So you’ve had a stroke…

What you can do to prevent another one

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Secondary Prevention Of Ischemic Stroke

What we can do in the hospital and more importantly what you can do outpatient
What we will not talk about

- Primary Prevention
- Hemorrhagic stroke
- Cardioembolic stroke
- Non modifiable risk factors: Age, gender, ethnicity, family history
- Obstructive Sleep Apnea
What we will talk about

Modifiable Risk Factors

- Hypertension
- Diabetes
- Dyslipidemia
- Smoking
- Physical Activity
Let’s start with a typical patient scenario..

65 year old female with right arm weakness and aphasia
Onset this morning when she awoke
Last known well time 9PM
Let’s assume TPA not indicated and symptoms have improved

- I introduce myself and she has one question for me…
Who are you and where is my doctor?
I am a “Hospitalist”

Not to be confused with “Hospice”

After I assure her she’s not dying today, we get to the actual all important question?
Why did I have a stroke and how can I keep from having another one?
The no-brainer

- Aspirin reduces recurrent stroke risk but about 13% depending on the study

- On occasion dual anti platelets are indicated
The Modifiable Risk factors

- Hypertension
- Diabetes
- Dyslipidemia
- Smoking
- Physical Activity
Do you have high blood pressure?

- My doctor and I have been working on it for years but my top number is never under 160 no matter what we do…
Hypertension

- In the acute setting
- Initial 24 hours goals
- Next few days goals
- Long term goals
Acute Stroke Blood Pressure Management

“Permissive Hypertension” during first 24-48 hours to theoretically augment cerebral blood flow and reduce expansion of ischemic core infarct

When to treat:

>220/120 or signs of end organ damage like coronary ischemia, aortic dissection, etc
or reperfusion candidates who need to be <185/110
When to initiate oral or home regimen

Are they neurologically stable?
- without fluctuating deficits or deterioration - if unstable - wait
  and only treat severe elevations

*This has to be a conversation with your Neurologist - as degree
of stenosis, penumbra, core infarct all can play a role in goal BP
lowering and timing

If stable and can be given oral meds, resume or
initiate at 24-48 hours
What to initiate?

Largest studies in 8 trial meta-analysis from 2017 ACC/AHA guidelines in secondary stroke prevention are with ace/arb and diuretics but no compelling evidence favoring one class over another

Look at comorbid:
* ACE/ARB in diabetes and CKDz
* Diuretics (chlorthalidone best studied and least used)
  - caution in elderly and sodium/potassium issues
* Calcium-channel blockers - not statistically different from ace or diuretics
* Combination of ACE/ARB with calcium channel blocker probably most beneficial

Notice: Beta-blockers NOT first line and considered suboptimal unless other indication, CAD s/p MI or Atrial fibrillation
Long-term Blood Pressure Goals

Previously JNC (Joint National Convention) began issuing HTN guideline since 1977, most recent JNC-7 2003. 2013, JNC 8 2014. Criticized for too many subgroups Transferred responsibility for guidelines to ACC and AHA.

2017 guidelines, eliminates “prehypertension”

Stage 1 130/80 (46% of U.S. adults) - discuss, modify lifestyle or treat
Stage 2 140/90 MUCH easier to remember and treat for ALL
How low should you go?

2014 AHA/ASA guidelines suggests treating patient with known ischemic cva or TIA at blood pressures **>120/70** based on PROGRESS trial that showed relative risk reduction of lowering BP at all baseline BP levels even as low as 120 systolic

Other points:
* Focus on out of office monitoring
* 10 year risk of MI and stroke calculator (patients can understand) acc.org
* 10 year risk of 10% defines high risk (valid only age 40-79)
* Probably reasonable to relax these goals in elderly >80 and those with diastolic <60
Hypertension Take Home Points

* Resume at 24 hours if stable
* 130/80 = Treat if no lifestyle modifications to be made or higher risk
* 140/90 = Treat ALL and continue altering regimen until at goal. Never accept higher numbers as a patient’s normal.
* Treat high risk down to 120/70 if they tolerate
* Probably ACE/ARB and add calcium channel blocker, then diuretic
* If goal to lower >20/10 probably start with 2 agents
Do you have Diabetes?

- I’m not a diabetic
- My doctor says my sugar runs a little high
- Results: A1C is 8.9 and fasting glucose 160
Diabetes

- Let’s focus on Type 2, due to insulin resistance
- Usually associated with the metabolic syndrome
The bad news....

To date, no randomized clinical trial has convincingly demonstrated beneficial effect on macrovascular outcomes in patients with longstanding Type 2 DM. However, study from UK has shown that newly diagnosed diabetes does have prevention benefit of A1C staying less than 7.
What is an A1C?

- Glycosylated Hemoglobin
- Corresponds with average red cell lifespan of 3 months
- Rough estimate is average glucose of 150 = A1C of 7 and about 30:1 thereafter
- Glucose targets: fasting 80-130, post-prandial under 180
What medications are available

- Metformin
- Sulfonylureas
- DPP4 inhibitors
- GLP-1 analogues
- SGLT2 inhibitors
- Insulin
Which medications claim to prevent strokes?

- No data showing stroke prevention for the first 3, nor do they claim to
Which medications claim to prevent strokes?

- GLP-1 analogues
  - glutide or exanetide injectable. BID, daily or weekly
  - no hypoglycemia and actually produce weight loss
  - LEADER: Liraglutide DID show decrease in all cause mortality and CV death, MI, stroke rates vs placebo (13 v 14.9%) and numerical but not statistically significant decrease in stroke rates
  - Exenatide did not show same results
  - REWIND trial ongoing for Dulaglutide
Which medicines claim to prevent strokes?

- **SGLT2 inhibitors**
  - -flozin, taken oral
  - prevent reabsorption of glucose in renal tubules, glycosuria
  - Empagliflozin - 2.2% absolute risk reduction in CV death, NNT 46 to prevent 1 death (median 3.1 years)
  - Canagliflozin - Decrease in combined outcome in CV death, MI, stroke but not individually (26.9 v 31.5%)
  - Caution due to mechanism, increased genital fungal infections and UTIs, along with hypovolemia and “rare” DKA
The Case for Insulin

- None of these have shown to lower A1C more than a few points and most have their own side effects.
- We use insulin acutely in the hospital and can be titrated to get to goals if you have an educated, motivated patient.
Diabetes Take Home Points

If caught early at time of TIA/stroke and get A1C down to under 7 probably can help

Remember the A1C lowering effects of each medicine - so if A1C is 7.5 or 8 it’s completely reasonable to discharge on single agent and followup. Not if A1C is 12. Insulin as an option for these patients.

In considering agents, liraglutide if willing to do injections and canagliflozin (or less so empagliflozin) if risks acceptable, especially if the patient has coexisting CHF. These patients probably need a multi specialist approach and close monitoring.
How is your diet and do you take anything for cholesterol?

- My doctor says my cholesterol is under 200 so I don’t need medicine and I’ve known people who couldn’t walk after taking that cholesterol medication.
Forgetting the numbers and focusing on the risk:

**High risk groups:** prior CVD event or uncontrolled CVD risk factors
**Very high risk:** ACS in past year, Diabetes, CKDz 3 or higher, CVD event while on statin

Prescribe moderate vs high intensity statin dosing depending on the risk, not the LDL

Statins best studied
High intensity lowers LDL by 50-60%, more effective than ezetimibe and less costly than PCSK9 inhibitor
Moderate-intensity:
- Pravastatin, Lovastatin, Simvastatin 40mg
- Atorvastatin 10-20mg
- Rosuvastatin 5-10mg

High-intensity:
- Atorvastatin 40-80mg
- Rosuvastatin 20-40mg
Is LDL level important?

LDL plays key role in pathogenesis and perpetuation of atherosclerotic CVD

Elevated LDL still CVD risk and lowering it associated with decrease in event rates
but not mortality as a single end point.

Although some guidelines gone away from statin treatment based solely on LDL, recommendations are to still try and get LDL down <70 because there was benefit shown there

Less evidence when you get under 70 but maybe even as far down as 55
There are some studies showing risk of ICH at low LDLs but not treating down to that number JUPITER trial as low as 50 and IMPROVE-IT and FOURIER patients had LDLs down to 30 and similar safety profiles
Anything but statins?

FOURIER trial suggests adding second LDL lowering drug in higher risk patients provides additional lowering in events, but needs weighed vs cost, side effects.

Example: 60 year old man with an MI 5 years ago on a high intensity statin and LDL of 75. Can bring his 10 year CVD risk from 20% to 18% with ezetimibe or 16% with PCSK9 inhibitor.
How long do we treat?

ACC/AHA guidelines say 75 years or younger continue high intensity if indicated and over 75 moderate should be considered based on life expectancy
Statin-induced myopathy

Statins inhibit conversion of HMG-VoA to mevalonic acid, early step in cholesterol synthesis.
Speculated that has effects on synthesis of Coenzyme Q10 or ubiquinone reducing it’s levels in skeletal muscle. Another proposed mechanism is sitosterol increased in skeletal muscle tissue, resulting in reduced fat synthesis, increased beta oxidation / fatty acid oxidation.
Statin-induced myopathy

1. **Myalgia**: flu-like, aches, normal CPK
   Some studies as high as 9% with 80mg Atorvastatin vs 4.6% placebo
2. **Myopathy**: Weakness with or without elevated CPK
3. **Myonecrosis**: moderate 10-fold,
   severe 50 fold increase in CPK levels
   0.5% in review of the large statin clinical trials
4. **Clinical Rhabdomyolysis**: myonecrosis with myoglobinuria or AKI

Large claims based study show hospitalization rate for rhabdo of 0.44% per 10,000 patient years.
Usually weeks to months but can occur any time/Usually symmetric proximal weakness.
Average of 6 months to symptoms and 2 months to resolve once stopped 60% completely resolve within a month and over 90% have complete resolution within six months.
Statin-induced myopathy

Risk factors:

**Statin choice**: fluvastatin, pravastatin (40mg pravastatin no diff from placebo)
- also neither metabolized by CYP3A4
- neither is rosuvastatin and probably just as low incidence

**Statin dose**: Simvastatin 20mg 0.02%, 40mg 0.07%, 80mg 0.3%

**Pre-existing neuromuscular disorders**

**Vitamin D deficiency and hypothyroidism**

**Genetic factors**: SLCO2B1 gene variant increased mild adverse effects and genetic test available but probably not cost effective

**Drugs**: CYP3A4 inhibitors nondihydropyridines (diltiazem, verapamil) - 10fold increased risk - probably not best choice when initiating both for secondary prevention
- HIV, HCV protease inhibitors
- Amiodarone: 6% risk of myopathy with amiodarone plus simvastatin 80mg daily*
- Fibrates like gemfibrozil - reason ezetimibe and the other inhibitor recommended as second line

Niacin

**Grapefruit juice**

NOT associated with exercise
What to do when / if occurs:
Stop the drug, >10x normalCPK but most clinicians will stop if symptoms and any elevation
Hydrate, can keep inpatient and monitor renal indices if myoglobinuria

1. Look for drug interactions
2. Possibly switching statin/rechallenge: (pravastatin, fluvastatin, rosuvastatin)
3. Check for vitamin D deficiency and hypothyroidism and rechallenging when treated
4. Consider alternate day dosing
5. Coenzyme Q10 meta-analysis of randomized trials have not shown benefit, especially in prevention but most were short term and not sufficient to get levels up and adequately supplement. Cheap and makes biochemical sense.
6. Red yeast rice - has a compound similar to lovastatin, probably similar LDL lowering as a mild potency statin but lacking clinical trials.
Dyslipidemia Take Home Points

- Statins are good
- Prescribe based on risk factors but also reasonable to titrate up to lower LDL
- Myopathy is rare and reversible
Do you smoke?

- I quit up for a year until last month and have cut back to just a few cigarettes a day.
- My son bought me e-cigarettes to try
Smoking

* 1 Pack/day smoker = 6X more likely to have a stroke
* ANY amount double risk of stroke
* You are twice as likely to DIE if you have a stroke
* Smoking also changes your HDL, LDL, increases blood pressure and risk of atrial fibrillation

Good news!
  Quitting after one year you are half the risk of an active smoker of having an MI
  After 15 years, SAME as non ever smoker.
Do the Math

- Average pack of cigarettes in 2017 from $5.40 (KY) to over $12 (NY)
- $6.07 in Arkansas
- Pack a day smoker = $2,215.55
- 20 pack years = $44,311
- Nonsmoker would save $184.63 monthly
Time to Quit

- Most recommendations include using both nicotine replacement and bupropion.
- Varenicline has good data especially if continued beyond 24 weeks but psychiatric side effects can limit its usefulness.
Vaping?

About the e-cigarettes:

Regular nicotine use still increases BP and HR, but honestly jury is still out. Public Health in England recommends it as a way to stop smoking but simply not around long enough to have data on stroke risk. News studies showing cognitive effects and “popcorn lung” - will not be surprised if more negative data comes out.
Smoking Take Home Points

- Probably the ONE most important thing you can do for secondary prevention
- Use cost savings as motivation
- Try everything at your disposal to help in cessation and continued remission
Do you exercise?

- “I only run if something is chasing me.”
- I tried walking in the mall in the 90s.
Let’s define “Physical Activity”

National Stroke Association recommends 150 minutes of moderate-intensity activity per week, and up 300 minutes continues to show benefit for the over-achievers/Type-As or 75 minutes of vigorous activity per week.

* can be a combination of the two

Moderate: brisk walk, water aerobics, bicycling
Vigorous: Jogging, running, swimming laps
(there is a list at health.gov)

Also recommends 2 or more days of muscle strengthening

AHA recommends 30 minutes a day “most days of the week”
Physical Activity

Benefits are independent of body weight, although the weight part IS linked to the other risk factors like HTN, DM

Biggest benefits occur when going from sedentary to being active just 60 minutes a week!

Key: Do what you like! Not all exercise involves running. Don’t sign up for water aerobics or swimming if you hate getting into a pool. Rowing, elliptical, hiking. Exercise during a show you watch.

“Slogging” - Runners world article a year or so ago showed higher risk of injury and much less likely to continue “running” versus a brisk walk - especially in the obese.
Let’s Review

- You Can’t Control..
- Age
- Gender
- Genetics
Let’s Review

Here’s what you can do…

- Take an aspirin
- Keep blood pressure at goal targets
- Keep your blood sugar under control, especially if recently diagnosed
- Take a statin
- Don’t smoke
- Exercise daily
Any Questions?