Strategies in Stroke Prevention

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Disclosures

• None
Objectives

- Discuss the epidemiology of stroke
- Review risk factors & management
- Summarize prominent trials for primary and secondary stroke prevention
- Discuss 2014 AHA/ASA guidelines for primary and secondary stroke prevention
- Discuss the role of antiplatelets and anticoagulation in prevention
Epidemiology of Stroke

- Each year, approximately 795,000 Americans experience a new or recurrent stroke.
- Stroke remains the 5th leading cause of death in the US, 2nd in the world.
- Stroke is the leading cause of disability in adults.
- Stroke costs the United States an estimated $36.5 billion each year. This total includes the cost of health care services, medications to treat stroke, and missed days of work.
Epidemiology of Stroke

- **Stroke**
  - 87% ischemic
  - 10% primary hemorrhages
  - 3% SAH

- Stroke incidence increases rapidly with age, doubling for each decade after age 55.

- Of the 795,000 strokes per year: 610,000 are new, 185,000 are recurrent

- Estimated 240,000 will experience a transient ischemic attack (TIA)
What is Stroke??

- Stroke=Brain Attack
- It can happen to anyone at any time
- It occurs when blood flow to an area of brain is cut off. When this happens, brain cells are deprived of oxygen and cause infarction of brain tissue and cell death
- 2 Million neurons lost for each minute delay in restoring blood flow after a stroke.
- TIME IS BRAIN
Transient Ischemic Attack

- TIA is a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with complete resolution of symptoms \textit{and without evidence of infarction}
- 15-23% of patients with ischemic stroke have had a TIA before their stroke
  - 17% within same day of stroke
  - 9% on previous day of stroke
  - 43% during 7 days prior to stroke
Risk Stratification with ABCD2

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1 point if &gt; 60 years</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>1 point if sBP &gt;140 or dBP &gt;90</td>
</tr>
<tr>
<td>Clinical features</td>
<td>2 points for unilateral weakness; 1 point speech deficit without weakness</td>
</tr>
<tr>
<td>Duration</td>
<td>2 points if &gt;60 min; 1 point if &gt;10-59 min</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 point</td>
</tr>
</tbody>
</table>

*2-day stroke risk: 1%(0-3 points), 4% (4-5 points), 8% (6-7 points)*

*90 day stroke risk up to 25%

Lancet 2007; 369:283-92
Stroke Etiology

1. Small Vessel Disease
2. Large Vessel Disease
3. Cardioembolic
4. Cryptogenic
5. Other
Stroke Outcomes

- 10% of stroke survivors recover almost completely
- 25% recover with minor impairments
- 40% experience moderate to severe impairments requiring special care
- 10% require care within a skilled care or long term facility
- 15% die shortly after stroke

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Stroke Prevention

- It has been suggested that up to 80% of recurrent stroke may be prevented by addressing the modifiable risk factors.
- Applying a mass stroke prevention approach can serve as complementary strategy to reduce the increasing burden of stroke and subsequent disability.
Stroke Prevention

- Primary Stroke Prevention
- Secondary Stroke Prevention
Stroke Risk Factors
Non-modifiable Stroke Risk Factors

- Age – doubles per decade over 55 years
- Sex – 24-30% greater in men
- Race
  - 2.4 fold increase in African Americans
  - 2.0 fold increase in Hispanics
  - Increase among Chinese
- Heredity – 1.9 fold increase in first degree relatives
- Genetics – ehlers danlos, marfans, etc..
Modifiable Stroke Risk Factors

- HTN
- DM
- Dyslipidemia
- Asymptomatic carotid bruit/stenosis
- Cardiac disease/A-fib
- Aortic arch atheromatosis
- Obesity
- Sleep Apnea

- Cigarette smoking
- EtoH consumption
- Illicit drug use
- Physical Inactivity
Blood Pressure Reduction

- HTN remains the most important modifiable cause of stroke (ischemic and hemorrhagic)
  - Affects over 75 million people in the US
- HTN contributes to stroke risk by aggravating atherosclerosis and accelerating heart disease
- HTN contributes to 70% of all strokes
  - Atheroma development in the carotids or aortic arch
  - Friability of small cerebral end arteries
  - LV dysfunction and A-fib
- In a meta-analysis of 23 randomized primary prevention trials, antihypertensive drug treatment reduced risk of first stroke by 32% compared to no drug treatment
### JNC 8 Recommendations

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Target SBP (mm Hg)</th>
<th>Target DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 years</td>
<td>&lt;150</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&gt; 18 years with CKD</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>&gt; 18 years with diabetes</td>
<td>&lt;140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure

There is no definitive evidence supporting specific classes of antihypertensive therapy over others as a means to prevent stroke.

Current guidelines support most antihypertensive agents for primary prevention of stroke, although specific subpopulations may benefit from certain medication class.
HTN- Secondary Stroke Prevention

- For secondary stroke prevention, antihypertensives may be resumed in patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA within the first 24 h of the stroke (Level of Evidence B) or beyond several days (Level of Evidence A).
- The goals for target BP level for secondary stroke prevention are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mmHg and a diastolic pressure <90 mmHg (Class IIa; Level of Evidence B).
Blood Pressure Reduction

- A meta-analysis of several post stroke trials through 2002 showed that overall, anti-HTN meds reduced risk of recurrent stroke and TIA
- Optimal drug regimen for BP reduction and secondary stroke prevention remains uncertain
  - PROGRESS (2001): HTN patient with h/o stroke or TIA treated in combo with ACE and diuretic showed that combo reduced secondary risk or TIA, ischemic, hemorrhagic stroke
  - PROFESS (2008): although telmisartan reduces BP in recurrent stroke patients, it does not affect disability or cognitive fxn at 30 months compared to placebo. No reduction in recurrent stroke.
HTN & Secondary Prevention

- In a meta-analysis of 7 randomized trials of almost 30,000 patients with a prior history of stroke, therapy with angiotensin inhibitors (ACE inhibitors or angiotensin receptor blockers) significantly, but modestly, reduced the risk of recurrent stroke (9.0 versus 9.7 percent) and major vascular events (14.3 versus 15.7 percent) compared with placebo.
BP- Bottomline!

- Treat HTN (new JNC-8 criteria)
- All studies support detection and treatment
- There is no compelling evidence favoring one class of antihypertensive drugs over another as monotherapy for secondary prevention in patients who have had a stroke.
- ACE or ARB + diuretic may be beneficial for secondary stroke prevention
Dyslipidemia Management

- A large meta-analysis of randomized trials using statins in primary and secondary prevention demonstrated a significant correlation between extent of LDL reduction and degree of protection from stroke.
- The study estimated that each 10% reduction of LDL reduced the risk of stroke by 15.6%.
- LDL-C is the primary target for treatment of dyslipidemia for patients with atherosclerotic vascular disease.
Hyperlidemia and CRP

- Several epidemiological studies have demonstrated that serum levels of the inflammatory marker CRP are positively associated with the risk of ischemic stroke.
  - CRP can be used as a marker of increased stroke risk, no randomized clinical trial date supports lowering CRP to lower stroke risk
- Many studies showed a significant relationship between elevated CRP and atherosclerosis
- JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin, 2008) confirmed the benefits of statins on stroke in a primary prevention population at elevated risk
JUPITER Trial

- JUPITER evaluated a cohort of men 50 years of age or older, and women 60 years of age or older, without cardiovascular disease, with LDL level <130 mg/dL and triglyceride level of <500 mg/dL, but hs-CRP level 2.0 mg/L.
- Patients were randomly assigned to rosuvastatin or placebo.
- The results showed a 51% reduction in ischemic stroke.
- The authors suggested that a healthy patient population at high risk and previously ineligible for statin therapy may benefit from rosuvastatin treatment if hs-CRP is elevated, even if LDL-C is within acceptable levels.
JUPITER Trial Conclusion

- CRP is a marker of inflammation with an uncertain direct pathogenic role in the risk of thrombus formation
  - Not routinely checked for primary or secondary prevention
- Whether or not the anti-inflammatory effect of statin treatment contributes to benefits, it does not alter the strong and direct correlation between a reduction in LDL-C and a reduction in CV events.
SPARCL Trial

- The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL, 2006) trial studied the effect of high dose atorvastatin and the risk of secondary stroke in patients with a previous stroke or TIA.
- Compared to placebo, daily treatment of 80 mg of atorvastatin resulted in a 16% relative risk reduction of fatal and nonfatal stroke among patients with a recent stroke or TIA.
SPARCL Trial

- There was a modestly higher rate of elevated liver enzymes and a rise in CK in the atorvastatin arm, but no cases of hepatic failure
- There was an association of statin treatment with a higher incidence of hemorrhagic stroke (2.3% vs 1.4% in the placebo group)
  - Incidence of fatal hemorrhage was not significantly different
  - Level of LDL did not predict the occurrence of hemorrhagic stroke
Dyslipidemia & LDL Goals

- The benefit of aiming for a given LDL-C target has not been definitively established in a major randomized clinical trial (RCT)
- Achieving an LDL-C level of <70 mg/dL was related to a 28% reduction in risk of stroke without a significant rise in the risk of hemorrhagic stroke in a post-hoc analysis
- Also stroke and TIA patients with ≥50% reduction in LDL-C had a 35% reduction in combined risk of nonfatal and fatal stroke
Dyslipidemia AHA Recommendations

- Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and CV events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other ASCVD. (Class I, LOE B)
Diabetes Mellitus

- Increases the risk of stroke up to 2-4x.
- It increases morbidity and mortality following stroke.
- Macrovascular disease due to atherosclerosis is the major mechanism of stroke in DM.
- Increased risk seen in DM is independent of HTN or age.
- DM in association with HTN, smoking or dyslipidemia significantly adds to the risk.
DM & Secondary Prevention

- Patients should be screened for diabetes with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA1c may be more accurate than other screening tests in the immediate post-event period. (Class I, LOE C)
- The optimal level of glucose control (i.e., HbA1c < 7%) should be for prevention of macrovascular disease
Atrial Fibrillation

- 2.7 million Americans have non-valvular AF, and 70% of patients with AF are 65-85 years of age.
- Increasing prevalence with age, leading heart arrhythmia in elderly
- AF increases stroke risk by 5-fold.
- Co-existent CHF/LV dysfunction, hypertension and prior CVAs or TIAs increases stroke risk, by almost 15%.
Atrial Fibrillation

- In the US, A-fib is responsible for > 70,000 ischemic strokes/yearly (about 12-15% of all ischemic strokes)
- About 10% of patients with acute ischemic stroke or TIA will have new AF detected during their hospitalization.
- An additional 11-23% may be found to have AF (if tested) within 30 days of discharge by continuous ECG monitoring.
- For preventing risk of stroke, scoring systems are used to estimate the risk of thromboembolic event
## CHADS<sub>2</sub> vs CHA<sub>2</sub>DS<sub>2</sub>-VASc Risk Scores

<table>
<thead>
<tr>
<th>CHADS2 Risk</th>
<th>Score</th>
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<tr>
<td>CHF</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Age &gt; 75</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2</td>
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</table>

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Risk</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>CHF or LVEF ≤ 40%</td>
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<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
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<tr>
<td>Vascular Disease</td>
<td>1</td>
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<tr>
<td>Age 65 - 74</td>
<td>1</td>
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<tr>
<td>Female</td>
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From ESC AF Guidelines
### CHADS\textsubscript{2} vs CHA\textsubscript{2}DS\textsubscript{2}VASc

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} score</th>
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<th>Adjusted stroke rate %/year</th>
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<td>2</td>
<td>523</td>
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<tr>
<td>3</td>
<td>337</td>
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<td>5</td>
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<td>12.5</td>
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<td>6</td>
<td>5</td>
<td>18.2</td>
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<table>
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<th>CHA2DS2-VASc score</th>
<th>Patients ( (n = 7329) )</th>
<th>Adjusted stroke rate %/year</th>
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<tr>
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<td>0</td>
</tr>
<tr>
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<td>422</td>
<td>1.3</td>
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<td>2</td>
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<td>1730</td>
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</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2</td>
</tr>
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</table>
## Approach to Thromboprophylaxis in AF

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>CHA$_2$DS$_2$-VASc Score</th>
<th>Recommended Antithrombotic Therapy$^1$</th>
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</thead>
<tbody>
<tr>
<td>One ‘major’ risk factor or $\geq$ 2 ‘clinically relevant non-major’ risk factors</td>
<td>$\geq 2$</td>
<td>OAC</td>
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</tbody>
</table>
| One ‘clinically relevant non-major’ risk factor’             | 1                         | • Either OAC or aspirin 75-325 mg daily  
• Preferred: OAC rather than aspirin |
| No risk factors                                              | 0                         | • Either aspirin 75-325 mg daily or no antithrombotic therapy  
• Preferred: no antithrombotic therapy rather than aspirin |

Antiplatelet vs Anticoagulation
Warfarin Outclassed by NOAC?

- Anticoagulation to prevent stroke in patients with AF has been well established
  - Warfarin and other vitamin K antagonists are effective treatments for primary and secondary prevention
  - Use is limited owing to a narrow therapeutic range, drug and food interactions, the need for consistent coagulation monitoring, and the risk of bleeding
- In the past decade, a major advance in stroke prevention owing to AF has been the use of new oral anticoagulants
  - Rapid onset of action, low potential for food and drug interactions, and predictable anticoagulant effect that removes the need for routine monitoring
Novel Anticoagulants

- Direct factor Xa inhibitors
  - rivaroxaban, edoxaban, and apixaban
- Direct thrombin inhibitors
  - Dabigatran
- The NOAC were compared with warfarin for stroke prevention among patients with AF in 3 pivotal randomized trials
- The benefits of the NOACs over warfarin have been partially offset by a lack of reversal agents and an inability to precisely monitor their anticoagulant effects as well as costs
RE-LY Trial

- RE-LY (2009): Randomized Evaluation of Longterm Anticoagulant Therapy
- Dabigatran 150 mg BID was superior to warfarin for reduction of the risk of stroke or systemic embolism, with a similar risk of major bleeding between groups (20% RRR compared to warfarin)
- The risk of ischemic stroke was significantly lower with dabigatran 150 mg than with warfarin, but was similar in both groups when dabigatran 110 mg was compared with warfarin
- The dabigatran 110 mg twice daily dosage was noninferior to warfarin in reducing the risk of stroke or systemic embolism, with a significantly lower risk of major bleeding
- Risk of ICH was lower in both dabigatran doses
- Risk of GI bleed was higher in the 150mg group, but same in the 110mg
ROCKET-AF Trial

- ROCKET-AF (2011): Rivaroxaban once daily oral direct factor Xa inhibition compared with vitaminK antagonism for prevention of stroke and embolism trial in atrial fibrillation
- Stroke, the primary end point, occurred at a higher rate among patients treated with warfarin compared to those treated with rivaroxaban, which was found to be noninferior to warfarin.
- Major bleeding was seen more in the rivaroxaban group compared to those taking warfarin.
- The rate of ICH was significantly lower with rivaroxaban treatment compared to warfarin treatment
ARISTOTLE Trial

- ARISTOTLE (2011): apixaban for reduction in stroke and other thromboembolic events
- The rate of the primary outcome (stroke or systemic embolism) was significantly reduced by apixaban compared with warfarin
- The risks of major bleeding, intracranial hemorrhage, and mortality were significantly decreased with apixaban compared with warfarin
Novel Anticoagulants

- The wide therapeutic window and convenience of no routine monitoring make the NOACs desirable first-line options
- Patients taking these drugs require close follow-up with frequent renal function assessments
Antiplatelet Therapy for Noncardioembolic Stroke or TIA

- The first line of treatment for secondary prevention of ischemic stroke.
- Evidence for primary prevention is less convincing.
- Four antiplatelet agents have been approved by the FDA for secondary stroke prevention
  - ASA, combination ASA/dipyridamole, clopidogrel or ticlopididine.
  - On average, these agents reduce the recurrent rate of stroke, MI, or death by 22%
Aspirin

- Aspirin at doses of 50 mg or more per day provide a 15-20% reduction for secondary prevention.
- Low doses are generally recommended (75-100mg) to reduce GI toxicity
- AHA/ASA recommends: 50-325mg
- Despite lack of efficacy in primary prevention trials, AHA recommends a minimum dose of 75 mg daily for patients at risk of CV events
Clopidogrel

- A randomized, blinded trial of clopidogrel vs ASA in patients at risk of ischemic events (CAPRIE, 1996) demonstrated superior efficacy of clopidogrel over aspirin for prevention of vascular end points.
- More effective than aspirin by 8.7% as determined in the CAPRIE trial.
- Diarrhea and rash are potential side effects. GI bleed is less common than with aspirin.
ASA/Dipyramidole

- More effective than ASA based on ESPRIT trial and ESPS-2 trial.
- Based on the PROFESS study (direct comparison of clopidogrel versus ASA+DYP), similar rates of recurrent stroke. No apparent advantage to ASA+DYP.
- Main side effects are diarrhea, headache and occasionally, dizziness.
- Recommended dose is one combination pill, comprising of 25 mg aspirin with 200 mg of dipyridamole each, bid.
Dual Antiplatelets??

- Recently, the safety and efficacy of dual antiplatelets in the acute phase of stroke have been examined.
- Two small trials: CARESS (2005) and CLAIR (2010), evaluated patients with symptomatic large artery stenosis, found that dual antiplatelets reduced number of microembolic signals detected on TCD
  - Limited: did not assess if this translated to long-term
- In the CHANCE (2013) trial, safety and efficacy of ASA and clopidogrel were compared to ASA alone in the prevention of stroke in Chinese patients with acute minor stroke or TIA.
Dual Antiplatelets

- CHANCE trial results indicated that dual antiplatelet therapy was more effective in reducing stroke risk at 3 months without increasing risk of moderate-severe bleeding.
- In a recent meta-analysis of 14 trials (n=9012) among patients with acute non-cardioembolic stroke and TIA within 3 days of symptom onset dual antiplatelets significantly reduced the risk of stroke recurrence as well as composite outcome of stroke, TIA, ACS, death compared to monotherapy.
  - Nonsignificant increase in risk of major bleeding
2 is Better than 1?

- In the Secondary Prevention of Small Subcortical Strokes (SPS-3, 2011) trial, did not significantly reduce the risk of recurrent stroke, but did increase major bleeding when compared to ASA alone.
- All-cause mortality was increased among patient receiving dual antiplatelets
- Conclusion based on SPS-3: in patients with lacunar stroke, the addition of clopidogrel to ASA did not reduce the risk of recurrent stroke and significantly increased the risk of bleeding and death.
Dual or not to Dual??

- The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and continuation for 90 days. (Class IIb, LOE B).

- Consider choosing dual antiplatelets in secondary prevention based on stroke subtype and in Chinese population.
Intervention
Revascularization

- Atherosclerosis of the large arteries accounts for 15-20% of ischemic strokes.
- Based on a Cochrane database review, CEA is appropriate for patients with symptomatic carotid stenosis resulting in TIA or non-disabling stroke with stenosis 50-99%.
- Timing of intervention is controversial, suggestions ranging from 2-6 weeks.
- Pooled analysis from CEA trials demonstrate that early surgery (< 3 weeks) can be performed on low-risk patients (minor stroke without ICH).
- Absolute risk reduction is 18.5% if CEA is performed within 2 weeks of stroke.
Revascularization for Extracranial Carotid Disease

- The stenting vs endarterectomy for treatment of carotid artery stenosis (CREST, 2010) trial suggested that stenting is non-inferior to CEA.
- Subgroup analysis indicated that patients aged > 70 years had better outcomes with CEA than CAS.
- Patients < 70 years who had CAS had less periprocedural strokes.
- Patients in the stenting arm had more post-procedural strokes, whereas endarterectomy patients had more post-procedural MI.
It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (i.e., over about 70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patient, CAS is equivalent to or possibly better than CEA in terms of risk for periprocedural complication (i.e., stroke, MI, death) or long term risk for ipsilateral stroke. (Class IIa, LOE B)
Intracranial Atherosclerosis

- Common cause for stroke and associated with high risk of recurrence
- The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial was designed to assess whether percutaneous transluminal angioplasty and stenting plus medical management is more effective than aggressive medical management
- Trial was stopped early because of high periprocedural stroke in the stenting arm
Intracranial Atherosclerosis

- SAMMPRIS: After a median of 32.4 months, 15% of patients in the medical group and 23% patients in the stenting group had a primary end point event (stroke or death).
- Adverse events occurred at higher rates in the stenting arm.
- Based on the results of the SAMMPRIS trial, medical therapy was superior to intracranial stenting for stroke prevention.
- Therefore, in patients with recent stroke or TIA (within 30 days) owing to severe stenosis (70–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days in addition to aggressive LDL and BP management, is recommended (Class IIb; Level of Evidence B).
Cryptogenic Stroke & PFO

- For patients with an ischemic stroke or TIA and a PFO who are not on anticoagulation therapy, antiplatelet therapy is recommended. (Class I, LOE B)
- For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. (Class I, LOE A)
- For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data does not support a benefit for PFO closure. (Class III, LOE A)
- In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. (Class IIb, LOE C)
Lifestyle Modification

- Quit Smoking!! (increases stroke risk up to 50% over nonsmokers)
  - Smoking increases endothelial damage predisposing to atherosclerosis, platelet aggregation, vasconstriction
- Physical Activity and exercise (30/min, 4+ days/wk)
  - Increases HDL, decreases BP, promotes weight loss
- Limited EtOH consumption
- Weight control/reduction
- Diet/Salt restriction
Thank you!

“I want a detailed analysis, your best educated guess, and then round it out with some wild speculation.”