State of the art medical management of carotid artery disease in the post COMPASS and VOYAGER Study era

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Disclosure

Dr. Raghu Kolluri reports following –

• **Uncompensated Consultant/Advisor**—Boston Scientific, Intact Vascular, InterVene, Medtronic, Pedra, Philips, Thrombolex, Vesper Medical, Inari Medical

• **Executive Board Member** – VIVA Physician Inc, a 501c3 Corp
Incidence of Major Stroke

By Stenosis Severity

Carotid stenosis

0-19%  20-29%  30-39%  40-49%  50-59%  60-69%  70-79%  80-89%  90-99%

0%  1%  2%  3%  4%  5%  6%

Lancet 1998;351:1379-87

Conclusions: Cardiovascular events and microemboli on TCD have markedly declined with more intensive medical therapy. Less than 5% of patients with ACS now stand to benefit from revascularization; patients with ACS should receive intensive medical therapy and should only be considered for revascularization if they have microemboli on TCD.

Arch Neurol. 2010;67(2):180-186
## Ischemic Stroke Etiology

### Table 1. Approximate Distribution of Major Subtypes of Ischemic Stroke.*

<table>
<thead>
<tr>
<th>Type of Stroke</th>
<th>Proportion of Strokes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-vessel atherothrombotic</td>
<td>15</td>
</tr>
<tr>
<td>Due to internal-carotid-artery stenosis</td>
<td>9</td>
</tr>
<tr>
<td>Small-vessel (lacunar)</td>
<td>25</td>
</tr>
<tr>
<td>Embolic</td>
<td>60</td>
</tr>
<tr>
<td>Due to atrial fibrillation</td>
<td>15</td>
</tr>
<tr>
<td>Other (due to dissection or other causes)</td>
<td>3</td>
</tr>
</tbody>
</table>

*The data are from the Stroke Data Bank of the National Institute of Neurological and Communicative Disorders and Stroke and the Framingham Study. The percentages do not total 100 because of a modification of the categories of stroke used.

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COMPASS Subgroup Analysis of Stroke

Ischemic stroke n=291
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALT [64]</td>
<td>n= 1360 patients</td>
<td>aspirin 75 mg vs. placebo</td>
<td>Primary: stroke or death from any cause; Secondary: Stroke (minor or major) Stroke or ( \geq 2 ) TIA's within a week of one another, MI</td>
<td>Aspirin reduced by 18% stroke or death</td>
</tr>
<tr>
<td>ACE study [109]</td>
<td>2849 patients underwent  [carotid endarterectomy]</td>
<td>aspirin (650 mg or 1300 mg) vs. (81 mg or 325 mg), during the postoperative period</td>
<td>Primary: Composite of all strokes, MIs, and deaths at 30 days and 3 months; Secondary: All strokes and deaths, ipsilateral strokes and deaths</td>
<td>Postoperative use of aspirin is associated with a lower risk of cardiac and neurological events</td>
</tr>
<tr>
<td>MATCH [110]</td>
<td>7599 high-risk patients with recent ischaemic stroke or TIA and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day</td>
<td>aspirin 75mg/d on top of clopidogrel vs. clopidogrel alone</td>
<td>A composite of ischaemic stroke, MI, vascular death, or rehospitalisation for acute ischaemia (including rehospitalisation for TIA, angina pectoris, or worsening of PVD)</td>
<td>aspirin on top of clopidogrel did not reduce major vascular events, while it increased the risk of life-threatening or major bleeding</td>
</tr>
<tr>
<td>CHARISMA [77]</td>
<td>15,603 patients with either clinically evident CV disease or multiple risk factors</td>
<td>clopidogrel (75mg/d) plus aspirin (75-162 mg/d) or placebo plus low-dose aspirin (75-162 mg/d)</td>
<td>Primary: first occurrence of either fatal or nonfatal MI, fatal or nonfatal stroke from any cause, or CV death (including hemorrhagic death); Secondary: A composite of the primary endpoint plus hospitalization for UA,</td>
<td>clopidogrel plus aspirin was not more effective than aspirin alone in reducing the rate of MI, stroke, or CV death</td>
</tr>
<tr>
<td>CAPRIE [73]</td>
<td>19,185 patients</td>
<td>clopidogrel 75 mg vs. aspirin 100 mg</td>
<td>Primary: ischemic stroke, MI, or death from vascular causes. Secondary: death from any cause</td>
<td>clopidogrel was more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction, or vascular death, similar safety profile</td>
</tr>
</tbody>
</table>
### Management of antiplatelet therapy in carotid artery stenosis

**Asymptomatic**
- SAPT: A or C
- Class I or A

**Carotid Artery Stenting**
- DAPT: A or C
- SAPT: A or C
- Class I or A

**Carotid Surgery**
- CD: Aspirin 75–100 mg/day
- SAPT: A or C
- Class I or A

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### Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class*</th>
<th>Level†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>23</strong></td>
<td>It is recommended that all patients undergoing carotid endarterectomy should receive antiplatelet therapy throughout the perioperative period and also in the long term.</td>
<td>I</td>
</tr>
</tbody>
</table>

#### HEPHRAX: Low-dose aspirin (75–325 mg daily) is recommended rather than higher doses (>625 mg daily) in patients undergoing carotid endarterectomy.

#### HEPHRAX: Early institution of aspirin + clopidogrel (or aspirin plus modified release dipyridamole) after transient ischaemic attack or minor stroke may be considered to reduce early recurrent events in patients with a >50% carotid stenosis awaiting carotid endarterectomy.

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*ESC Guidelines* 2018

**COMPASS - MACE, MALE, or Major Amputation**

- **Overall COMPASS**
- **Overall PAD**
- **Symptomatic PAD**
- **PAD Lower Extremities**
- **Carotid Artery Disease**

- 27,395 participants
- Carotid stenosis ≥50% or previous carotid intervention - in 1919 (7%) participants.
- 24,601 (90%) – on lipid-lowering drugs
- 19,518 (71%) were on ACEI or ARB

*Anand, et al. Lancet 2017*
COMPASS Subgroup Analysis of Stroke

Aim: Analyze COMPASS regimen in various types of ischemic events in this cohort

N = 291 patients with stroke
Follow up = 3 years

Intention to treat model
All 1919 patients with > 50% stenosis or prior intervention (7%) included
ACE Inhibition Prevents Recurrent Stroke
The Progress Trial

• N = 6105
• Previous stroke randomly
• Perindopril & Perindopril + Indapamide (n=3051) or placebo (n=3054)
• Mean follow up of 3.9 years

BMJ 2004;329:968–71
The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators


- N= 4731 patients who had had a stroke or TIA within one to six months before study entry
- Low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter)
- Had no known coronary heart disease
- Double-blind treatment with 80 mg of atorvastatin per day or placebo.
- The primary end point was a first nonfatal or fatal stroke.
FOURIER

- Evolocumab vs placebo on the background of lipid lowering tx
- N=27,562; LDL ≥70 mg/dL + ASCVD
- ~20% stroke
- ~70% of pts were on statins
- Median f/u 2.2 years
- 59% reduction LDL; median 92→30 mg/dL

Conclusions

• Optimal medical therapy with or without intervention or surgery is important
• Smoking cessation + Diabetes control
• Antiplatelet therapy should be tailored
• Hypertension
• Statins
• Low dose rivaroxaban + ASA 81mg is promising
• PSCK-9 inhibitors?

Circulation. 2011;124:e54-e130