheng Y, Wang S, Wang Y, Liu P, Wu H. Review: the development of risk factors and cytokines in retinal vein occlusion. Front Med. (2022) 9:910600. doi: 10.3389/fmed.2022.910600
[18]. ShimaD,AdamisA,FerraraN,YeoK,YeoT, AllendeR,etal.Hypoxicinduction of endothelial cell growth factors in retinal cells: identification and characterization of vascular endothelial growth factor (VEGF) as the mitogen. Mol Med. (1995) 1:182–93.
[19]. Tolentino M, Miller J, Gragoudas E, Chatzistefanou K, Ferrara N, Adamis A. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. Arch Ophthalmol. (1996) 114:964–70. doi: 10.1001/archopht.1996.01100140172010
[20]. Adamis A, Shima D, Tolentino M, Gragoudas E, Ferrara N, Folkman J, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol. (1996) 114:66–71. doi: 10.1001/archopht.1996.01100130062010
[21]. Bhisitkul R, Robinson G, Moulton R, Claffey K, Gragoudas E, Miller J. An antisense oligodeoxynucleotide against vascular endothelial growth factor in a nonhuman primate model of iris neovascularization. Arch Ophthalmol. (2005) 123:214–9. doi: 10.1001/archopht.123.2.214
[22]. Pe’er J, Folberg R, Itin A, Gnessin H, Hemo I, Keshet E. Vascular endothelial growth factor upregulation in human central retinal vein occlusion. Ophthalmology. (1998) 105:412–6. doi: 10.1016/S0161-6420(98)93020-2
[23]. Jung S, Kim K, Sohn S, Yang S. Association of aqueous humor cytokines with the development of retinal ischemia and recurrent macular edema in retinal vein occlusion. Invest Ophthalmol Vis Sci. (2014) 55:2290–6. doi: 10.1167/iovs.13-13587

[24]. Gao G, Ma J. Tipping the balance for angiogenic disorders. Drug Discov Today. (2002) 7:171–2. doi: 10.1016/s1359-6446(01)02160-2

[25]. Spranger J, Osterhoff M, Reimann M, Ristow M, Francis M, Cristofalo V, et al. Loss of the antiangiogenic pigment epithelium-derived factor in patients with angiogenic eye disease. Diabetes. (2001) 50:2641–5. doi: 10.2337/diabetes.50.12.2641