Best Medical has improved: but how much and will BMT be good enough to replace repair?

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Disclosure

Isabelle Van Herzeele has the following potential conflicts of interest to report:

☑ Consulting
   - Silk Road Medical, Sunnyvale, CA, USA
   - Medtronic Academia, Tolochenaz, Swiss

☑ Research Grant
   - Simbionix, Cleveland, Ohio, USA
   - W.L. Gore & Associates, Inc., Flagstaff, USA
   - Medtronic Academia, Tolochenaz, Swiss
   - Silk Road Medical, Sunnyvale, CA, USA
Why is the management of asymptomatic carotid disease so controversial?

A. Ross Naylor

Who Benefits Most from Intervention for Asymptomatic Carotid Stenosis: Patients or Professionals?

A.R. Naylor a,*, P.A. Gaines b, P.M. Rothwell c

From the Editors

The Story of Anybody, Somebody, Nobody and Everybody

A.R. Naylor, MD a,*, J.-B. Ricco, MD, PhD b

Carotid Intervention

Is It Warranted in Asymptomatic Individuals if Risk Factors Are Aggressively Managed?

Katherine Pahigianis, PhD; Petra Kaufmann, MD; Walter Koroshetz, MD

Carotid Stenting—Why Treating an Artery May Not Treat the Patient

Mark J. Alberts, MD

Revascularization of asymptomatic carotid stenosis is not appropriate in patients on dialysis

Theodore H. Yuo, MD, MS, Joseph Sidaoui, MD, Luke K. Marone, MD, Michel S. Makaroun, MD, and Rabih A. Chaer, MD, MS, Pittsburgh, Pa
BEST MEDICAL TREATMENT?
ANTIPLATELETS

Symptomatic carotid disease

• Antiplatelet Trialists Collaboration
  ASA (75-150 mg) **20-25% RR reduction of tromboembolic stroke**
  *BMJ 2002; 324: 71-86*

• CARESS ASA + clopidogrel ↓ microemboli
  *Circulation 2005; 111: 2233-40*

• CHANCE ASA + clopidogrel for 21 days after initial TIA
  – N= 5170 – China
  – Stroke 8.2% vs. 11.7% - HR 0.68 95% CI 0.57-0.81
    *NEJM 2013; 369: 11-9*

• + clopidogrel – day before surgery ↓ microemboli
  *Circulation 2004; 109: 1476-81*

• ASA +dipyridamole, clopidogrel, trifusal ...
<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
<th>RRR %</th>
<th>ARR % per year</th>
<th>NNT to avoid 1 event per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardioembolic ischaemic stroke or TIA</td>
<td>aspirin / PCB</td>
<td>13</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>aspirin + DIP / PCB</td>
<td>28</td>
<td>1.9</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>aspirin + DIP / aspirin</td>
<td>18</td>
<td>1.0</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>Clop / PCB</td>
<td>23</td>
<td>1.6</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Clop / aspirin</td>
<td>10</td>
<td>0.6</td>
<td>166</td>
</tr>
<tr>
<td>Atrial fibrillation (primary prevention)</td>
<td>warfarin / PCB</td>
<td>62</td>
<td>2.7</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>aspirin / PCB</td>
<td>22</td>
<td>1.5</td>
<td>67</td>
</tr>
<tr>
<td>Atrial fibrillation (secondary prevention)</td>
<td>warfarin / PCB</td>
<td>67</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>aspirin / PCB</td>
<td>21</td>
<td>2.5</td>
<td>40</td>
</tr>
</tbody>
</table>
ANTIPLATELETS

Asymptomatic carotid stenosis

• Meta-analysis: ↓ coronary or cardiovasc events – no reduction in stroke

• US Preventive Task Force - ASA in high risk patients ≥ 3% per 5 years
  Stroke 2011; 42: 517-84

• CHARISMA
  – ASA vs. ASA + clopidogrel – no benefit in asympt carotid artery disease (>70%)
INTENSIVE STATIN THERAPY

• **Heart Protection Study**  Simvastatin 40 mg OD vs. placebo
  *Lancet* 2002; 360: 7-22
  – All patients N= 20,536 (CHD, TIA/Stroke, CEA)
  – 25% reduction in stroke, 30% reduction in ischemic stroke

• **SPARCL trial**  Atorvastatin 80 mg OD or placebo
  *NEJM* 2006; 355: 549-59
  – N= 4,731 (recent stroke or TIA < 6 months)
  – 33% reduction in any stroke
  *Stroke* 2008; 39: 3297-302
  – N= 1,007 (known carotid stenosis) – ARR of stroke = 1% per year – NNT= 20 over 5 years

• Meta-analysis
  Each 10% reduction in LDL chol – reduction stroke risk by 15.6%
  *J Vasc Surg* 2007; 46: 373-86

• Intensive statin treatment + **Ezetimibe** - reduction in plaque area
  *Stroke* 2012; 43: 1153-55
  to be confirmed by **IMPROVE-IT trial**
ACSRS Study: Impact of statins

Regression Free Survival

YEARS

Lipid Lowering Therapy
- No
- Yes

Numbers at risk
Lipid lowering therapy
No 704 420 262 117
Yes  276 175 112  56
Best Medical Treatment

• **Medical**
  
  — **DIABETIC CONTROL** – no significant stroke reduction
    - ACCORD *NEJM* 2008; 358: 2545-59
    - ADVANCE *NEJM* 2008; 358: 2560-72
  
  — **ANTI-HYPERTENSIVES**  **30-40% reduction in stroke**
    - PROGRESS perindopril (TIA/Stroke) 30% stroke reduction
    - **Ideal antihypertensive agent ???**
      Thiazides, ACE inhibitors, beta-blockers
      HOPE, CAPPP, PATS, LIFE, ALLHAT, Veterans Administration Cooperation Study Group Trial

• **Life style**
  
  — Smoking cessation *smoking doubles risk of ischemic stroke*
    *BMJ* 1989; 298: 789-94
  
  — Lifestyle modification
    - Moderate exercise
    - Mediterranean Diet (healthy incl. fish, fruit, vegetables, fibers)
      Northern Manhattan Study – composite outcome of ischemic stroke, MI and vascular death
      *Am J Clin Nutr* 2011; 94: 1458-64
<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Treatment</th>
<th>RRR %</th>
<th>ARR % per year</th>
<th>NNT to avoid 1 event per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population with increased blood pressure</td>
<td>Antihypertensive</td>
<td>42</td>
<td>0.4</td>
<td>250</td>
</tr>
<tr>
<td>General population with increased vascular risk</td>
<td>ACE-Inhibitor</td>
<td>22</td>
<td>0.65</td>
<td>154</td>
</tr>
<tr>
<td>Post-stroke / TIA with increased blood pressure</td>
<td>Antihypertensive</td>
<td>31</td>
<td>2.2</td>
<td>45</td>
</tr>
<tr>
<td>Post-stroke / TIA with normal blood pressure</td>
<td>ACE-inhibitor ± diuretic</td>
<td>24</td>
<td>0.85</td>
<td>118</td>
</tr>
<tr>
<td>Post-stroke / TIA</td>
<td>Statins</td>
<td>16</td>
<td>0.44</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Smoking cessation</td>
<td>33</td>
<td>2.3</td>
<td>43</td>
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</table>
IMPROVEMENT OF BMT
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>year published</th>
<th>study years</th>
<th>5 year rate of ‘any’ stroke</th>
<th>5 year rate of ‘ipsilateral’ stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>1995</td>
<td>1-5</td>
<td>17.5% (3.5%pa)</td>
<td>11.0% (2.2%pa)</td>
</tr>
<tr>
<td>ACST</td>
<td>2004</td>
<td>1-5</td>
<td>11.8% (2.4%pa)</td>
<td>5.3% (1.1%pa)</td>
</tr>
<tr>
<td>ACST</td>
<td>2010</td>
<td>6-10</td>
<td>7.2% (1.4%pa)</td>
<td>3.6% (0.7%pa)</td>
</tr>
</tbody>
</table>

*EJVES 2009; 37: 625-32*

*The Surgeon 2015; 34-43*
Changes in risk factor profile of patients recruited to carotid endarterectomy trials over 20 years

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>53%</td>
<td>23%</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Mean cholesterol</td>
<td>6.4 mmol/L</td>
<td>5.3 mmol/L</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>30-day death/stroke after CEA</td>
<td>Stroke Rate including 30-day death/stroke</td>
<td>strokes prevented per 1000 CEAs</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------</td>
<td>-------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>BMT</td>
</tr>
<tr>
<td>ACAS&lt;sup&gt;11&lt;/sup&gt; 5 yrs</td>
<td>2.3%</td>
<td>5.1%</td>
<td>11.0%</td>
</tr>
<tr>
<td></td>
<td>Modeled at 0.0%*</td>
<td>2.8%</td>
<td>11.0%</td>
</tr>
<tr>
<td>ACST&lt;sup&gt;12&lt;/sup&gt; 5 yrs</td>
<td>2.8%</td>
<td>6.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td></td>
<td>Modeled at 0.0%*</td>
<td>3.5%</td>
<td>11.8%</td>
</tr>
<tr>
<td>ACST&lt;sup&gt;13&lt;/sup&gt; 10 yrs</td>
<td>2.8%</td>
<td>13.4%</td>
<td>17.9%</td>
</tr>
<tr>
<td></td>
<td>Modeled at 0.0%*</td>
<td>10.5%</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

The benefits were calculated using the procedural risks observed in the constituent trial. They were then remodelled assuming a 0% procedural risk to see whether this significantly increased the number of strokes prevented.

*The Surgeon 2015; 34-43*
BMT GOOD ENOUGH TO REPLACE REPAIR (CEA OR CAS)?
TIMELY INITIATION OF BMT

Symptomatic disease

**EXPRESS** study = Effect of urgent treatment of TIA and minor stroke on early recurrent stroke

- GP initiates BMT
- Outpatient clinic – BMT initiated
- 10% vs. 2% (p= 0.0001) risk of stroke within 90 days

*Lancet 2007; 370: 1432-42*
WHAT DOES THE PATIENT WANT?
PATIENT COMPLIANCE

- 50% - 80%
  - Forgetfulness
  - Being away from home
  - Drug shortage
    
    *Arch Pharm Res 2011; 34: 1143-52*
    
    *EJVES 2015; 49: 366-74*

- Better compliance in acute than in chronic conditions
  
  *NEJM 2005; 353: 487-97*

- Patient Education

- In clinical trials 43- 78%
  
  • More access to clinicians
Figure 1. Current therapy at 1-month follow-up. Blue = carotid endarterectomy; red = carotid artery stenting.
Treatment of asymptomatic significant carotid artery stenosis

- USA 90%
- Italy 70%
- Hungary and Switzerland 40%
- UK, Finland, Sweden and Norway 15-20%
- Denmark 0%

EJVES 2012; 44: 11-7

... Enthusiasm of revascularization is driven by the worst nightmare of clinicians that a patient with a known carotid artery stenosis on BMT experiences a disabling stroke and that “they should have done more”...
STOP !!!

Mortality Risk after CAS among Medicare Beneficiaries

Original Investigation
Outcomes After Carotid Artery Stenting in Medicare Beneficiaries, 2005 to 2009 N = 22,000

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asymptomatic</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Periprocedural Period</td>
<td>After the Periprocedural Period</td>
</tr>
<tr>
<td>Overall</td>
<td>11,839</td>
<td>1.2 (0.9-0.1)</td>
<td>27.7 (26.4-28.9)</td>
</tr>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66-69</td>
<td>2,122</td>
<td>0.6 (0.3-1.0)</td>
<td>18.1 (15.6-20.7)</td>
</tr>
<tr>
<td>70-74</td>
<td>2,928</td>
<td>0.7 (0.4-1.0)</td>
<td>23.1 (20.5-25.6)</td>
</tr>
<tr>
<td>75-79</td>
<td>3,186</td>
<td>1.2 (0.8-1.6)</td>
<td>28.4 (25.7-31.1)</td>
</tr>
<tr>
<td>≥80</td>
<td>3,603</td>
<td>1.4 (1.0-1.8)</td>
<td>36.8 (34.2-39.2)</td>
</tr>
</tbody>
</table>

JAMA Neurol 2015; 72(3): 276-86
JAMA Neurol 2015; 72(3): 263-4
Progression of asymptomatic carotid stenosis despite optimal medical therapy.
At the 5-year of follow-up, OMT failed to prevent carotid disease progression or development of ipsilateral symptoms in 45% of patients with AMCAS.

Asymptomatic carotid artery stenosis

**Identify high-risk**

- History of contralateral stroke or TIA - *HR 3*
- Baseline degree of stenosis - *weak predictor*
- Microemboli on TCD ≥ 2 embolic signals/ hour
- Unstable carotid plaque
  - US – plaque echolucency, ulceration, rupture - ACSRS study
  - MRI – intraplaque hemorrhage, luminal thrombus
- Reduced Cerebral Blood Flow Reserve
- Silent embolic infarcts brain CT or MRI *double stroke risk*
- Progression in severity of asymptomatic carotid stenosis despite BMT – *double ipsilateral stroke risk 2%*

*Stroke 2013; 2955-6
Stroke 2014; 3720-4*
Trials awaited

- **AMTEC** = BMT vs. BMT+CEA (atorvastatin, asa, losartan, amlodipine) Aggressive Medical Treatment Evaluation for asymptomatic carotid stenosis
  Completed (N=400)

- **Compass trial** = rivoroxaban +ASA vs. rivoroxaban (Bayer)
  Cardiovascular OutcoMes for People Using Anticoagulation Strategies
  Enrolling

- **ACT 1** = 3 CAS vs. 1 CEA asympt carotid
  (Abbott) – Halted (business decision)

- **SPACE 2** = 3 to 2 arm strategy BMT+CAS vs.
  BMT+ CEA asympt carotid – Halted Jan 2015
  (>500)

- **ACST 2** = CAS vs. CEA asympt carotid
  (enrolled 1849/3600)

- **CREST 2** = BMT vs. BMT+CEA; BMT vs.
  BMT+CAS (enrolled 36/2480)

- **ECST 2** = sympt or asympt moderate or severe
  carotid stenosis at low or intermediate risk of
  future stroke (CAR score) – BMT (deferred CEA) vs.
  BMT + CEA (CAS) -(enrolled 81/2000)
• BMT has improved
  – Initiate and control BMT

• At present BMT will NOT replace carotid treatment
  – Interdisciplinary teams
    • Treat symptomatic carotid disease early
    • Treat asymptomatic carotid stenosis selectively
  – WE must participate in RCT