Retinal Vascular Diseases: Treatment Updates

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Retinal Artery Occlusion

Branch Retinal Artery Occlusion (BRAO)

Pathogenesis
- 2/3 Embolic
  - Cholesterol (Hollenhorst plaque)
  - Atheromatous plaques from ipsilateral carotid
  - Yellow-orange & refractile
- Platelet-Fibrin
  - Carotid or cardiac thromboses
  - Long, smooth, white, intra-arterial plugs
- Calcific
  - Calcification of heart valve or aorta
  - Solid white non-refractile plugs

BRAO - Treatment

No proven treatment
- Ocular massage
- Paracentesis
- Hyperbaric oxygen
- Laser photocoagulation

CRAO - Treatment

Increased retinal oxygenation
- Carbogen (95% O2 & 5% CO2)

Increased retinal arterial blood flow
- Lowering IOP
  - Ocular massage
  - Paracentesis
  - IOP lowering medications

Reverse arterial obstruction
- Anticoagulation (IV Heparin)
- Fibrinolytic (tPA, streptokinase, urokinase)

Prevent hypoxic retinal damage
- Antioxidant
- N-methyl D-aspartate (NDMA) inhibitors
Thrombolysis

- Tissue Plasminogen Activator – tPA
  - Fibrinolytic agent for clot lysis
  - tPA administration
    - Intra-venous → IV-tPA
    - Improved access
    - Reduced procedural time
    - No neuro-intervention (Decreased risk of direct vascular injury & hemorrhagic complications)
    - Intra-arterial → IA tPA

European Assessment Group for Lysis in the Eye (EAGLE) Study

- IA tPA vs. Conservative Standard Treatment
- No statistically significant difference in clinical improvement

Retinal Vein Occlusion

- Pathogenesis
  - Typically presents at arterio-venous crossing (artery & vein share common adventitial sheath)
  - Thickened artery results in compression of the venous tributary within spatial limits of sheath
  - Compression results in:
    - Turbulent blood flow
    - Endothelial cellular damage
    - Thrombosis and vein occlusion

Branch Retinal Vein Occlusion (BRVO)

- BRVO Classification
  - PERFUSED
    - 70-75% of BRVO
    - Perfusion on FA
    - Better VA
    - Improved prognosis
    - Hemorrhages
    - Cotton wool spots
    - Macula edema
  - NON-PERFUSED
    - 25-30% of BRVO
    - Non-perfusion on FA
    - Poorer VA
    - Worsen prognosis
    - Increased hemorrhages
    - Cotton wool spots
    - Macula edema
    - APD

Branch Retinal Vein Occlusion Study (BVOS)

- Multi-center randomized controlled prospective clinical trial
- Independent angiographic reading center
To determine whether macular argon laser photocoagulation can improve visual acuity in eyes with macular edema reducing vision to 20/40 or worse.

To determine whether scatter argon laser photocoagulation can prevent the development of neovascularization in a non-perfused eye.

To determine whether peripheral scatter argon laser photocoagulation can prevent vitreous hemorrhage.

**BVOS Goals**

**BVOS: Results & Recommendations**

<table>
<thead>
<tr>
<th>3-year VA ≥ 20/40</th>
<th>3-year VA ≤ 20/200</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREATED</td>
<td>60%</td>
</tr>
<tr>
<td>NON-TREATED</td>
<td>34%</td>
</tr>
</tbody>
</table>

**Recommendation:**

Laser photocoagulation (3 months after onset of vein occlusion) for perfused macular edema significantly improves visual outcome in BRVO with vision 20/40 or worse.


**Recommendation:**

The development of neovascularization was less in treated non-perfused eyes.

No advantage to PRP before neovascularization occurred even in presence of extensive capillary non-perfusion.


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The development of neovascularization was less in treated non-perfused eyes.

No advantage to PRP before neovascularization occurred even in presence of extensive capillary non-perfusion.
To determine whether peripheral scatter argon laser photocoagulation can prevent vitreous hemorrhage.

**Recommendation:**
The development of vitreous hemorrhage was significantly less in treated eyes.

**Pathogenesis**
- Common connective tissue sheath surrounding vasculature
- Thickened central retinal artery walls
- Compression of the central retinal vein
- Thrombus formation at or posterior to the lamina cribosa
- Central retinal vein occlusion (CRVO)

**Classification of CRVO**

**PERFUSED**
- 75-80% of CRVO
- Perfusion on FA
- Better VA
- Improved prognosis
- Hemorrhages
- Cotton wool spots
- Disc edema

**NON-PERFUSED**
- ~30% of CRVO
- Non-perfusion on FA
- Poorer VA
- Worsen prognosis
- Increased hemorrhages
- Cotton wool spots
- Disc edema
- APD

**CVOS Goals**

- Does early PRP prevent iris neovascularization?
- Does macula grid photocoagulation improve visual acuities in eyes with reduced vision secondary to CRVO macular edema?
- What is the natural history of eyes with CRVO with little or no evidence of ischemia?
- Is early PRP more effective at first identification of NVI in preventing ocular morbidity and regression of neovascular glaucoma?

**CVOS Study Groups**

- **GROUP P (PERFUSED)**
  - CRVO < 1 year
  - <10DD on FA
  - Evaluated for natural history of disease progression
  - May also be monitored in Group M

**Central Retinal Vein Occlusion Study (CVOS)**

- Multi-center randomized controlled prospective clinical trial
- 9 Study centers
- Independent angiographic reading center
- 728 eyes with CRVO
CVOS STUDY GROUPS

- **GROUP N (NON-PERFUSED)**
  - CRVO < 1 year
  - >10DD on FA
  - Group N eyes were randomly assigned to PRP or monitor

- **GROUP I (INDETERMINATE)**
  - CRVO < 1 year
  - Hemorrhages resulting in obscuration of fundus and evaluation of perfusion status

- **GROUP M (MACULA EDEMA)**
  - CRVO >/= 3 months
  - Macula edema confirmed on FA @ angiographic reading center
  - No macular non-perfusion resulting in decreased VA
  - VA between 20/50 - 5/200
  - Macula edema was randomly assigned for observation or grid photocoagulation

CVOS RESULTS & RECOMMENDATIONS

- Does early PRP prevent iris neovascularization?
- Is early PRP more effective at first identification of NVI in preventing further ocular morbidity and progression to neovascular glaucoma?

What are the risks factors for retinal ischemia?
- CRVO of duration < 1 month
- VA < 20/200
- 5-9DD of retinal capillary non-perfusion

- What are the risk factors for progression to NVI / NVA?
  - Non-perfusion is significantly correlated to neovascularization.
  - <30DD nonperfusion, < neovascularization
  - >70DD nonperfusion, > neovascularization
  - Large amounts of retinal hemorrhages
  - Recent onset CRVO
  - Male gender
Group N (NON-PERFUSED)

- 16% of all patients developed NVI
- New NVI developed with less frequency in prophylactically treated eyes (20%) vs. the non-treated group (35%) (not significant)
- Regression of NVI within 1 month of laser tx:
  - 56% Prompt regression in untreated group
  - 22% Prompt regression in prophylactic group

Non-perfusion is a significant predictor of neovascularization.

Eyes which are indeterminate should be treated as non-perfused.

CLINICAL PEARLS GROUP N (NON-PERFUSED)

- Prophylactic PRP failed to prevent future NVI development.
- Prophylactically treated eyes with PRP demonstrated slower regression of NVI upon retreatment.
- Prophylactic PRP CRVO only in cases when retinal integrity can not be assessed.
- PRP should be performed upon initial observation of NVI / NVA.

CVOS RESULTS & RECOMMENDATIONS

<table>
<thead>
<tr>
<th>FA INITIAL VA</th>
<th>FINAL VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREATED &lt;EDEMA</td>
<td>20/60 20/200</td>
</tr>
<tr>
<td>NON-TREATED &gt;EDEMA</td>
<td>20/125 20/160</td>
</tr>
</tbody>
</table>

Grid photoocoagulation decreased angiographically evident macular edema.

No statistically significant improvement in VA between treated and untreated eyes with macular edema.

Grid photoocoagulation is NOT recommended for CRVO macular edema.
What is the natural history of eyes with CRVO which demonstrate little or no evidence of ischemia (<10DD of non-perfusion)?

What are Group P (perfused) results?

Progression of group P and I eyes to non-perfusion occurs most rapidly during the first 4 months of disease presentation.

Conversion to ischemia can occur at any time during CRVO duration.

Conversion to ischemia:
- 34% of Group P (perfused)
- 83% of Group I (indeterminate)

The strongest predictor of neovascularization development are:
- FA
- VA

Prospective randomized clinical trial
- 12 Month
- N=397

To evaluate the efficacy and safety of anti-VEGF therapy for BRVO macular edema

Recommendation:
- Alternative treatment for BRVO macular edema vs. laser photocoagulation.
- Ranibizumab beneficial for
  - Retinal hemorrhage prevent laser photocoagulation
  - Avoid laser photocoagulation scotoma.

Prospective randomized clinical trial
- 12 Month
- N=392

To evaluate the efficacy and safety of anti-VEGF therapy for CRVO macular edema
CRUISE Ranibizumab 0.3mg (n=132) Ranibizumab 0.5mg (n=130) Sham (n=133)

VA Improvement of ≥15 Letters
- 6 Months: 46.0% 47.7% 16.9%
- 12 Months: 47.0% 50.8% 33.1%

Change in Letters
- 6 Months: +12.7 +14.9 +0.8
- 12 Months: +13.9 +13.9 +7.3

Recommendation:
- Alternative treatment for BRVO macular edema vs. laser photocoagulation.
- Ranibizumab beneficial for:
  - Retinal hemorrhage prevent laser photocoagulation
  - Avoid laser photocoagulation scotoma.

COPERNICUS - Controlled Phase 3 Evaluation of Repeated Intravitreal Administration of VEGF Trap-Eye in Central Retinal Vein Occlusion

COPERNICUS Aflibercept Sham

VA Improvement of ≥15 Letters
- 6 Months: 46.0% 47.7% 16.9%
- 12 Months: 47.0% 50.8% 33.1%

Change in Letters
- 6 Months: +12.7 +14.9 +0.8
- 12 Months: +13.9 +13.9 +7.3

Recommendation:
- Gain ≥15 letters (56% aflibercept vs. 12% sham).
- Suggest benefit of early anti-VEGF intervention.

GALILEO - General Assessment Limiting Infiltration of Exudates in Central Retinal Vein Occlusion with VEGF Trap-Eye

GALILEO Aflibercept Sham

VA Improvement of ≥15 Letters
- 6 Months: 60.2% 22.1%

Change in Letters: +18 +3.3

Recommendation:
- Intravitreal triamcinolone compared with standard care for the treatment of vein occlusion macular edema.

SCORE Standard care versus Corticosteroid for Retinal vein occlusion (SCORE) Study

SCORE

Inclusion Criteria:
- CME ≥ 3 months & ≤ 18 months
- ETDRS BVA between 20/40 and 20/200
- OCT thickness ≥ 250µm

Exclusion Criteria:
- 4 months pre-trial use of systemic steroids
- Pregnancy
- Uveitis
- Diabetic retinopathy
- Recent neural events
- Glaucoma
- Neovascularization
- Previous treatments with TA, FA, or PRP

Patient classification: CRVO (Preferred VA <30, or Glaucoma), BRVO (Preferred VA <60 or Glaucoma)

Intravitreal triamcinolone compared with standard care for the treatment of vein occlusion macular edema.

SCORE – Intravitreal Triamcinolone
Follow-up: Q4months x 3 years

CRVO Macular Edema:
- IV TA (4mg)
- IVTA (4mg)
- Standard care (Observation of macular edema)

BRVO (HRVO) Macular Edema:
- IV TA (4mg)
- IVTA (4mg)
- Standard Care (Grid laser photocoagulation)
Standard care versus Corticosteroid for Retinal vein occlusion (SCORE) Study

<table>
<thead>
<tr>
<th>SCORE</th>
<th>Triamcinolone 1mg</th>
<th>Triamcinolone 4mg</th>
<th>Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Improvement of ≥ 15 Letters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRVO</td>
<td>27%</td>
<td>26%</td>
<td>7%</td>
</tr>
<tr>
<td>BRVO</td>
<td>26%</td>
<td>27%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Recommendation

- CRVO: Improved VA in treatment groups compared to observation
- BRVO: No difference in VA in treatment arms
- TA: Higher rates of IOP & cataract
- Standard improved safety profile

Ocular Manifestations of Carotid Artery Disease

- Supplies anterior two-thirds of cerebrum
  - Anterior cerebral artery
  - Middle cerebral artery
- Supplies the globe via ophthalmic artery
  - Short posterior ciliary arteries
  - Central retina artery

ANATOMY

- The carotid circulation is derived from the aortic arch:
  - Left common carotid artery is a direct descendant of the aortic arch
  - Right common carotid artery arises from the brachiocephalic trunk

INTERNAL CAROTID

- Supplies anterior two-thirds of cerebrum
  - Anterior cerebral artery
  - Middle cerebral artery
- Supplies the globe via ophthalmic artery
  - Short posterior ciliary arteries
  - Central retina artery

INTERNAL CAROTID

- Supplies the globe via ophthalmic artery
  - Short posterior ciliary arteries
  - Central retina artery

Ozurdex®

GENEVA Study Group

<table>
<thead>
<tr>
<th>GENEVA</th>
<th>DEX Implant 6.35mg</th>
<th>DEX Implant 6.75mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Response to 15 Letter @ Day 180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>41%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Central Retinal Thickness (µm) @ Day 180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-123±212</td>
<td>-119±203</td>
<td>-119±188</td>
<td></td>
</tr>
</tbody>
</table>
VERTEBRAL BASILAR SYSTEM

- Arises from subclavian artery
- Supplies posterior one-third of cerebrum

VERTEBRAL BASILAR SYSTEM

- Arises from subclavian artery:
  - Aorta → L subclavian → L Vertebral artery
  - Aorta → Brachiocephalic trunk → R subclavian → R Vertebral artery
  - R & L Vertebral arteries form a single basilar artery
  - Basilar artery bifurcates to form the R & L posterior cerebral arteries → Connects with the Circle of Willis

Ocular Ischemic Syndrome

- Demographics
  - Age range = 50-80 years
  - Mean age = 65 years
  - 67% male vs. 33% female

Ocular Ischemic Syndrome

- Risk factors
  - Hypertension
  - Ischemic Heart Disease
  - Smoking
  - Atherosclerotic Disease
  - Diabetes Mellitus
  - Hyperlipidemia / Hypercholesterolemia
  - Cerebral & Ocular TIA
  - CVA
  - Peripheral Vascular Disease

Ocular Ischemic Syndrome

- Symptoms
  - Reduced visual acuities
  - Ocular angina
  - Lost of vision in bright illumination
  - Cerebral and ocular TIA

Ocular Ischemic Syndrome

- Signs → Anterior Segment Findings
  - Ciliary flush
  - Edematous cornea
  - Sluggish pupil
  - Neovascularization of iris
  - Intra-ocular pressure
  - Ischemic uvexis

- Signs → Posterior Segment Findings
  - Mid-peripheral hemorrhages
  - Hollenhorst plaques
  - Cholesterol emboli
  - Dilated venous vasculature
  - Neovascularization of retinal
  - Central retinal artery occlusion with cherry red macula
  - Spontaneous CRA pulsation
Ocular Ischemic Syndrome

- Testing → Fundus Fluorescein Angiography (FFA)
  - Non-perfusion
  - Patchy choroidal filling
  - Increased arm to retina transit time
  - Increased artery to vein transit time
  - Late arterial staining
  - Electroretinogram (ERG)
    - Delayed recovery of b wave following photostress
  - Ophthalmodynamometry
    - Low ophthalmic artery pressure
  - Carotid auscultation

- Systemic Assessment
  - Carotid assessment
    - Non-invasive
      - Auscultation
      - Duplex
      - Magnetic resonance angiography (MRI / MRA)
      - Computerized tomography (CT)
    - Invasive
      - Arteriography
      - Digital subtraction angiography
  - Cardiac assessment
  - Laboratory assessment

Ocular Ischemic Syndrome

- Treatment and Management
  - Ocular
  - Systemic
    - Medical
    - Surgical
    - Interventional

Systemic Management of Carotid Artery Disease

- Medical
- Surgical

Ocular Ischemic Syndrome

- Ocular treatment and management
  - PRP
  - Manage glaucoma
  - Patient education of cerebral and ocular TIA

Carotid Endarterectomy (CEA)

- Procedure
  - General anesthesia with nerve block
  - Incision along sternocleidomastoid muscle
  - Exposure of surgical field comprised of common carotid artery and branches
  - Alteration of blood flow
    - Carotid shunt - plastic tube between ICA and CCA to provide a continuous flow of blood to brain
    - Temporary stoppage of blood
  - Atherosclerotic plaque dissected from artery wall
  - Artery wall debrided and flushed with heparin
  - Arterial wound closed by stitching patch of fabric or vein into the incision
GOAL: Does endarterectomy reduce risk of stroke with recent adverse CVA?

POPULATION:
- >80 years of age
- H/O hemispheric TIA
- Monocular TIA (<24 hrs)
- Non-debilitating CVA within previous 120 days
- Subgroups:
  - 30-69% stenosis
  - 70-99% stenosis
- All patients in both groups placed on ~1300 mg ASA therapy

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North American Symptomatic Endarterectomy Trial (NASCET)

Severe Stenosis (70-99%)

<table>
<thead>
<tr>
<th></th>
<th>Surgically Treated</th>
<th>Medically Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-operative CVA*</td>
<td>5.8%</td>
<td>3.3%</td>
</tr>
<tr>
<td>2 years S/P Treatment</td>
<td>9.0%</td>
<td>26%</td>
</tr>
</tbody>
</table>

*N: Pre-operative * 2 days preceding and 30 days S/P surgery

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European Carotid Surgery Trial (ESCT) Results

<table>
<thead>
<tr>
<th>Severe Stenosis (70-99%)</th>
<th>Surgically Treated</th>
<th>Medically Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-operative CVA*</td>
<td>7.5%</td>
<td>--%</td>
</tr>
<tr>
<td>3 years S/P Treatment</td>
<td>10.3%</td>
<td>16.8%</td>
</tr>
</tbody>
</table>

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Ocular Ischemic Syndrome

Surgical:
- NASCET (Sx)
  - Medical: 26% Stroke
  - Surgical: 9% Stroke
- Asx Carotid Endarterectomy Trial
  - Medical: 9.4% Stroke
  - Surgical: 4.7% Stroke
- EC-IC bypass (STA-MCA bypass)

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Carotid Stenting

- Carotid stents
  - Expandable balloon stent:
    - Stent mounted on balloon catheter
    - Catheter advanced to narrowed zone
    - Balloon inflated \( \rightarrow \) forces stent against the vessel wall
    - Balloon deflated
    - Catheter removed
  - Self-expanding stent:
    - Stent, "spring-loaded" into catheter & secured to catheter with deployer
    - Catheter & stent advanced to narrowing
    - Stent retracted facilitating stent expansion
    - Stent expands to normal size of vessel
    - Catheter extracted
    - Artery musculature maintains stent in position
    - Subsequently, artery forms a cellular layer over the stent \( \rightarrow \) stent becomes a part of the vessel

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Carotid Stenting

- Interventional cardiology
  - Local anesthetic to groin area
  - Introduction of catheter at groin area to engage leg femoral artery
    - (Alternative – arm entry)
  - Catheter advanced under x-ray guidance
  - Possible insertion of distal protection device for embolic protection
  - Catheter delivers stent
  - Stent deployed against the side of vessel \( \rightarrow \) opening vessel
SAPPHIRE

- Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)
  - Compared CAS to CEA
  - Cordis Carotid Stenting System
    - AngioGuard filter
    - PRECISE self-expanding stent
  - Population
    - Symptomatic patients \( \Rightarrow \) 50% stenosis by ultrasound
    - Asymptomatic patients \( \Rightarrow \) 80% stenosis by ultrasound

SAPPHIRE

- Co-morbidities
  - Congestive heart failure
  - Open heart surgery within 6 weeks
  - Recent myocardial infarction (\( > 24 \) hours and \( < 4 \) weeks)
  - Unstable angina
  - Concomitant severe coronary artery disease requiring carotid and coronary revascularization
  - Severe pulmonary disease
  - Contra-lateral carotid occlusion
  - Contra-lateral laryngeal palsy
  - Post-radiation treatment
  - Previous CEA recurrent stenosis
  - High cervical ICA lesions
  - CCA lesions below the clavicle
  - Severe tandem lesions
  - Greater than 80 years of age

SAPPHIRE

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS Carotid Artery Stenting</td>
<td>4.2%</td>
<td>6.7%</td>
<td>5.8%</td>
</tr>
<tr>
<td>CEA Carotid Endarterectomy</td>
<td>15.4%</td>
<td>11.2%</td>
<td>12.6%</td>
</tr>
</tbody>
</table>

- Percentage (%) endpoints:
  - Stroke, death, or myocardial infarction at 30 days
  - Ipsilateral stroke or death from neurologic causes within 31 days to one year

SAPPHIRE

- 1 year update
  - MI
    - CAS 2.5%, CEA 7.9%
  - Death
    - CAS 6.9%, CEA 12.6%
  - Stroke
    - CAS 5.7%, CEA 7.3%
  - Overall
    - CAS 11.9%, CEA 19.9%

- Conclusion:
  - Significant benefit of stenting over endarterectomy for in high risk patients

ARCHeR

- CCULINK for Revascularization of Carotids in High Risk Patients (ARCHeR)
- Prospective CAS clinical trial for:
  - High-surgical-risk patients
  - Non-surgical patients
- Risks
  - CABG / Valve surgery
  - Dialysis
  - Myocardial infarction within last 30 days
  - Uncontrolled diabetes
  - Unstable angina
  - S/P radical neck surgery
  - Contraindication to aspirin
  - Severe neck disease
  - Greater than 65 years of age
- ACCUNET Embolic Protection System (Guidant Corporation, Indianapolis, IN)

- Population
  - Symptomatic patients \( \Rightarrow \) 50% stenosis determined by angiography
  - Asymptomatic \( \Rightarrow \) 80% stenosis determined by angiography

ARCHeR

- ARCHeR study demonstrated:
  - Carotid stenting with a distal embolic protection device can be performed safely in a high-risk surgical population

<table>
<thead>
<tr>
<th>Event Free Survival (%)</th>
<th>CAS</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCHeR 1</td>
<td>91.7%</td>
<td>85.5%</td>
</tr>
<tr>
<td>ARCHeR 2</td>
<td>89.8%</td>
<td>85.5%</td>
</tr>
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</table>
Carotid Revascularization Endarterectomy versus Stent Trial (CREST)

- Multi-center randomized trial
- Sponsored by the National Institutes of Health (National Institute of Neurological Disorders and Stroke)
- Compare the efficacy of CAS (ACCULINK; Guidant, Temecula, CA, USA) versus carotid endarterectomy (CEA) in symptomatic patients with carotid stenosis. Moreover, CREST evaluates carotid stenting in a subset of patients that has been shown to gain the most benefit from carotid revascularization.

Population (Expected n=2500)
- Symptomatic (transient ischemic attack or ipsilateral non-disabling stroke within the prior 180 days) patients in accordance with NASCET classification
- Duplex imaging criterion is a 70% internal carotid artery stenosis
- In patients with intermediate stenoses (50%–70% by duplex), eligibility determined by angiographic documentation of a 50% stenosis.

Primary outcomes will be
- Stroke, myocardial infarction, or death during a 30-day peri-procedural period; and
- Ipsilateral stroke over the follow-up period extending up to 4 years

Crest

Conclusion:
- Increased age = increased death and stroke
- Octogenarians high risk
- Overall 30 day stroke/death rates
- Ongoing clinical trial

<table>
<thead>
<tr>
<th>30 Day Lead-in Phase to CAS</th>
<th>&lt;60 years old</th>
<th>60-69 years old</th>
<th>70-79 years old</th>
<th>&gt;80 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke &amp; Death</td>
<td>1.7%</td>
<td>1.3%</td>
<td>5.3%</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

CaRESS

- Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS)
- Population
  - N = 397 patients (254 CEA and 143 CAS)
  - Symptomatic (>50% stenosis) represented 32% of population
  - Asymptomatic (with >75% stenosis) represented 68% of population
- Procedure ratio
  - 2:1 :: CEA : CAS
- Primary endpoints
  - Death, stroke, or MI from 0 to 30 days
  - Death or stroke from 31 days to 1 year

CaRESS

Rates

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Day</td>
<td>2.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td>1 year</td>
<td>10.0%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Death Stroke MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Day</td>
<td>2.1%</td>
<td>4.4%</td>
</tr>
<tr>
<td>1 Year</td>
<td>10.9%</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

Anatomy

- Carotid based disease:
  - Occlusion of ipsilateral common and/or internal carotid artery
  - Stenosis results in poor hemodynamic flow to ipsilateral structures downstream including the ipsilateral ophthalmic artery
  - Ischemia to the ipsilateral anterior cerebral cortex (ipsilateral frontal, temporal and parietal lobe)
- Vertebral-basilar based disease:
  - Occlusion of the subclavian or innominate artery proximal to the origin of the vertebral artery
  - Blood is siphoned from the vertebral artery opposite to the side with the occluded artery
  - Shunted blood passes through the basilar artery and enters the ipsilateral vertebral artery through retrograde flow
  - Blood is “stolen” secondary to vertebral-basilar insufficiency
  - Partial ischemic to the brainstem, cerebellum, and medulla

Vertebral Basilar System

- Arises from subclavian artery
  - Aorta → L subclavian → L Vertebral artery
  - Aorta → Brachiocephalic trunk → R subclavian → R Vertebral artery
  - R & L Vertebral arteries form a single basilar artery
  - Basilar artery bifurcates to form the R & L posterior cerebral arteries → Connects with the Circle of Willis
  - Supplies posterior one-third of cerebrum
Anatomy

- Vertebral-basilar based disease:
  - Occlusion of the subclavian or innominate artery proximal to the origin of the vertebral artery
  - Blood is siphoned from the vertebral artery opposite to the side with the occluded artery
  - Shunted blood passes through the basilar artery and enters the ipsilateral vertebral artery through retrograde flow
  - Blood is “stolen” secondary to vertebral-basilar insufficiency
  - Partial ischemia to the brainstem, cerebellum, and medulla

Ocular Symptoms

- Carotid based disease:
  - Monocular reduced VA
  - Monocular loss of vision in bright illumination
  - Ocular angina
  - Ipsilateral ocular TIA

- Vertebral-basilar based disease:
  - Vertigo with associated sensation of moving objects
  - Inability to focus
  - Diplopia
  - Bilateral dimming / blurring of vision

Ocular Signs

- Carotid based disease:
  - Ciliary flush
  - Sluggish pupillary response
  - Neovascularization of the iris
  - Ischemic uveitis
  - Hemorrhages and microaneurysms of the mid-peripheral fundus
  - Dilated congested venous vasculature
  - Cherry red macula
  - Spontaneous central retinal artery pulsation
  - Neovascularization of the posterior segment

- Vertebral-basilar based disease:
  - Unilateral, bilateral or alternating hemianopsia
  - Unilateral, bilateral or alternating deficits of cranial nerves III, IV, and VII
  - Unilateral, bilateral or alternating Horner’s syndrome

Treatment & Management

- Medical management may include the use of anti-platelet aggregate or anti-coagulant therapeutic agents.
- Surgical management may include carotid-subclavian bypass.
- However, operative procedures are not performed in asymptomatic patients.

Systemic Symptoms

- Carotid based disease:
  - Contra-lateral systemic transient ischemic attack

- Vertebral-basilar based disease:
  - Claudication upon exercise
  - Limb/extremity paresthesia, numbness and/or tingling
  - Sensation of coldness of the arm
  - Dizziness / vertigo
  - Fatigue
  - Headache
  - Vomiting

Systemic Signs

- Carotid based disease:
  - Motor and sensory deficits contra-lateral to the side with carotid stenosis
  - Deficits associated with vascular compromise to the frontal, temporal and parietal lobes
  - Carotid bruits upon auscultation

- Vertebral-basilar based disease:
  - Blood pressure differential reported an average systolic differential of 45mm Hg
  - Weak ipsilateral brachial & radial pulse
  - Coldness of the ipsilateral arm / hand
  - Supraclavicular systolic bruit upon auscultation
  - Dysphagia
  - Dysphonia
**Diabetes Mellitus**

**Diabetic Eye Disease**

**Standard of Care**

- Photocoagulation
  - Eliminate photoreceptor oxygen demand
  - Reduction of capillary area to reduce leakage
  - Restoration of blood-retinal barrier

**Diabetic Eye Disease**

**Steroid**

- Decreasing arachidonic acid release
- Reducing vascular permeability
- Reducing retinal inflammation
- Increasing tight junction protein expression
- Inhibiting VEGF production

**FAME – Fluocinolone Acetonide for Macular Edema**

<table>
<thead>
<tr>
<th>FAME</th>
<th>Fluocinolone Acetonide Insert 0.2µg/day</th>
<th>Fluocinolone Acetonide Insert 0.5µg/day</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Improvement of ≥ 15 Letters</td>
<td>28.7%</td>
<td>27.8%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Change in Letters</td>
<td>+4.4</td>
<td>+5.4</td>
<td>+1.7</td>
</tr>
</tbody>
</table>

**Recommendation:**

- Fluocinolone acetonide vitreal insert to provide drug delivery for up to 3 years
- Approved in Europe
- No US FDA approval
- Safety profile:
  - Cataract progression with steroid
  - Sustained IOP elevation with steroid

**Diabetic Eye Disease**

**Anti-VEGF**

- Increased VEGF observed in individuals with diabetic macular edema
- VEGF increases vascular permeability
- VEGF increases inflammation
- Anti-VEGF agents target VEGF

**Ranibizumab for diabetic macular edema:**

**Results from 2 phase III randomized trials: RISE and RIDE**

<table>
<thead>
<tr>
<th>Ranibizumab 0.3mg</th>
<th>Ranibizumab 0.5mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Improvement of ≥ 15 Letters</td>
<td>RISE 44.8%</td>
<td>39.2%</td>
</tr>
<tr>
<td>RIDE 33.6%</td>
<td>45.7%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

**Recommendation:**

- Ranibizumab significantly improved VA for the treatment of diabetic macular edema
**BOLT Study: Bevacizumab or Laser Therapy**

<table>
<thead>
<tr>
<th>RESTORE</th>
<th>Bevacizumab Q6Wks x 3 Then PRN</th>
<th>Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Improvement of ≥15 Letters (%)</td>
<td>32%</td>
<td>4%</td>
</tr>
<tr>
<td>Change in Letters</td>
<td>+8.6</td>
<td>+0.5</td>
</tr>
<tr>
<td>Central Retinal Thickness (µm)</td>
<td>-146</td>
<td>-118</td>
</tr>
<tr>
<td>Mean Treatments (d)</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

**Recommendation:**
- Bevacizumab resulted in significantly improved visual acuities vs. laser
- Bevacizumab resulted in significantly reduced central macular thickness vs. laser

**DAVINCI - DME And VEGF Trap-Eye: INvestigation of Clinical Impact**

<table>
<thead>
<tr>
<th>DAVINCI</th>
<th>Aflibercept 0.5mg Q4Wks</th>
<th>Aflibercept 0.5mg Q8Wks</th>
<th>Aflibercept 2mg Q4Wks</th>
<th>Aflibercept 2mg Q8Wks</th>
<th>Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Improvement of ≥15 Letters (%) (1 Year)</td>
<td>49.9%</td>
<td>45.5%</td>
<td>23.8%</td>
<td>42.2%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Change in Letters (% 6 Months)</td>
<td>+11.0</td>
<td>+13.1</td>
<td>+9.7</td>
<td>+120</td>
<td>-1.3</td>
</tr>
<tr>
<td>Central Retinal Thickness (µm) (1 Year)</td>
<td>-165.4</td>
<td>-227.4</td>
<td>-187.8</td>
<td>-180.3</td>
<td>-38.4</td>
</tr>
</tbody>
</table>

**Recommendation:**
- Aflibercept Groups demonstrated greater visual improvement and central macular thickness reduction compared with laser
- Safety profile – no new signals

**Diabetic Eye Disease**

**Combination**

**RESTORE Study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema**

<table>
<thead>
<tr>
<th>RESTORE</th>
<th>Ranibizumab 0.5mg (Monotherapy)</th>
<th>Laser (Monotherapy)</th>
<th>Combination Ranibizumab 0.5mg &amp; Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Improvement of ≥15 Letters (%)</td>
<td>22.6%</td>
<td>22.9%</td>
<td>8.2%</td>
</tr>
<tr>
<td>BVA Letter Score &gt;20/40</td>
<td>53%</td>
<td>44.9%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Change in Letters</td>
<td>+6.1</td>
<td>+5.9</td>
<td>+0.8</td>
</tr>
<tr>
<td>Central Retinal Thickness (µm)</td>
<td>-18.7</td>
<td>-128.3</td>
<td>-61.3</td>
</tr>
</tbody>
</table>

**Recommendation:**
- Ranibizumab monotherapy and combination therapy superior to laser monotherapy in improving vision
- Ranibizumab monotherapy and combination therapy significantly reduced central retinal thickness compared with laser monotherapy
- Safety profiles Ranibizumab monotherapy or combination therapy were not associated with an increased risk of cardiovascular or cerebral vascular events

**READ 2 - Ranibizumab for Edema of the Macula in Diabetes**

<table>
<thead>
<tr>
<th>READ 2</th>
<th>Ranibizumab 0.5mg (Monotherapy)</th>
<th>Laser (Monotherapy)</th>
<th>Combination Ranibizumab 0.5mg &amp; Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Improvement of ≥15 Letters (%)</td>
<td>24.5%</td>
<td>36.5%</td>
<td>15.2%</td>
</tr>
<tr>
<td>Change in Letters</td>
<td>+3.4</td>
<td>+11.1</td>
<td>+8.4</td>
</tr>
<tr>
<td>Mean Injections (d)</td>
<td>13</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Recommendation:**
- Ranibizumab provides benefit
- Combination therapy decreased frequency of injection