Recent Advances in Retinal Vascular Diseases
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Course Description
This course will provide the latest information on retinal vascular diseases, such as diabetic retinopathy (DR) and retinal vascular occlusions (RVO).

Goal
Provide attendees with recent developments in the early diagnostic strategies and therapeutic advances for DR and RVO and discuss integration of these innovations into clinical practice.

Learning Objectives
At the conclusion of this course, attendees will be able to:

• Understand clinical relevance of accurate diagnostic evaluation of patients with DR and RVO.
• Identify patients at risk of developing serious DR and RVO
• Understand emerging imaging technology such as SD OCT, OCTA and Fundus Autofluorescence
  Analyze the rationale for emerging treatments for DR and RVO
• Enhance patient care by evaluating the current array of treatment options and clinical trial opportunities
• Encourage a collaborative approach between the patient, the primary care physician, the optometrist and the ophthalmologist

Abstract
Retinal vascular diseases, such as DR and RVO are on the rise. Detecting early clinical findings can prevent vision loss and, more importantly, disability and premature death from these conditions. This course will provide the latest information on diagnostic strategies and treatment advances to help clinicians improve patient outcomes and preserve vision.
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Course Outline

I. Diabetic Retinopathy

- Diabetic retinopathy is a leading cause of new cases of legal blindness among working-age Americans and represents a leading cause of blindness in this age group worldwide.
- The prevalence rate for retinopathy for all adults with diabetes aged 40 and older in the United States is 28.5% (4.2 million people).
- An estimate of the prevalence rate for vision-threatening diabetic retinopathy in the United States is 4.4% (0.7 million people).
- An estimated 11% (25.6 million) of Americans aged 20 years or older have either been diagnosed or remain undiagnosed with diabetes.

II. Natural history

- Diabetic retinopathy (DR) progresses in an orderly fashion from mild to more severe stages when there is not appropriate intervention.
  - It is important to recognize the stages when treatment may be most beneficial
- Non-proliferative (NPDR) stages of diabetic retinopathy are characterized by:
  - Retinal vascular related abnormalities - microaneurysms, intraretinal hemorrhages, venous dilation, and cotton-wool spots.
  - As DR progresses, there is a gradual closure of retinal vessels that results in impaired perfusion and retinal ischemia. Signs of increasing ischemia include venous abnormalities (e.g., dilation, beading, loops), IRMA, and more severe and extensive vascular leakage characterized by increasing retinal hemorrhages and exudation. When these signs progress beyond certain defined thresholds, severe non-proliferative diabetic retinopathy (NPDR) is diagnosed.
    - Such patients should be considered candidates for treatment with panretinal photocoagulation.
- Diabetic Macular Edema (DME)
  - Increased retinal vascular permeability that occurs at these or later stages of retinopathy may result in retinal thickening (edema) and lipid deposits (hard exudates).
  - Clinically significant macular edema (CSME) is a term used to describe retinal thickening and/or adjacent hard exudates that either involve the center of the macula or threaten to involve it:
    - Hard exudates within 500 µm of the fovea with associated retinal thickening
    - Retinal thickening within 500 µm of the fovea
    - An area of retina thickening more than 1500 µm in diameter that is less than 1500 µm from the fovea
  - Patients with CSME should be considered for prompt treatment, particularly when the center of the macula is already involved or if retinal thickening and/or...
hard exudates are very close to the center.

- **Proliferative Diabetic Retinopathy (PDR)**
  - Charactized by the onset of neovascularization at the inner surface of the retina induced by more global retinal ischemia.
  - New vessels on or near the optic disc (NVD) and new vessels elsewhere in the retina (NVE) are prone to bleed, resulting in vitreous hemorrhage.
  - These new vessels may undergo fibrosis and contraction; this and other fibrous proliferation may result in epiretinal membrane formation, vitreoretinal traction bands, retinal tears, and traction or rhegmatogenous retinal detachments.
  - When new vessels are accompanied by vitreous hemorrhage, or when new vessels at the optic disc occupy greater than or equal to about one-quarter to one-third disc area, even in the absence of vitreous hemorrhage, PDR is considered high-risk.
  - Neovascular glaucoma can result from new vessels growing on the iris (NVI) and anterior chamber angle structures. Patients with neovascular glaucoma or high-risk PDR should receive prompt pan retinal photocoagulation and should consider initiating anti-vascular endothelial growth factor (VEGF) therapy.

### III. DR Management

- **Healthy diet and lifestyle**
  - That includes exercise and weight control may decrease the risk of developing diabetes in some patients.
  - The *Diabetes Control and Complications Trial (DCCT)* demonstrated that improved blood sugar control can delay the onset and slow the progression of diabetic retinopathy.
  - It also showed a strong exponential relationship between the risk of diabetic retinopathy and the mean hemoglobin A1c (HbA1c) level.
    - Good glycemic control is a AIC 6-7%
    - For each 10% decrease in the HbA1c (e.g., from 9% to 8.1%), there was a 39% decrease in the risk of progression of retinopathy

- **Mild and moderate NPDR**
  - Patients with retinal microaneurysms and occasional blot hemorrhages should be re-examined within 6 to 12 months.

- **Severe NPDR**
  - In eyes with severe NPDR, the risk of progression to proliferative disease is high.
  - Half of patients with severe NPDR will develop PDR within 1 year, and 15% will have high risk NPDR.
  - Currently, thanks to the *Panorama study and the DRCR network*, there is role for the use of Anti-VEGF therapy in the management of severe NPDR
• **High-risk PDR**
  
  o These patients should be re-examined within 2 to 4 months. The presence of any three of the following four features characterizes high-risk PDR:
    - Neovascularization (at any location)
    - Neovascularization at the optic disc
    - New vessels within one-disc diameter of the optic nerve that are larger than 1/4 to 1/3-disc area in size
    - Vitreous or preretinal hemorrhage
  
  o The risk of severe visual loss among patients with high-risk PDR is reduced substantially by treatment using pan retinal photocoagulation (PRP).
    - It usually induces regression of retinal neovascularization.
  
  o Very recently, the **DRCR study protocol S** has demonstrated that the use of anti-VEGF agents (ranibizumab), may be an alternative to PRP.
    - The ranibizumab group did appear to have better average visual acuity, less visual field loss and fewer number of vitrectomies, but did involve a higher number of treatments.
    - Some physicians still consider that PRP remains the first choice for management of PDR. The anti-VEGF alternative is particularly effective for patients who can follow-up regularly.

• **Diabetic Macular Edema (CSME)**
  
  o The traditional treatment for CSME has been laser surgery.
  
  o However, current data from multiple well-designed studies demonstrate that intravitreal anti-VEGF agents provide a more effective treatment for center-involved CSME.

  o **Anti-VEGF Therapy**: Multiple studies have demonstrated the benefit of anti-VEGF therapy in center-involving diabetic macular edema.
    - At the present time, anti-VEGF therapy is the initial treatment choice for center-involving macular edema, with possible subsequent or deferred focal laser treatment.
    - The **READ-2** and the **DRCR Protocol I** also showed that anti-VEGF with either prompt or deferred laser photocoagulation was better than either laser alone. The **DRCR protocol T** demonstrated that anti-VEGF therapy using bevacizumab, ranibizumab, or aflibercept is an effective treatment for center-involving CSME.
    - In 2017, the FDA approved ranibizumab for all stages of diabetic retinopathy, based on the Protocol S, RIDE and RISE studies.
    - The **RIDE and RISE studies** found that more patients receiving ranibizumab treatment had a > 2 or a > 3 step DR improvement, compared with the sham crossover group at a median level of moderate NPDR.
IV. DR Management Conclusion

- The clinical indications for use in patients with mild-moderate NPDR also depend upon other factors such as systemic blood glucose control, compliance with follow-up examinations, and clinical judgment is extremely important for guiding therapy.
- Should note that severe adverse side effects are associated with intravitreal injections.
  - These include infectious endophthalmitis, cataract formation, retinal detachment, and elevated IOP, particularly for the corticosteroids such as triamcinolone and Ozurdex.

V. Retinal vein Occlusions (RVO)

- Second most common retinal vascular disorder.
- The patient population includes people over 40 years of age.
  - The most common age range is from the 6th to the 7th decade.
- The prevalence of RVOs is about 0.5% in the general world population and is estimated to affect more than 16 million people worldwide.
  - African Americans have a similar incidence of CRVO to white Americans and a gender predilection does not seem to exist. The main risk factor for both CRVO and BRVO is older age.
- A prior RVO is a risk factor for an RVO in the fellow eye.
  - The chance of a person with a pre-existing CRVO developing a CRVO in the fellow eye is 1% per year.
  - Patients with a BRVO in one eye have a 10% risk of developing an RVO of either type in the fellow eye over 3 years.
- Risk factors for BRVO include arterial hypertension, hyperlipidemia, diabetes, and coronary artery disease, retinal phlebitis and, local vascular factors such as arterial-venous crossing.
- Risk factors for CRVO are glaucoma, carotid occlusive disease, sleep apnea and other hematologic conditions such as factor V Leiden and elevated homocysteine.

Younger patients, below the age of 50 years, warrant consideration of an evaluation for other hematologic risk factors.

VI. Natural History

- Patients with CRVO’s are likely to develop macular edema. Additionally, approximately 25% of patients with CRVO will develop iris neovascularization, and occasional patients may develop retinal neovascularization.
- Once diagnosed with a CRVO, patients need to be evaluated every 4 to 6 weeks for
• approximately 6 months by means of a slit lamp biomicroscopic examination and undilated gonioscopy to detect iris or angle neovascularization that leads to neovascular glaucoma.
• An extensive study of the natural history of RVO categorized BRVOs as mild, moderate, or marked, based on the level of capillary nonperfusion seen angiographically.
  o Eyes with BRVO and significant capillary nonperfusion can develop retinal neovascularization and vitreous hemorrhage, but they are much less likely to develop neovascular glaucoma than eyes with CRVO.
  o Macula- involving RVOs are usually acutely symptomatic with the sudden onset of visual symptoms, including a decrease in central vision and/or a corresponding visual field defect.
  o Early clinical findings include vascular tortuosity, venous dilation of the affected veins, retinal edema, intraretinal hemorrhages, cotton-wool spots, and occasionally hard exudates or even retinal detachment in the affected region.
  o Over time, the acute process resolves, and the hemorrhages may clear, along with the cotton-wool spots. In general, the macular edema persists and is a common cause of visual dysfunction unless appropriately treated.
  o Collaterals may also develop between the retinal venules and the choroidal circulation at the disc following a CRVO and between the superior and inferior retinal veins in a BRVO.
  o The prognosis for vision loss due to BRVO depends on the degree of perfusion and the location of the occlusion. Recovery of visual acuity usually occurs due to the development of collateral vessels that help with the venous drainage and subsequent resolution of retinal edema and ischemia.

VII. RVO Management
• Prevention
  o There is a strong relationship between BRVO and systemic vascular disorders such as arterial hypertension and peripheral vascular disease. The best prevention is to manage risk factors aggressively by optimizing control of diabetes mellitus, hypertension, and hyperlipidemia.
• BVOS (1984) demonstrated a benefit of grid laser treatment for visual acuity outcomes in eyes with BRVO and macular edema.
  o It also demonstrated the benefit of laser for ischemic BRVO in reducing complications related to retinal neovascularization.
  o This has been the standard of care until only recently, when the results of intravitreal corticosteroids and anti-VEGF agents in this setting were reported.
• Anti-VEGF
  o In several studies, anti-VEGF agents have been shown to be both safe and effective in treating the macular edema as well as in limiting neovascularization associated with RVO’s.
  o Currently, three anti-VEGF agents are used routinely for the treatment of
BRVOs; two are FDA-approved (ranibizumab and aflibercept), but bevacizumab remains off-label. Initial treatment for patients with macular edema and CRVO is similar.

- **BRVO**: The BRAVO study and the subsequent HORIZON trial demonstrated efficacy of monthly intravitreal ranibizumab. Other smaller, level 2 studies have demonstrated the efficacy of bevacizumab for BRVO macular edema. The VIBRANT trial demonstrated the efficacy of aflibercept over grid laser treatment for macular edema in BRVO.

- **CRVO**: Several randomized controlled trials have also shown the efficacy of intravitreal anti-VEGF agents in treatment of macular edema with CRVO. The CRUISE trial showed improved vision. In the COPERNICUS study, aflibercept improves vision as well. Similar findings were shown in the GALILEO study with the use of bevacizumab.

- **Steroids**
  - Subsequent clinical trials have evaluated the efficacy of anti-VEGF agents and/or intravitreal corticosteroid injections.
  - The SCORE study for BRVO and CRVO evaluated the use of intravitreal corticosteroids vs laser.
    - The SCORE recommendations for BRVO were to consider macular grid laser treatment in eyes with BRVO and perfused macular edema leading to vision loss because the efficacy was similar in all treatment arms.
      - The SCORE CRVO trial also substantial visual gains at 1 year.
    - The GENEVA study evaluated the use of the intravitreal dexamethasone implant (Ozurdex) with either a CRVO or a BRVO. There was significant visual acuity gain at 90 days. The dexamethasone implant was FDA-approved in 2009. Fluocinolone (ILUVIEN), has also been shown to be beneficial in the treatment of BRVO macular edema up to 3 years following injection.
  - Severe adverse effects of intravitreal injections include endophthalmitis, cataract formation, retinal detachment, and elevated IOP.
    - Intraocular pressure elevations are particularly common with the use of intravitreal corticosteroids.
    - In conclusion, because of the favorable risk-to-benefit profile, the use of anti-VEGF agents is the preferred initial therapy. Either corticosteroids and/or grid laser treatment can be considered when there is an inadequate response.

**VIII. Retinal Artery Occlusion (RAO)**

- CRAO is a rare condition that has an incidence of approximately 1 per 100,000 in a U.S. population.
  - Risk Factors: Cigarette smoking, hypertension, body mass index, high serum lipid levels, diabetes, and cardiac disease are all important modifiable risk factors associated with retinal emboli.
- A CRAO commonly leads to retinal ischemia and subsequent cell death.
IX. RAO Management:

- A careful systemic evaluation for any underlying disorder(s) should guide therapy.
  - Specifically, causes of vasculitis, such as GCA, represent an ophthalmologic emergency.
    - In cases of GCA, prompt initiation of systemic corticosteroid therapy is critical to prevent vision loss in the fellow eye or vascular occlusion elsewhere.
- Acute, symptomatic CRAO and BRAO represent urgent ophthalmic conditions and require prompt evaluation.
  - Such occlusions may represent an important clinical indicator of a more severe systemic disorder (embolic or inflammatory) that may require a systemic medical evaluation that is targeted to the patient’s presentation and medical history. In
most cases of CRAO, a prompt referral to a stroke center for a medical evaluation is recommended because the risk of ischemic stroke is particularly increased during the first 1 to 4 weeks.

- The rationale for acute management of the ophthalmologic implications following a CRAO, whether conservative, thrombolytic, or interventional, is to attempt recover vision in the affected eye. Current evidence for effective interventional treatment for the ocular condition, other than corticosteroids for GCA, is controversial. Thrombolytic or interventional treatments that attempted to preserve or recover vision in CRAO or BRAO have not been proven to be effective at this time.

- Long-term pan retinal photocoagulation (PRP) treatment is recommended for patients who develop iris or retinal neovascularization.
  - Although PRP will not improve the visual acuity, it will likely decrease VEGF production and progression to iris neovascularization and neovascular glaucoma.

- For anterior segment neovascularization in the setting of profound retinal ischemia, a complete PRP treatment is also warranted. Again, off-label anti-VEGF agents may be considered to supplement the PRP.