A Tale of A Stroke Program:

Why We Do What We Do

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Once upon a time, not so very long ago,
There were people who wanted to explore the best way to treat people having a stroke.
This is their story. . . . . .

- Hippocrates was first to describe sudden paralysis around 400 BC.
- It was referred to as apoplexy
- Record does exist of familial stroke over 1000 years before Hippocrates
- Johann Webfer (1620-1695) identified vertebral and carotid arteries, hemorrhagic apoplexy and the thought that apoplexy was also caused by a blocked artery.

"Size of Treatment Effect"

"Estimate of Certainty (Precision) of Treatment Effect"	Class I *Benefit >>> Risk* Procedure/Treatment SHOULD be performed/administered	Class IIa *Benefit >> Risk* *Additional studies with focused objectives needed* IT IS REASONABLE to perform procedure/administer treatment	Class IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; Additional registry data would be helpful* Procedure/Treatment MAY BE CONSIDERED	Class III *Risk ≥ Benefit* *No additional studies needed* Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
Level A *Multiple (3-5) population risk strata evaluated** *General consistency of direction and magnitude of effect*	• Recommendation that procedure or treatment is useful/effective • Sufficient evidence from multiple randomized trials or meta-analyses	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation that procedure or treatment not useful/effective and may be harmful • Sufficient evidence from multiple randomized trials or meta-analyses
Level B *Limited (2-3) population risk strata evaluated**	• Recommendation that procedure or treatment is useful/effective • Limited evidence from single randomized trial or non-randomized studies	• Recommendation in favor of treatment or procedure being useful/ effective • Some conflicting evidence from single randomized trial or non-randomized studies	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from single randomized trial or non-randomized studies	• Recommendation that procedure or treatment not useful/effective and may be harmful • Limited evidence from single randomized trial or non-randomized studies
Level C *Very limited (1-2) population risk strata evaluated**	• Recommendation that procedure or treatment is useful/effective • Only expert opinion, case studies, or standard-of-care	• Recommendation in favor of treatment or procedure being useful/ effective • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation's usefulness/efficacy less well established • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation that procedure or treatment not useful/effective and may be harmful • Only expert opinion, case studies, or standard-of-care
Suggested phrases for writing recommendations †	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/ beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

Chapter 1

Figuring Out the Risk Factors

- **Framingham Heart Study-** 1948
  - Term RISK FACTOR first used
  - HTN
- **JNC 7 report**, regular BP screening and appropriate treatment, including both lifestyle modification and pharmacological therapy, are recommended (*Class I; Level of Evidence A*)
- **NOMASS study-**(Northern Manhattan Stroke Study)-1997
- **GCN Kentucky-** 2005
  - DM increases risk for ischemic stroke at ALL ages

- Abstention from cigarette smoking by nonsmokers and smoking cessation by current smokers are recommended based on epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH (*Class I; Level of Evidence B*).
- **Strong Heart Study**
  - Cardiovascular disease mortality, morbidity and risk factors in Native Americans
- **Southwest US Native American Stroke Study** (2007)
- **REGARDS Study-** (Reasons for Geographic And Regional Differences in Stroke)- Why is there an American "Stroke Belt?"

ABCD2 Score

Age > 60 years	1 point
Blood Pressure > 140/90	1 point
Unilateral Weakness	2 points
Speech Impairment w/o weakness	1 point
Duration > 60 minutes	2 points
Duration 10-59 minutes	1 point
Diabetes	1 point

S. Johnston, LANCET 2007

ABCD2 Score

» **TABLE 2B** Early stroke rates in acute TIA patients stratified by the ABCD2 score

ABCD2 score	2-day risk	7-day risk	90-day risk
0–3 (low risk)	1.0%	1.2%	3.1%
4–5 (moderate risk)	4.2%	5.9%	9.8%
6–7 (high risk)	8.1%	11.7%	17.8%

Chapter 2

Emergency Response to Stroke

- EMS and "Stroke Chain of Survival"
  - Rapid recognition
  - Rapid EMS dispatch
  - Rapid transport w/ prenotification
  - Rapid in-hospital diagnosis and treatment

Class 1, Level of Evidence B

Stroke Teams

- The use of acute stroke teams improves stroke care and increases the appropriate use of stroke therapies through established protocols.

Recommendations for Stroke Systems of Care (2005)

ED Response Times

- The "Golden Hour"
  - 0 to 10 min
  - 0 to 25 min
  - 0 to 45 min
  - 0 to 60 min

CT interpreted
tPA infusion initiated
CT completed
Doctor assessment

*Walk in **AND** EMS patients should be triaged with same urgency as would an acute MI patient.*

NINDS rtPA Stroke Study, 1996

Stroke Assessment

- NIHSS
- Diagnostic tests
  - All patients
  - Noncontrast brain CT (Class 1 LOE A) or brain MRI
  - Blood glucose
  - Serum electrolytes/renal function tests
  - ECG
  - Markers of cardiac ischemia
  - Complete blood count, including platelet count*
  - Prothrombin time/international normalized ratio (INR)*
  - Activated partial thromboplastin time*
  - Oxygen saturation

Class 1 Level of Evidence B

NIHSS

- Developed by the National Institute of Health in the 1980's for acute stroke trials as a research study tool.
  - To assist researchers in grading the severity of stroke symptoms.
- Helps determine level of stroke severity
  - Helps guide therapy for patient
- Strongly predicts likelihood of patients recovery after stroke with or without IV-tPA.
- Helps assess risk of hemorrhage after IV-tPA.
- High inter-rater reliability and simplicity
- Also available since 2006 in Spanish

Class 1 Level of Evidence B

Chapter 3

Thrombolytics

- Thrombolytic agents in 1980's and 90's
  - Streptokinase
  - Urokinase
  - Tissue plasminogen activator
- Early MI thrombolytic trials impacted knowledge of thrombolysis in AIS
- tPA had less death or disabling stroke than streptokinase (1993)
- 1992 – Studies using tPA demonstrated that doses lower than .95mg/Kg given early into stroke (90-180 min) were safe.
- STREPTOKINASE trials stopped early due to bleeding risk. (1995)

Thrombolytics

- NINDS rt-PA Study
  - Dosed 0.9mg/Kg
  - Risk of hemorrhage is proportional to the degree to which the NINDS protocol is not followed.
  - Treatment w/in 90 minutes of onset had favorable outcome compared to placebo.
  - 3 month outcome favorable for those treated w/ rt-PA in 91-180 min window.

Thrombolytics

- **Other tPA trials**
  - **ECASS I** – European Cooperative Acute Stroke Study (1995) 1.1mg/Kg treated w/in 6 hrs from onset
    - tPA treated pt. with improved mRS at 90 days
    - 17.4% protocol violations
    - No difference in 30 day mortality, but ICH rate higher in tPA group
  - **ECASS II** – (1998) 0.9mg/Kg tPA in AIS w/in 6 hours
    - Less severe strokes treated. 8.8% ICH
    - Death or dependency lower among pts. treated with tPA.
  - **ECASS III** – (2008) Efficacy and safety of alteplace administered between 3-4.5 hours of onset of AIS
    - Disability at 90 days mRS
      - mRS 0-1 52.4% tPA group, 45.2% in control group

Thrombolytics

- **Other Trials**
  - Thrombolytic Therapy in Acute Stroke Trial, Part A. (1991) 0-6 hrs tx. stopped 1993.
  - ATLANTIS- 0-5 hr treatment window
    - More tPA treated pts. had a decrease >11 NIHSS at 30 days
  - SITS-MOST (2007)- Norway and Iceland outcome study
  - SITS-ISTR (2008) – 3-4.5 hr pts compared with pt. in ISTR
    - Outcomes: no significant differences in sICH, mortality or mRS
  - IST-3 (2008) IV-tPA in 0-6 hours including more elderly patients > 80 years.

Chapter 4

Intra Arterial Intervention

- High concentration thrombolytic delivered to thrombus
- PROACT II (1999) Prourokinase testing as intra-arterial thrombolytic agent for MCA occlusions
  - Prourokinase not FDA approved, so extrapolation to rt-PA is based on consensus and case studies.

Intra Arterial Intervention

- MERCI I- (2005)
  - Recanalization in 48%
  - sICH 7.8%
  - mRS 0-2at 90 days 46% of those recanalized (10% nonrecanalized)
- Multi-MERCI Trial (2008)
  - Same criteria using new L5 retriever
  - 57% recanalization and 69.5% in conjunction with IA tPA
  - mRS 0-2 in 36%
  - Mortality 34%
  - sICH 9.8%

IA procedures must have informed consent.

Intra Arterial Intervention

- **IMS I Trial** (2004)
  - IV-tPA at 0,6mg/Kg over 30 min then IA tPA given up to 22 mg over 2 hours
  - sICH 6.3%
  - No outcomes results
- **IMS II Trial** (2007)
  - Same as IMS I but used EKOS catheter to deliver IA tPA, combining ultrasound with thrombolysis.
- **IMS III Trial-** Enrollment stopped in May 2012.

Intra Arterial Intervention

- Penumbra (2008)
  - Approved for "clot retrieval"
- "Stentrievers"
  - Solitaire, Trevo
    - Approved 2012
- Multi-modal approaches
  - Combination of IV/IA thrombolysis

Arterial Dissections

- Options include:
  - Anticoagulation
  - Antiplatelet therapy
  - Angioplasty w or w/o stenting
  - Observation w/o medical therapy
- Anticoagulation w/ heparin or LMWH most common
  - Risk of stroke in first few days is greatest at diagnosis
- Cochran review
  - No s. s. difference in death or disability between antiplatelet and anticoagulant therapy

PFO

- 15-25% of adults have PFO
  - 2-3% of those have atrial septal aneurysm
  - Increased risk of stroke to those <55
- PICSS trial- Patent Foramen Ovale in Cryptogenic Stroke
  - No difference in those treated w/ ASA vs. warfarin
- PFO-ASA study (2002)
  - 18-55 year olds treated with ASA
  - 2.3% risk stroke w/ PFO alone
  - 15.2% if PFO and atrial septal aneurysm
  - 4.2% if no PFO or atrial septal aneurysm

PFO Closure

- CLOSURE 1 trial
  - no differences in outcomes between the device and medical therapy
- RESPECT trial
  - Results due out this year
- REDUCE trial
  - ongoing

Chapter 5

Swallow Screen

- Swallow
  - 50 pairs of muscles must work together
  - Dysphagia in 42-67% of stroke pt.
  - Silent Aspiration in up to 50%
- Assessment of swallowing before starting eating or drinking is recommended (Class I, Level of Evidence B).

DVT Prophalaxis

- Considered the most preventable cause of death in hospitalized pt.
- The risk of deep vein thrombosis is highest among immobilized and older patients with severe stroke.
- Now required (pay for performance metric)- prophalaxis w/in 24 hours.
- Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent deep vein thrombosis (Class I, Level of Evidence A). The ideal timing for starting these medicationsis not known.

Chapter 6

Secondary Prevention

- Antiplatelet vs. Anticoagulant
  - WARSS trial (Warfarin Aspirin Recurrent Stroke Study)
  - WASID trial (Warfarin vs Aspirin for Symptomatic Intracranial Disease)

Antiplatelet Therapy

- Aspirin: alone, 75mg-100mg q day lower stroke risk 15%.(all stroke types)
- Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events **(CAPRIE)** trial
  - Stroke, MI, PVD pts assigned to ASA 325mg or Clopidogrel 75mg q day.
    - For stroke, study was not designed to determine if Clopidogrel is equivalent to ASA.
- **MATCH** trial (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke)
  - Clopidogrel 75mg plus ASA
  - Clopidogrel 75mg
  - No benefit for combo therapy accept in ACS

Antiplatelet

- ESPS 2: European Stroke Prevention Study 2 (1997)
  - ASA/ER-DP vs ASA vs ER/DP (all BID)
  - Results: ASA/ER-DR vs ASA 23.1% stroke prevention
    - ASA vs Placebo is 18.1% prevention
    - ER-DP vs Placebo is 16.3% prevention
- European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) (2006)
  - 13% combination group had stroke/MI/vascular death/major bleeding
  - 16% aspirin alone

Antiplatelet

- CHARISMA- Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial
  - Clopidogrel and aspirin vs. asa alone
    - Increased bleeding risk of combo therapy but no benefit compared to aspirin alone
- ProFESS trial-clopidogrel vs. asa/dipyridamole
  - More hemorrhagic events in asa/dipyridamole
  - Less well tolerated (headache)
  - Did not show inferiority of asa/dipyridamole

Antiplatelet

- **Summary**
  - Non cardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events *(Class 1; Level of Evidence A)*
  - Aspirin monotherapy (Class 1; LOE A), combo of ASA/dipyridamole BID (Class 1; LOE B) and clopidogrel 75 mg monotherapy (Class IIa; LOE B are acceptable options for initial therapy.

Anticoagulation

- Warfarin- Vitamin K antagonist approved in 1954
- Afib on coumadin, revealed INR 2-3 (1996)
- WARSS- Warfarin Aspirin Recurrent Stroke Study for **noncardioembolic stroke**
  - Warfarin (INR 1.4 – 2.8) compared to ASA 325mg
    - No difference between treatment
- ESPRIT- (came out of SPIRIT trial)
  - Warfarin (INR 2.0-3.0) vs ASA (30mg to 325mg) or ASA/dipyridamole
  - Major differences in bleeding warfarin vs. others

CHADS 2

	Condition	Points
C	Congestive heart failure	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S_2	Prior Stroke or TIA or Thromboembolism	2

Anticoagulation

- RE-LY trial -2010
  - Dabigatran vs. Warfarin
  - BID dabigatran dosing
  - Once a day dosing noninferior to warfarin
- ROCKET-AF trial -2011
  - Rivaroxaban vs. Warfarin
  - Once a day dosing noninferior to warfarin
  - Similar rate of major bleeding
- ARISTOTLE trial – 2011 not yet FDA approved
  - Apixaban vs Warfarin
  - Superior to warfarin
  - Fewer major bleeding events
- All 3 trials showed less ICH than warfarin

Hypertension

- BP lowers in most AIS pt. about 15% the first day.(Class I, Level of Evidence C)
  - Aggressive lowering of BP is discouraged, but BP meds can usually be restarted after 24 hours.
- BP lowering is associated with a 30% to 40%reduction in risk of stroke
  - Larger reductions in systolic BP were associated with greater reduction in risk recurrent stroke.

Hypertension

- **1 out of every 4 adults has HTN**
  - 31.6% are unaware (JNC 7)
- An absolute target BP level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of approximately 10/5 mm Hg, and normal BP levels have been defined as 120/80 mm Hg by JNC 7 *(Class IIa; Level of Evidence B).*

Lipids

- National Cholesterol Education Program (NCEP)
  - Recommendations CHD w/ 2 or more risk factors: LDL <100mg/dl ***(Class I; Level of Evidence B).***
- Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, 2003
  - LDL <70: 28% reduction in ischemic stroke w/o an increase in hemorrhagic stroke ***(Class IIa; Level of Evidence B).***
- FDA limits use of Simvastatin 80mg due to muscle injury (2011)

Diabetes

- ACCORD Trial
- ADVANCE Trial
- Veterans Affairs DM Trial

→

- All 3 trials result that glycemic targets should NOT be lowered to < 6.5% for secondary prevention

- PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive)
  - 47% RRR in recurrent stroke
- The Insulin Resistance Intervention after Stroke (IRIS)
  - Ongoing trial that randomizes pt. to pioglitazone or placebo

Smoking

- Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit *(Class I; Level of Evidence C)*.
- Counseling, nicotine products, and oral smoking cessation medications are effective for helping smokers quit *(Class I; Level of Evidence A)*

Lifestyle Changes

- **Obesity**- BMI >30 KG/m2 all research is in area of primary prevention.
- **Low Fat/ Low Sodium Diet-** the consumption of a diet rich in fruits, vegetables, and low-fat dairy products
- **Physical Activity**
  - For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise, typically defined as vigorous activity sufficient to break a sweat or noticeably raise heart rate, 1 to 3 times a week (eg, walking briskly, using an exercise bicycle) may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrent stroke *(Class IIb; Level of Evidence C)*.
- **Alcohol**
  - Light to moderate levels of alcohol consumption (no more than 2 drinks per day for men and 1 drink per day for nonpregnant women) may be reasonable; nondrinkers should not be counseled to start drinking *(ClassIIb; Level of Evidence B)*.

Chapter 7

Telemedicine

- Telestroke services
  - Treatment options for remote hospitals
  - Consultation for tPA administration feasible and safe
  - Reimbursement issues

Chapter 8

Putting it all Together

Set No. Harmonized DSC Stroke Measure Name

STK-1 Deep Vein Thrombosis (DVT) Prophylaxis
STK-2 Discharged on Antithrombotic Therapy
STK-3 Patients with Atrial Fibrillation Receiving Anticoagulation Therapy
STK-4 Thrombolytic Therapy Administered
STK-5 Antithrombotic Therapy By End of Hospital Day Two
STK-6 Discharged on Cholesterol Reducing Medication
STK-7 Dysphagia Screening
STK-8 Stroke Education
STK-9 Smoking Cessation / Advice
STK-10 Assessed for Rehabilitation

Stroke (STK) Core Measure Set

STK-1	Venous Thromboembolism (VTE) Prophylaxis
STK-2	Discharged on Antithrombotic Therapy
STK-3	Anticoagulation Therapy for Atrial Fibrillation/Flutter
STK-4	Thrombolytic Therapy
STK-5	Antithrombotic Therapy By End of Hospital Day 2
STK-6	Discharged on Statin Medication
STK-8	Stroke Education
STK-10	Assessed for Rehabilitation

The Real Heros

And they lived happily ever after.

The End

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