Ischemic Stroke

General Ischemic Stroke

Definition

Disruption of blood supply to the brain resulting in ischemia->infarction of underlying brain tissue

Focal arterial ischemia of CNS causing symptoms: >24h OR pathological/imaging evidence

Proposed decision tree for determination of a cerebrovascular event definition:


Epidemiology


Third leading cause of death

Leading cause of long term moderate to severe disability

Incidence ~795,000/yr (new or reccurent)


Incidence by Age


Risk Factors

Risk factors from INTERSTROKE trial

Intercontinental case-control study of surveyed/self-reported measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=3000)</th>
<th>Ischemic stroke (n=2337)</th>
<th>ICH (n=663)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>32%</td>
<td>55% (OR 2.37)</td>
<td>60% (OR 3.80)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>24%</td>
<td>37% (OR 2.32)</td>
<td>31% (OR 1.45)</td>
</tr>
<tr>
<td>Wait-to-hip (T3 vs T1)</td>
<td>33%</td>
<td>43% (OR 1.69)</td>
<td>35% (OR 1.41)</td>
</tr>
<tr>
<td>Diet (T2 vs T1)</td>
<td>36%</td>
<td>37% (OR 1.29)</td>
<td>41% (OR 1.53)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>12%</td>
<td>8% (OR 0.68)</td>
<td>7% (OR 0.70, ns)</td>
</tr>
<tr>
<td>DM</td>
<td>12%</td>
<td>21% (OR 1.60)</td>
<td>10%</td>
</tr>
<tr>
<td>Alcohol &gt;1 drink/d</td>
<td>11%</td>
<td>16% (OR 1.41)</td>
<td>16% (OR 2.01)</td>
</tr>
<tr>
<td>Psych/Depression</td>
<td>14%</td>
<td>21% (OR 1.47)</td>
<td>16%</td>
</tr>
<tr>
<td>Cardiac causes</td>
<td>5%</td>
<td>14% (OR 2.74)</td>
<td>4%</td>
</tr>
<tr>
<td>ApoB:A1 (T3 vs T1)</td>
<td>33%</td>
<td>49% (OR 2.40)</td>
<td>35%</td>
</tr>
</tbody>
</table>

Subvariables: Benefit for fish & fruits. No clear relationship of BMI or former smoking (>1y ago). Total or non-HDL cholesterol not clearly associated with ischemic stroke, possibly lower risk ICH. HDL associated with lower risk for ischemic stroke, higher for ICH.

Framingham study


10 year risk probability by sex

Predictors:

Age

HTN/SBP

Diabetes


Prior cardiovascular disease

Atrial fibrillation

Left ventricular hypertrophy

Use of hypertensive medication

Other risk factors

Estrogen/OCP (REF: Arch Neurol. 2010;67(2):195-201)


Lipids - weaker factor for primary stroke: adjusted HR: nonHDL 1.12, HDL 0.93 (0.84-1.02) (REF: JAMA. 2009;302(18):1993-2000 http://www.ncbi.nlm.nih.gov/pubmed/1993920)

White Matter hyperintensities: HR stroke 3.3, dementia 1.9, death 2.0 (REF: BMJ. 2010 Jul 26;341:c3666. doi: 10.1136/bmj.c3666. http://www.bmj.com/content/341/bmj.c3666.long)

Severe psoriasis (RR 2.98 in pts <50y) (REF: http://eurheartj.oxfordjournals.org/content/early/2011/08/12/eurheartj.ehr285.abstract)

Depression RR ~ 1.12-1.5 (REF: http://jama.ama-assn.org/content/306/11/1241.full)


Sodium intake/excretion

![Graph showing sodium intake/excretion](http://jama.ama-assn.org/content/306/20/2229.full)

Potassium intake/excretion

![Graph showing potassium intake/excretion](http://jama.ama-assn.org/content/306/20/2229.full)

Genetics


Potential Stroke Triggers

- Air pollution
- Anger & other negative emotions
- Cervical trauma/manipulation
- Coffee consumption
- Heavy exertion
- Heavy meal/alcohol binge
- Hospitalization for infection
- Pregnancy/postpartum
Recreational drugs

Sudden postural change

URI

UTI

Weather changes


Primary Prevention

Women: Stop smoking, low BMI, moderate alcohol, exercise, healthy diet = HR 0.45 (REF: Arch Intern Med. 2006 Jul 10;166(13):1403-9)


ASA not beneficial for pts w/ABI < 0.95 but otherwise healthy (REF: JAMA. 2010 Mar 3;303(9):841-8)

Pathophysiology

Timing

Underperfused brain becomes ischemic; ions build up, electrochemical gradients run down, calcium accumulates, glutamate builds up & becomes toxic

Ischemia = <20ml/100g tissue/min, tissue death in 1 hr when <16ml/100g, absence of blood flow = death of tissue in 4-10 min

Reperfusion injury?

No-reflow phenomenon (sludging, endothelial dysfunction)

<table>
<thead>
<tr>
<th>CBF ml/100g/min</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>Normal</td>
</tr>
<tr>
<td>23</td>
<td>Ischemia</td>
</tr>
<tr>
<td>10-12</td>
<td>Infarct</td>
</tr>
<tr>
<td>In vitro hypoxia</td>
<td>5 min ok, &gt;20-30min death</td>
</tr>
<tr>
<td>Limited flow 5-6h</td>
<td>Partial ischemia</td>
</tr>
</tbody>
</table>


Mechanism

Occlusion of lumen by embolus

Occlusion by thrombus

Rupture of a vessel

Vessel dissection

Altered permeability of vessel wall

Vasospasm

Trauma

Compression

Hypotension

Hypertension

Arteritis (infectious, autoimmune)
Auto/dysregulation
Increased viscosity or other change of blood
Modulated by collateral flow, metabolic complications
(REF: Adams & Victor, 8th ed)

Basic Science

Etiology

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic</td>
<td>40%</td>
</tr>
<tr>
<td>Lacunar/Small-vessel disease</td>
<td>26%</td>
</tr>
<tr>
<td>Cardiac embolism</td>
<td>18%</td>
</tr>
<tr>
<td>Atherosclerosis (Extra- or intracranial)</td>
<td>15%</td>
</tr>
<tr>
<td>Other (Dissection, Hypercoag, Sickle...)</td>
<td>1%</td>
</tr>
</tbody>
</table>


TOAST trial classification (REF: http://stroke.ahajournals.org/cgi/reprint/24/1/35.pdf)

<table>
<thead>
<tr>
<th></th>
<th>Large-artery athero</th>
<th>Cardioembolic</th>
<th>Small-artery occlusion</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical or cerebellar dysfunction</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Lacunar syndrome</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical, cerebellar, brain stem, or subcortical infarct &gt;1.5 cm</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Subcortical or brainstem infarct &lt;1.5cm</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis of extracranial ICA</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac source of emboli</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other abnormality on tests</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

(REF: Causative Classification System for Ischemic Stroke. https://ccs.mgh.harvard.edu/ccs_form.php)

Large-artery atherosclerosis (embolus/thrombosis)
Significant stenosis (>50%) or occlusion of major brain artery or branch cortical artery
Exclude cardioembolism
Clinical support: h/o claudication, TIA in same territory, bruit, or diminished pulses

Large vessel disease
Atherosclerosis: eg. carotid artery stenosis 15-20% all strokes (REF: AHA Proceedings on CEA)
Arteritis (Takayasu / giant cell)
Fibromuscular dysplasia
Dissection
Vasculopathy
Moyamoya
Vasoconstriction / spasm
Arteriopathy (i.e., CADASIL)
Small vessel disease
Lipohyalinosis
HTN/aging
Atheroma at penetrator origin

Cardioembolism (high-risk/medium-risk)
Clinical support: stroke or TIA in >1 vascular territory or systemic emboli
Exclude large-artery athero
Less clear/newer category: aortic atheroma

High-risk sources
Mechanical prosthetic valve
Mitral stenosis w/atrial fibrillation
Atrial fibrillation (other than lone atrial fibrillation)
Left atrial/atrial appendage thrombus
Sick sinus syndrome
Recent myocardial infarction (<4 weeks)
Left ventricular thrombus
Dilated cardiomyopathy
Akinetic left ventricular segment
Atrial myxoma
IE

Medium-risk sources
Mitral valve prolapse
Mitral annulus calcification
Mitral stenosis w/o atrial fibrillation
Left atrial turbulence (smoke)
Atrial septal aneurysm
Patent foramen ovale
Atrial flutter
Lone atrial fibrillation
Bioprosthetic cardiac valve
Nonbacterial thrombotic endocarditis
Congestive heart failure
Hypokinetic left ventricular segment
Myocardial infarction (>4 weeks, <6 months)

Small-vessel occlusion (lacune)
Appropriate noncortical syndrome
Clinical support: h/o HTN, DM; also smoking & LDL
Imaging: <1.5cm infarct
Exclude large-artery athero & cardioembolism

7mm diameter (lypohyalinotic): age, ever-smoking, DM, black ethnicity

8-20mm diameter (microatheroma): age, ever-smoking, HTN, LDL

Stroke of other determined etiology

Migraine

Subclinical cerebrovascular disease

Inflammatory processes (elevated CRP or chronic infections)

(REF: http://www.uptodate.com/online/content/topic.do?topicKey=cva_dise/15463)

Systemic hypoperfusion

Pump failure

Hypoxemia

Compression (elevated ICP)

Blood disorders

Sickle cell

PCV

Thrombocytosis

Hypercoagulable states (eg antiphospholipid or occult cancer)

Stroke of undetermined etiology

Two or more causes identified

Negative evaluation

Incomplete evaluation

Multifocal strokes

Neoplasia: including hematologic

Infection: Endocarditis, Meningoencephalitis

Cardioembolic

Multivessel stenoses

Vasculitis

Angiopathies: Moyamoya, Cocaine

Connective tissue disease: systemic sclerosis, lupus

Hypercoagulopathies: antiphospholipid, homocysteine

Hemoglobinopathies: sickle cell

Mitochondrial abnormalities: MELAS

Genetics Syndromes: CADASIL, CARASIL, COL4A, RVCL, Fabry (REF: https://www.clinicalkey-com.epz-prod1.hul.harvard.edu/#!/ContentPlayerCtrl/doPlayContent/1-s2.0-S0022510X12003942)

Stroke in young person

<table>
<thead>
<tr>
<th>Definite causes</th>
<th>n=318</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombosis</td>
<td>49</td>
</tr>
<tr>
<td>PFO-ASA</td>
<td>43</td>
</tr>
<tr>
<td>Cervical or cerebral artery dissection</td>
<td>30</td>
</tr>
</tbody>
</table>
Small-Vessel disease  25
Cardioembolism       26
Atrial fibrillation  14
Intracardiac tumor†  4
IE                  3
Intravascular coagulation associated w/cancer  3
Ejection fraction < 35%  2
Thrombosis of unruptured cerebral artery aneurysm  2
Iatrogenic (intra-arterial catheter)  2
Lupus anticoagulant  2
Aortic Arch Atheroma >4mm  2
Acute myocardial infarction  1
Ventricular aneurysm  1
Thrombus in left atrium  1
Moyamoya disease  1
Buerger disease  1
Reversible cerebral vasconstriction syndrome  1
Radiation cerebral arteritis  1
Syphilitic cerebral arteritis  1
Heparin-induced thrombocytopenia  1

(REF: http://www.neurology.org/content/76/23/1983.full)

Presentation

Sudden onset loss of brain function

Usually focal, nonconvulsive deficit

Can involve motor, sensory, cognitive, autonomic parts of nervous system.

H&P: focus on onset, risk factors for etiology

Onset at awakening suggests lacunar, onset w/movement suggests embolic (REF: CMF via Verne Caveness via Brian Edlow) but see (REF: http://www.neurology.org/content/76/19/1662.full)

Even if symptoms have resolved, a stroke may have occurred. “30% to 50% of classically defined TIs show brain injury on diffusion-weighted magnetic resonance (MR) imaging (MRI).” (REF: Stroke. 2009;40:2276). Under new definitions, these are now strokes.


Syndromes/Common locations

Common syndromes: recognition speeds diagnosis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Temporal Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAH</td>
<td>Sudden onset, HA, n/v</td>
</tr>
<tr>
<td>IPH</td>
<td>Rapid worsening min-hr</td>
</tr>
<tr>
<td>TIA</td>
<td>Symptoms resolved &lt;24h (&lt;1h)</td>
</tr>
<tr>
<td>Embolic</td>
<td>Sudden onset, slow resolution</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>Variable, stuttering course min-hr</td>
</tr>
</tbody>
</table>
Localization: Oxfordshire Classification of Subtypes of Cerebral Infarction

Total anterior circulation infarction syndrome (TACS)
A combination of new higher cerebral dysfunction (ie, dysphasia, dyscalculia, visuospatial disorder); homonymous visual field defect; & ipsilateral motor and/or sensory deficit of at least 2 areas of the face, arm, & leg.

Partial anterior circulation infarction syndrome (PACS)
Only 2 of the 3 components of the TACS syndrome are present, w/ higher cerebral dysfunction alone, or w/a motor/sensory deficit more restricted than those classified as LACS (ie, confined to 1 limb or to face & hand, but not to the whole arm).

Lacunar infarction syndrome (LACS)
Pure motor stroke, pure sensory stroke, sensori-motor stroke, ataxic hemiparesis, clumsy-hand dysarthria

Posterior circulation infarction syndrome (POCS)
Any of the following: ipsilateral cranial nerve palsy w/ contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; disorder of conjugate eye movement; cerebellar dysfunction w/o ipsilateral long-tract deficit (ie, ataxic hemiparesis); or isolated homonymous visual field defect.

Circulatory collapse - Watershed
Usually from cardiac arrest
ACA/MCA watershed & MCA/PCA watershed
“sickle-shaped strip of variable width from the cortical convexity of the frontal lobe, through the high parietal lobe, to the occipitoparietal junction” (REF: Adams & Victor, 8th ed, p669)
Deeper infarcts may be “contiguous extensions of the cortical infarctions into subjace white matter”

Common Carotid
Similar to ICA neurologically

ICA
30-40% silent? (REF: Adams & Victor, 8th ed)
Local athero -> thrombotic occlusion -> artery-to-artery embolus vs. hypoperfusion ischemia
Distal fx may be smaller because of collateral flow: pial vessels, ECA-opthalmic, AComm (contra), PComm (posterior)
Distal fx may be bigger because of occlusions or anomalous vasculature: 2x ACA, fetal PCA
Complete MCA + ACA = combined fx + drowsy/stupor 2/2 ill defined effect on RAS
May include headache: above the eyebrow, 2/2 carotid fx
Most affected area may be watershed areas btw MCA & ACA: cortical (shoulder/hip worse than hand /face) or deep territories (subfrontal/parietal centrum semiovale)
Also optic nerve & retina

MCA
Distal M1 (usually embolic): contralateral hemiplegia, hemianesthsesia, homonymous hemianopia (LGN)
Global aphasia (L>R) vs. anosognosia & amorphosynthesis (R>L), alertness may be impaired initially
Sup-ant division: rolandic & prerolandic areas. Weak contra F&A>L, eyes deviate ipsi; usu motor>sensory; global->expressive aphasia (effortful, hesitant, grammatically simplified, & dysmelodic speech < comprehension)
Inf-post division: lat temporal, inf parietal. Receptive aphasia, superior quadrantonopia. Right lesions -> L neglect, rarely agitated state (dominant > nondominant?)
Deep penetrating/lenticulostriate: part of head/body caudate, putamen, GPe, posterior limb internal capsule, coral radiata, LGN. Motor > language/attention
May include headache: more lateral, at temple

ACA
Cortical: Medial forebrain, corpus callosum. Contra weak foot>leg>shoulder>>hand&face, motor>sensory, eyes may deviate ipsi, incont, personality changes

Deep (eg, recurrent art of Heubner): ant limb int capsule, inf head caudate, ant GP. Abulia (or agitation?), motor aphasia, dyskinesia

Ant Choroidal
Usually fromICA

GPi, post limb int capsule, Optic tract, Choroid plexus -> post choroidal art

Motor, sensory, vis >> language/attn/cog

Lacunar
Occlusion of small arteries

Strong correl w/HTN & athero > DM

Loc: putamen/caudate > thalami > pons > IC > deep hemispheric WM

Cavities 3-15mm diameter

Pure hemiplegia (F/A/L): lenticulostriate, IC/corona radiate or pons. Can evolve stepwise over days, usual recovery

Pure sensory stroke: Lateral thal (less often parietal WM)

Clumsy-hand dysarthria: mid-pons contra to hand

Ipsi hemiparesis-ataxia: pons/midbrain/IC/parietal WM

Can can pseudobulbar palsy w/accumulation

PCA

70% B basilar, 20-25% 1 basilar, 1ICA(fetal), 5-10% BICA(fetal)

May include headache: in or behind the eye

Anterior & Proximal Syndromes

Interpeduncular branches (mesencephalic): red nuc, SN, medial cerebral peduncles, CN3&4, retic upper brainstem, sup cerebellar peduncles, MLF, medial lemnisci. Central midbrain & subthalamic syndromes. Vertical/third w/contra weak

Thalmo perforate (paramedian thalamic): inf, med, ant thal. Artery of Percheron variants. Extrapyramidal movt dis; vascular amnestic syndrome

Thalamogeniculate branches: LGN, central/post thal. Sensory loss: pain/temp > touch/vib/pos (anes -> pain)

Posterior choroidal: post/sup thal, choroid plex, post hippocampus

Cortical syndromes

Cortical branches: inferomedial temporal, medial occipital

Homonymous hemianopia (U>L; relative macular sparing)

“Release”/positive phenomena

Dominant: alexia+agraphia, anomia (esp color), visual agnosias, amnesea

Bilateral syndromes

Top of the basilar thrombus

Cortical blindness (denial = Anton syndrome)

Central vision may be spared (MCA, ACA collaterals)

Severe memory impairment w/inferiomedial infarcts

Vertebral

10% practically 1 vert
-75% of supply to medulla

Usu intracranial atherothrombosis

Arterial dissection: cervico-occipital pain, can be B deficits

Occlusion of 1 vert may have few signs

Subclavian steal (stenosis of subclavian + demand via exercise, draws blood from contra vert)

Medial medullary syndrome: contr weak arm & leg, contra loss pos/vib, ipsi tongue weak

May include headache: behind ear or above eyebrow

Lateral Medullary

Vestibular nuclei (vertigo, nystagmus, oscillopsia, n/v), spinothalamic tract (contra>ipsi impaired pain /temp), descending sympathetic tract (ipsi Horner), CN 9&10 fibers (hoarse, dysphagia, palate/vocal cord, "gag", otolith (vertical diplopia, tilting vision), cerebellar tracts (ipsi ataxia/falling), CN5 (pain, burn, impaired sense ipsi face), nucleus & tractus solitarius (loss of taste), rarely cuneate/gracile nuclei (ipsi numb)

Vert 80% > PICA or lateral medullary arteries

Classic PICA: Lat med & inf cerebellum: Wallenberg lat med syndrome

Most do well w/considerable recovery, however, some sudden death

Basilar

Complete basilar syndrome: B long tract signs (S&M), variable cerebellar, CN, brainstem abnormalities ± coma vs. locked-in (dep on midbrain)

Basilar branch occlusion: various, complex syndromes. "Top-of-the-basilar" or crossed CN vs. long tract signs

Eyes may deviate to weakness in pontine strokes

Pain/temp > two-point/pos suggests subcortical/brainstem

May include headache: occiput ± forehead

SCA

Ipsi cerebellar ataxia of limbs, n/v, slurred speech, loss of pain/temp contra (spinothal tract)

AICA

Variable infarct size (inversely related to PICA)

Vertigo, n/v, nystagmus, tinnitus/deafness, facial weak, ipsi cerebellar ataxia, ipsi Horner, contr loss of pain/temp (lat spinothalamic tract)

If proximal: corticospinal involvement

If distal: cochlear/labyrinthine infarct

Usually does not cause cerebellar swelling

ASA

Emergent Workup


General: ABC & VitalsàHistory àEKG, labsàSTAT CT/CTA. Document NIHSS. Determine if pt. meets criteria for IV TPA or intravascular intervention

History:
Time of onset

Last known normal (i.e. time last seen awake & “normal”)

Initial symptoms & progression

Check with witnesses.

PMH:
CV risks, h/o drug abuse, migraine, sz, infections, trauma, or pregnancy

Physical Exam:

<table>
<thead>
<tr>
<th>System</th>
<th>Looking for</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEENT</td>
<td>e/o trauma/seizure</td>
</tr>
<tr>
<td>CV</td>
<td>AFib, murmurs, dissection, bruits, JVD</td>
</tr>
<tr>
<td>Resp/Abd</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Skin/Ext</td>
<td>Emboli/needle tracks, hepatic/jaundice, coagulopathy/purpura, plt/petechia</td>
</tr>
</tbody>
</table>

Differential Diagnosis:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Characteristic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH or SAH</td>
<td>Onset headache &amp; vomiting</td>
</tr>
<tr>
<td>SAH</td>
<td>Abrupt onset impaired cerebral function w/o focal symptoms</td>
</tr>
<tr>
<td>Seizure</td>
<td>h/o or seizure activity</td>
</tr>
<tr>
<td>Syncope</td>
<td>Sudden LOC, prodrome</td>
</tr>
<tr>
<td>Migraine</td>
<td>h/o similar events, aura, headache</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>h/o DM/insulin, low BS,</td>
</tr>
<tr>
<td>Overdose</td>
<td>h/o drug use</td>
</tr>
<tr>
<td>Hypertensive emergency</td>
<td>Headache, delirium, HTN</td>
</tr>
<tr>
<td>Conversion disorder</td>
<td>Nonvascular pattern, no CN findings</td>
</tr>
<tr>
<td>Trauma</td>
<td>h/o mechanism</td>
</tr>
</tbody>
</table>

NIH Stroke Scale (NIHSS)

(REF: http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf)

Correlates w/stroke size by MRI

Reliability of subcomponents variable

<table>
<thead>
<tr>
<th>#</th>
<th>NIH Stroke Scale</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>LoC</td>
<td>0 Alert &amp; responsive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Arouses to minor stim</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Arouses to repeated or painful stim</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Reflex response or unarousable</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>LoC ?: month/age</td>
<td>0 Both correct</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 One correct (dysarth, intub foreign)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Neither correct</td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>LoC commands:</td>
<td>0 Both correct</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open/close eyes, grip/release any hand, mimic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 One correct</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Neither correct</td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>---</td>
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</tr>
</tbody>
</table>
| 2 | Best Gaze: Horizontal EOM | 0 Normal  
Voluntary or reflexive/OCR | 1 Partial gaze palsy: abnl in 1 or both  
2 Forced eye deviation or paresis despite OCR |
| 3 | Visual Field | 0 No visual loss  
Counting, BTT, or orient to movt | 1 Partial hemianopia, quad, extinction  
2 Complete hemianopia  
3 Bilateral hemianopia or blindness |
| 4 | Facial Palsy: show teeth, raise eyebrows, close eyes | 0 Normal  
If dec response: check symmetry of grimace to pain | 1 minor paralysis (flat NLF, asymmetry on smiling)  
2 partial paralysis (total or near paralysis of lower face)  
3 complete paralysis (upper & lower face) |
| 5 | Motor Arm: Outstretched 90° (sit) or 45° (supine) x 10 sec | 0 No drift x 10 sec  
R | 1 Drift but does not hit bed  
L  
2 Some antigravity effort, cant sustain  
3 No antigravity effort, minimal movement counts  
X unable to assess (amput, fusion, fx) |
| 6 | Motor Leg: Raise to 30° supine x 5 sec | 0 No drift x 5 sec  
R | 1 Drift but doesn’t hit bed  
L  
2 Some antigravity effort, cant sustain  
3 No antigravity effort, minimal movement counts  
X unable to assess (amput, fusion, fx) |
| 7 | Limb Ataxia: finger-nose-finger & heel-to-shin | 0 No ataxia (aphasic/hemiplegic)  
score only if out of proportion to paralysis | 1 ataxia in upper or lower extremity  
2 ataxia in upper & lower extremity  
X unable to assess (amput, fusion, fx) |
| 8 | Sensory: Safety pin | 0 Normal  
score only stroke related losses | 1 mild-mod loss: less sharp but aware  
2 Total loss, pt unaware of touch F/A/L |
| 9 | Best Language: Name objects, read sentences | 0 Normal  
X unable to assess (amput, fusion, fx) | 1 mild-mod aphasia (partly comprehensible)  
2 severe aphasia; (almost no info exchange)  
3 mute, global aphasia, coma |
| 10 | Dysarthria: read list of words | 0 Normal | 1 mild-mod; slurred speech but intelligible  
2 severe; unintelligible or mute  
X intubation or mech barrier |
| 11 | Extinction/Inattention: Visual, aud, sens, spatial, body parts | 0 Normal, none detected | 1 Inattention or extinction to 2 stim in 1 modality  
2 Profound hemiinattention or extinction to >1 modality |
| Total |   |   |   |

**Imaging**

STAT imaging to r/o hemorrhage, mass lesion, or acute infarct (performance measure)
Door-to-scanner time <25min, Door-to-interpretation time <45min


Noncontrast CT
r/o bleed, look for arterial occlusion/hyperdense vessel, loss of the gray-white differentiation, sulcal effacement, hypodense tissue/edema/mass effect

Multimodal CT
Perfusion CT: cerebral blood volume, flow, ischemia
CT angiography (CTA): occlusion, stenosis, aneurysm

Multimodal MRI
Diffusion-weighted imaging (DWI): early ischemia
Associated Diffusion Constant (ADC): confirms DWI finding
Perfusion-weighted imaging (PWI): penumbra
MR angiography (MRA): proximal occlusion, stenosis
Gradient echo: hemorrhage, prior microbleeds
FLAIR: slow fluid flow, prior infarcts

If not tPA candidate: MRI better for acute, small cortical, small deep, & posterior fossa infarcts; acute vs chronic ischemia; subclinical satellite ischemic lesions re: mechanism. Also no radiation or contrast. MRI limited by cost, availability, & contraindications such as claustrophobia, cardiac pacemakers, or metal implants

May be initially negative in brainstem or lacunar strokes vs 30d (REF: http://stroke.ahajournals.org/cgi/content/full/39/6/1898)

Vascular Imaging
MRA, CTA, Carotid U/S, angiogram all acceptable according to standard considerations (performance measure)


Which test depends on institutional expertise. Consider getting 2 concordant findings if pre-op. (REF: Stroke. 2009;40:2276)

Conventional angio: gold standard, but higher risk

Other
PET, SPECT

Labs
Fingerstick glucose
Chem 7, CBC, PTT/INR (can do point of care INR)
A1c
Fasting lipids
Cardiac: enzymes & EKG (r/o MI, arrhythmias/AFib)

Selected pts

LFTs
Blood alcohol level
Tox in young-mid age
Urine HCG if female of reproductive age
HIV (REF: http://jama.ama-assn.org/content/306/16/1747.full)
ABG if hypoxic
CXR (REF: http://jama.ama-assn.org/content/306/16/1747.full) or if suspect lung disease
LP to r/o SAH if CT neg
EEG to r/o sz
ESR, CRP, homocysteine
Fibrinogen, D-dimer

Stroke in Young People/Multifocal
(REF: http://www.neurology.org/content/76/23/1983.full)
BCx
TTE -> TEE

Hypercoag workup

Hypercoag workup if <55yo w/out clear risks (REF: Stroke. 2009;40:2276). Most more commonly studied for VTE
Protein C, protein S, antithrombin III deficiency
Activated protein C resistance/Factor VLeidenmutation Arg506Gln
Prothrombin gene G20210A mutation
Methylenetetrahydrofolate reductase (MTHFR) C677T mutation
Homocysteine
Fibrinogen
D-Dimer
Antiphospholipids: Lupus anticoagulant, Anticardiolipin, anti-2 glycoprotein 1
Factor VIII
Von Willebrand factor
Plasminogen activator inhibitor-1
Endogenous tissue plasminogen activator activity
Also HIT±T, DIC, cancer-related

Thrombolysis/Treatment
(REF: NINDS rtPA Stroke Study, ECASS, ECASS-II, ATLANTIS)

IV tPA


Figure 2. Outcome at Three Months in Part 2 of the Study, According to Treatment.

Scores of <1 on the NIHSS, 95 or 100 on the Barthel index, <1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome. Values do not total 100 percent because of rounding.

Symptomatic ICH risk: 2.1% (SITS), 7.0% (ECASS-II), & 9.4% (NINDS)
Indications

Diagnosis of ischemic stroke causing measurable neurological deficit

The neurological signs should not be clearing spontaneously

The neurological signs should not be minor & isolated

Caution should be exercised in treating a pt w/major deficits

Symptoms of stroke should not be suggestive of subarachnoid hemorrhage

Onset of symptoms <3 h before beginning treatment

No head trauma or prior stroke 3 mo

No MI 3 mo (but possibly safe after 7wk, (REF: http://www.neurology.org/content/76/21/1838.abstract)

No GI or GU hemorrhage 21 d

No major surgery 14 d

No arterial puncture at a noncompressible site 7 d

No h/o previous intracranial hemorrhage

SBP <185 mmHg & DBP <110 mmHg (can try meds as below)

No e/o active bleeding or acute trauma (fracture) on examination


If heparin <48 h, aPTT wnl

Pit count 100k

Glucose 50 mg/dL

No sz w/postictal residual neurological impairments

CT does not show a multilobar infarction (hypodensity >1/3 cerebral hemisphere)

Pt or family members understand the potential risks & benefits from treatment (recommended, written consent not necessary)

Additional criteria for 3-4.5h

80 yo, no anticoagulation at all, NIHSS 25, no h/o stroke & DM (REF: Stroke. 2009;40:2945 http://stroke.ahajournals.org/content/40/8/2945.short)

Additional recommendations

Imaging: No e/o hemorrhage or multilobar infact w/"frank" hypodensity >33% of hemisphere

No intracranial or spinal surgery <3 mo

No h/o intracranial hemorrhage, brain aneurysm, vascular malformation, or brain tumor (can consider if low likelihood bleed, e.g. small aneurysms or low vascularity, benign tumors)

No known coagulopathy

NIHSS 22

Life expectancy > 1 y w/o severe comorbid illness

Glucose 50-400 mg/dL

No Left heart thrombus

No increased risk of bleeding found due to any of the following:

Acute pericarditis

Subacute bacterial endocarditis (SBE)
Hemostatic defects including those secondary to severe hepatic or renal disease

Pregnancy

Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions

Septic thrombophlebitis or occluded AV cannula at seriously infected site

Advanced age

Protocol

Dose: 0.9 mg/kg (max 90 mg), 10% as bolus / 1 min, rest / 1 hr

Admit to ICU or stroke unit

If headache, HTN, or n/v, d/c tPA & get STAT CT

Neuro check q15min during infusion, q30min x6h, q60min x24h after treatment

BP check q15min x2h, q30min x6h, q60min x24h after treatment

If SBP 180 mmHg or DBP 105 mmHg, give anti-HTN meds, increase BP checks

Delay NG tube, Foley, or A-lines

CT @24h before anticoag or antiplt

Monitor for bleeding or angioedema

BP Control

Pre-tPA, If SBP>185 or DBP>110

Labetalol 10-20 mg IV / 1-2min, can repeat x1

Nicardipine 5-15 mg/hr, titrate by 2.5mg/hr q5-15min. When controlled, reduce to 3mg/hr

Nitropaste 1-2 in

BP during & after reperfusion intervention

BP check q15min during treatment + 2hr, then q30min x6hr, then q60min x 16hr

If 180-230/105-120: labetalol

If >230/>120: labetalol or nicardipine, nitroprusside if refractory

(REF: [http://www.bmj.com/content/341/bmj.c6046.full](http://www.bmj.com/content/341/bmj.c6046.full))
labetalol 10 mg IV / 1-2 min, q10-20 min, max dose 300 mg
labetalol 10 mg IV, then 2 to 8 mg/min
nicardipine 5-15 mg/hr, titrate by 2.5mg/hr q5min

**IA tPA**

IA tPA is an option for selected pts w/major stroke due to MCA occlusion <6h.

<table>
<thead>
<tr>
<th></th>
<th>IA prourokinase n=121</th>
<th>control n=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recanalize MCA</td>
<td>66%</td>
<td>18%</td>
</tr>
<tr>
<td>ICH &lt;24h</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>mRankin 0-2 @90d</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>Death @90d</td>
<td>25%</td>
<td>27%</td>
</tr>
</tbody>
</table>


IA tPA is reasonable in pts w/contraindications to IV thrombolysis such as recent surgery.

(REF: Stroke. 2011 Apr;42(4):993-7. Bridging intravenous-intra-arterial rescue strategy increases recanalization & the likelihood of a good outcome in nonresponder intravenous tissue plasminogen activator-treated patients: a case-control study. PMID: 21372307)

Combined IV + IA tPA trial is ongoing (REF: www.IMS3.org)

**Mechanical Clot Retrieval**


Stopped early for no clear benefit of IV tPA + IA vs. IV tPA alone (REF: http://www.ninds.nih.gov/disorders/clinical_trials/IMS-III.htm)


"When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci (Class I; Level of Evidence A)." (REF: Guidelines 2013)

**MERCI** (Mechanical Embolus Removal in Cerebral Ischemia)

(REF: http://www.maringeneral.org/jsp/new_stroke.jsp)

Animation (REF: http://www.youtube.com/watch?v=99x_APzvD1c)

May improve recanalization (80%) more than good outcomes (32%) (REF: http://my.americanheart.org/ids/groups/ahamah-public/wcm@sop@scon/documents/downloadable/ucm_427798.pdf)

May be useful outside tPA window (REF: Arch Neurol. 2008 Aug;65(8):1024-30)

Mechanical removal of thrombus using MERCI device (spring, suction, & balloon system) may be reasonable in carefully selected pts (REF: Stroke 2005 Jul;36(7):1432-8), but utility in improving outcomes after stroke is unclear (REF: Stroke 2005 Feb;36(2):400-3)

Penumbra w/Aspiration
Thrombolysis for Basilar Artery Occlusion

Recommended treatment ASAP, esp <9hr.

IV thrombolysis should probably be first line treatment, w/possible rescue IA thrombolysis


Decompressive Surgery

Remove necrotic tissue & decrease ICP


Criteria

Neuro ICU for monitoring

Most likely to benefit: meets all STATE criteria

Uncertain to benefit: age <75, many but not all STATE criteria

Unlikely to benefit: age >75, terminal illness, active herniation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scores</td>
<td>NIHSS item 1a ≥1 OR GCS ≤8, AND NIHSS &gt;15 (non-dominant) or &gt;20 (dominant)</td>
</tr>
<tr>
<td>Time</td>
<td>48h since last seen without neurological deficits</td>
</tr>
<tr>
<td>Age</td>
<td>60yo</td>
</tr>
<tr>
<td>Territory</td>
<td>Infarct &gt;150 cm³ or &gt;50% MCA territory</td>
</tr>
<tr>
<td>Expectations</td>
<td>Life expectancy ‘reasonable’ with appropriate expectations</td>
</tr>
</tbody>
</table>

If all criteria met: hemicrani (to OR <4-6h)

If criteria & signs of herniation (asymmetric pupils, >10mm midline shift at septum, >5mm shift at pineal gland): emergent hemicrani

Surgical RCTs

Results: Decreased Death (OR 0.19) without significantly improving disability (mRS>3: OR 0.56, 0.27-1.15)

134 pts 60yo, prestroke mRS <2

Surgery <30-96h from onset

50-66% MCA distribution ± mass effect, midline shift

NIHSS 1a 1-2


12mo Outcomes


Other potential tx

IV tenecteplase


Tirofiban

Glycoprotein IIb/IIIa platelet receptor antagonist - Placebo group (n=124) ~4d: HTI 14.5%, HTII 8.1%, PHI 2.4%, PH II 0.8% (REF: Stroke. 2011 Sep;42(9):2388-92. Safety of Tirofiban in acute Ischemic Stroke: the SaTIS trial. PMID: 21852609. http://stroke.ahajournals.org/content/42/9/2388.long)

Management

Respiratory


Prevent early aspiration & protect airway

Correlated w/pre&post M&M (REF: doi: 10.1212/WNL.0b013e31823152b1 Neurology October 4, 2011 vol. 77 no. 14 1338-1345; http://www.neurology.org.ezp-prod1.hul.harvard.edu/content/77/14/1338.full)

<table>
<thead>
<tr>
<th>PNA (n=587)</th>
<th>Non-PNA (n=7664)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Crude  Adj</td>
</tr>
</tbody>
</table>

Ventilation

Greatest risk of airway compromise: decreased consciousness or brainstem dysfunction

Intubation may also help for effects of ICP & edema on breathing


Oxygenation

Causes of hypoxia: partial airway obstruction, hypovent, aspiration PNA, atelectasis

Keep $O_2$ 92%, but no clear benefit for $O_2$ w/o hypoxia

Hyperbaric $O_2$ only for air embolism or bends

BP

High & low BP associated w/poor outcome (REF: Stroke. 2004; 35: 520–526)


Best range appears to be 161-200 / 91-110

BP drop > 20mmHg associated w/worse outcomes

Balance: decrease edema, hemorrhage, recurrent strokes but maintain perfusion pressure

Candesartan x7d may worsen outcomes (REF: http://dx.doi.org/10.1016/S0140-6736(11)60104-9)

“Evidence from one clinical trial indicates that initiation of antihypertensive therapy within 24 hours of stroke is relatively safe. Restarting antihypertensive medications is reasonable after the first 24 hours for patients who have preexisting hypertension and are neurologically stable unless a specific contraindication to restarting treatment is known (Class IIa; Level of Evidence B).” (REF: Guidelines 2013)

HTN

Urgent comorbid: hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or ACS/MI

Only treat SBP >200 or DBP >120 mmHg, decrease 15-25% / first day

For mild-mod strokes w/o ICP, can restart BP meds 24 hr after event

HypoBP

Causes: aortic dissection, volume depletion, blood loss, decreased cardiac output 2/2 MI or arrhythmias, SIRS/sepsis

NS/IVF as needed

Correct arrhythmias such as slowing rapid AFib

Vasopressors such as DA

Cardiac Monitoring

MI & arrhythmias: share risks w/stroke but also may be causes & complications

R insula stroke may have increased risk of cardiac complications, presumably secondary to disturbances in ANS function.

EKG changes 2/2 stroke: ST-segment depression, QT dispersion, inverted T waves, & prominent U waves

Cardiac monitoring for 24 hr

Fevers

Fever associated w/poor outcome
Goal normothermia

Possible benefit of antipyretic treatment w/acetaminophen, cooling blankets, ice packs (hypothermia being studied)

Search for infection as cause or complication of stroke: endocarditis, PNA, UTI. No role for prophylactic antibiotics but treat suspected infections

Minimize indwelling catheters, consider intermittent straight-cath. Condom catheters are not satisfactory (REF: Stroke. 2007;38:1655)

Cooling being studied

Blood sugar

Avoid hypoglycemia

Hyperglycemia & h/o DM are associated w/poorer outcomes


DM: regular wt based basal (NPH bid), bolus, & sliding scale regular insulin

Glucose >140-180 mg/dl: continuous IV insulin or regular sliding scale insulin


Anti-platlet medication

(performance measure)

ASA 325 mg <24-48 hr reduces death or dependence @ 6 mo (NNT ~100) (REF: IST, Lancet. 1997; 349: 1569–1581) (REF: CAST, Lancet 1997;349:1641-9)

<table>
<thead>
<tr>
<th></th>
<th>2 wk (REF: IST)</th>
<th>4 wk (REF: CAST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>2.8% vs 3.9%</td>
<td>1.6% vs 2.1%</td>
</tr>
<tr>
<td>Death</td>
<td>9.0% vs 9.4% (p=ns)</td>
<td>3.3% vs 3.9%</td>
</tr>
</tbody>
</table>


There may be a benefit to using ASA + clopidogrel after minor stroke or TIA in first few days (REF: Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial. http://www.nejm.org/doi/full/10.1056/NEJMoa1215340)

No antiplt if hemorrhage or <24h from thrombolysis

No data on ticlopidine, clopidogrel, or dipyridamole acutely


Anticoagulation

(performance measure)

Do not anticoagulate in standard acute stroke. IV heparin or SC LMWH increase bleeding w/o a clear benefit on initial or recurrent stroke (performance measure)

Possible indications for heparin: Dissection, symptomatic stenosis, venous thrombosis, cardiac clot

Deep Vein Thrombosis (DVT)/Venous ThromboEmbolism (VTE) prophylaxis

(REF: http://www.angiologist.com)
Heparin SC, LMWH SC, or LDUH
If pharm anticoag contraindicated, pneumatic compression devices ± ASA
Early mobilization
ACP recommendations
Assess risks for VTE & bleeding prior to pxx
Pharma ppx, unless risk of bleeding outweighs benefits
Rec against mechanical prophylaxis w/graduated compression stockings

<table>
<thead>
<tr>
<th>Stroke pts</th>
<th>Heparin n</th>
<th>Heparin %</th>
<th>No n</th>
<th>No %</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1175/15742</td>
<td>7.46</td>
<td>1669/20380</td>
<td>8.19</td>
<td>0.93</td>
</tr>
<tr>
<td>PE</td>
<td>127/15481</td>
<td>0.82</td>
<td>222/20098</td>
<td>1.10</td>
<td>0.70</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>120/15607</td>
<td>0.77</td>
<td>114/20245</td>
<td>0.56</td>
<td>1.61</td>
</tr>
</tbody>
</table>

Incidence
8.8% in Chinese rehab, in hemiparetic calf muscles (REF: Keio J Med. 2008 Dec;57(4):196-204. PMID: 19110532)

Singapore series
341 pt screened 23 days poststroke at entry to rehab
198 (58.1%) had elevated d-dimer
18 (9% of d-dimer) had DVT: 7 proximal, 11 distal
No pt had PE during rehab in Singapore
Similar after TBI (REF: J Head Trauma Rehabil. 2009 May-Jun;24(3):178-86. PMID: 19461365)

Prophylaxis
1: ACP recommends assessment of the risk for thromboembolism & bleeding in medical (including stroke) pt prior to initiation of prophylaxis of venous thromboembolism.
2: ACP recommends pharmacologic prophylaxis w/heparin or a related drug for venous thromboembolism in medical (including stroke) pt unless the assessed risk for bleeding outweighs the likely benefits.
3: ACP recommends against the use of mechanical prophylaxis w/graduated compression stockings for prevention of venous thromboembolism.


Anticoag

Guidelines (REF: http://chestjournal.chestpubs.org/content/133/6_suppl/454S.long)

Prevention of clinical PE: anticoag/IVC filter

Prevention of post-thrombotic syndrome (PTS): elastic compression stockings


2011 Metaanalysis more cautious

Heparin prophylaxis had no statistically significant effect on any outcome in pt w/acute stroke except for an increase in major bleeding events (OR, 1.66) (REF: http://www.annals.org/content/155/9/602.full)

IVC Filters


Mechanical Compression


2011 Metaanalysis more cautious

No improvements in clinical outcomes were seen in the 3 studies of mechanical prophylaxis in pt w/stroke, but more pt had lower-extremity skin damage (RR 4.02)

(REF: http://www.annals.org/content/155/9/602.full)

Below the knee/Distal DVT

Summary: Patient individualized decision. No clear benefit for anticoagulation vs rescan in 4-8 days (REF: Ido Weinberg).

Diagnosis

Wells score not helpful (REF: Thromb Res. 2011 Mar 2. PMID: 21376372)

Isolated muscular calf vein (gastroc) may have a slightly higher rate of progression than deep calf vein. (REF: Ido Weinberg, but not according to J Vasc Surg. 2010 Oct;52(4):932-8, 938.e1-2. PMID: 20630688).

VTE (on anticoag): MCVT 1.5% vs DCVT 1.4%

Pain: MCVT 30.4% vs DCVT 22.4%

Swelling: MCVT 47.9% vs DCVT 62.7%


Progression Proximally

Mean ~10% (0% to 25-33%)

Silent PE

Scanned for silent PEs w/V/Q scans
Progression after 60d 3% w/ & w/o anticoag, after 10d 13 & 8%

Distal DVT embolized in 33% pts

Trauma pts

85/601 pts (14.1%) had 113 BKDVTs <34 days, ½ in 1st wk

4/85 pts (4.7%) propagate above-knee (4-8d)

1/85 (1.2%) had PE w/o propagation

Treatment

3 month anticoag (REF: http://chestjournal.chestpubs.org/content/133/6_suppl/454S.long)

Prospective LMWH series: 171 pts: 2.9% proximal extension, 1.7% minor bleeding, 2.9% recurrence

Arm/Upper Extremity DVT

Peripherally Inserted Central Catheters (PICC)

Weighted frequency of PICC-related DVT highest in patients who were critically ill 13.91% & cancer 6.67%

PICC DVT vs. CVC: OR 2.55

Baseline PICC-related DVT rate of 2.7%

Superficial Vein Thrombosis

Fluids/Nutrition/GI

IVF

Dysphagia screen prior to eating via bedside water test (listen for cough & wet voice -> videofluoroscopic modified barium swallow) (performance measure)

NG tube if necessary for nutrition or oral meds (consider longer term PEG)

Treat n/v to decrease risk of aspiration

Bowel regimen

Dysphagia

Studies: endoscopic evaluation, modified barium swallow

Difficulty swallowing secretions

Aspiration pneumonia


General Care

Stroke unit/comprehensive care plan

Mobilization as soon as condition is stable (watch for orthostatic symptoms & assess fall risk)

Skin surveillance & turning to prevent sores

Performance Measures

DVT prophylaxis

Antiplatlet agent at d/c

Anticoagulation at d/c
tPA considered
Dysphagia screen
Rehab services
Carotid stenosis measurement
CT or MRI to r/o hemorrhage, mass lesion, or acute infarct
Avoid IV heparin
Statin at d/c (if LDL-c >100, not measured, or already on lipid med)

CDC State/Stroke registry (REF: http://jama.ama-assn.org/content/305/16/1649.full)

Can not recommend as of 2007

Hemodilution (except for polycythemia vera)
Vasodilators such as methylxanthing derivatives such as pentoxifylline
Induced HTN (except in rare circumstances w/close monitoring)
Emergent CEA or extracranial-intracranial bypass
Neuroprotective interventions including cooling
Neuroprotective chemicals (failed clinical trials, but what If studied at time of CABG?)

**Neuro Complications**

**Deterioration**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>% Deterioration &lt;1wk</th>
<th>Acute mortality w/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACI</td>
<td>41.9%</td>
<td>47.2%</td>
</tr>
<tr>
<td>PACI</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>LACI</td>
<td>26.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td>POSI</td>
<td>21.7%</td>
<td>38.5%</td>
</tr>
</tbody>
</table>

Acute mortality ~0 w/No Deterioration

For TACI: deriorating pts (n=36) 86.1% early CT abnorm vs. 18.4% ND

Significant stenosis: TACI 68.4% D vs. 34.9% D, POCI 71.4% D vs. 31.1% ND


**Swelling/Edema**

Timing: MCA occlusion swelling (10-20%) usually ~4d; Reperfusion/tPA edema can be <24h, causing herniation; Cerebellar infarct swelling can cause more rapid brainstem compression, apnea, arrhythmia


Clinical risks: B ptosis, nondominant hemisphere, h/o HTN, h/o HF, elevated WBC, >50% MCA hypodensity, additional vascular territory (REF: Stroke. 2001; 32: 2117–2123), need for intubation
Initial Management: free water restriction; correct hypoxemia, hypercarbia, hyperthermia; elevate head of bed 20-30°; avoid anti-HTN meds, esp causing cerebral vasodilatation

Management of ICP: hyperventilation (temporary effect), osmotic diuretics (mannitol 0.25-0.5 g/kg IV / 20 min q6h), CSF/ventricular drain. See Critical Care.


Seizures

Sz on first day 2-23%

Late sz 3-67%. Higher risk w/preexisting dementia


Prophylactic AED not recommended w/o sz.

If sz, follow usual AED recs.

By stroke type: ICH (16.2%), infarct w/hemorrhagic transformation (12.5%), ischemic infarct (4.2%). Mostly focal sz, <24h, cortical location (OR 3.4) (REF: Neurology. 2011 Nov 15;77(20):1785-1793. Incidence & predictors of acute symptomatic seizures after stroke. PMID: 21975208. http://www.neurology.org/content/77/20/1785.full.pdf)

Hemorrhagic Transformation (HT)

~5% of infarctions spontaneously developed symptomatic hemorrhagic transformations from frank hematomas


Hemorrhagic conversion in pts w/cerebellar infarct significantly increased the risk of deterioration (REF: Stroke. 2000; 31:2062–2067)

Pathophysiology

Reperfusion of previously ischemic tissue (REF: Caplan’s Stroke, p320)

Classification

Hemorrhagic Transformation: Petechial infarct w/out mass effect (I = small petechiae; II = more confluent petechiae)

Parenchymal Hemorrhage: Hemorrhage w/mass effect (I = 30% of infarct w/mild mass effect; 2 = >30% infarct area w/mass effect of clot remote from infarct)

ECASS I: CT at 24-36h, 4-10d
Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration & 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. PMID: 10548658. [http://stroke.ahajournals.org/content/30/11/2280.full](http://stroke.ahajournals.org/content/30/11/2280.full)

Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? PMID: 11387495. [http://stroke.ahajournals.org/content/32/6/1330.full](http://stroke.ahajournals.org/content/32/6/1330.full)

**Timing**

Most often 2-7d (REF: Caplan’s Stroke, p317), 68.8% ≤10d (REF: Stroke. 1989 May;20(5):598-603. Hemorrhagic transformation in cerebral embolism. PMID: 2718199. [http://stroke.ahajournals.org/content/20/5/598.full.pdf](http://stroke.ahajournals.org/content/20/5/598.full.pdf))

43% of infarcts (28/65) have hemorrhagic transformation in 1 prospective study up to 3 wks (retrospective studies or fewer scans less sensitive) (REF: Stroke. 1986 Mar-Apr;17(2):179-85. Hemorrhagic cerebral infarction— a prospective study. PMID: 3515635. [http://stroke.ahajournals.org/content/17/2/179.full.pdf](http://stroke.ahajournals.org/content/17/2/179.full.pdf))

**Management**

No specific recs for asymptomatic hemorrhagic transformation

See ICH section for management of symptomatic hemorrhagic transformation

Risks


Cardioembolic strokes tend to be larger (73.7 ml vs. 48.9 ml) (REF: Caplan’s Stroke, p318)

![Risk increased with antithrombotics, esp anticoagulants (heparin) & thrombolytics (tPA)](http://brushstroke.ahajournals.org/content/17/2/179.full.pdf)

Risk increased w/antithrombotics, esp anticoagulants (heparin) & thrombolytics (tPA)

Hyperglycemia (glucose 180-200, esp not DM), higher risk bleed after tPA (OR 2.86) (REF: Arch Neurol. 2010;67(9):1123-1130)

Associated with


Matrix metalloproteinase-9 activity (MMP9)

Albuminuria

Low plt


High CRP (weak effect)


Early recurrent stroke

New lesion/recurrence w/in initial perfusion deficit (vs. distant): Any lesion 34%, distant 15%, clinical 2%

Initial multiple DWI lesions -> any lesion recurrence (HR, 2.83), distant lesion recurrence (HR 5.99)

Large-artery athero most frequent stroke subtype associated w/recurrence
Definition: new lesion (new noncontiguous DWI+) vs. enlargement (enlargement of contiguous DWI+)

Unclear clinical significance

Pathophys: new thromboembolus (primary stroke mech, intervention), hypoperfusion->ischemic death, delayed neuronal death, reperfusion injury

74 acute MCA stroke pts: 23 no acute tx, 14 IV tpa, 11 IA, 26 IV+IA

New DWI: 39/74 (52.7%), Med # 3 (IQR 2-5), 70.6% 10mm diameter. Mostly multiple, small, cortical/superficial, mild perfusion delay regions, - s/p IA

Enlargement: 52/74 (70.3%). Med vol 10.1ml (IQR 3.0-38.9). Mostly w/in severe perfusion delay region, -- NIHSS, unclear impact of reperfusion as presented
Late Recurrent Stroke

<table>
<thead>
<tr>
<th>TOAST</th>
<th>30d rate of recurrent stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherostenosis</td>
<td>18.5%</td>
</tr>
<tr>
<td>Cardiac Embolus</td>
<td>5.3%</td>
</tr>
<tr>
<td>Lacunar</td>
<td>1.4%</td>
</tr>
<tr>
<td>Uncertain cause</td>
<td>3.3%</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Annual stroke rate</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Asymp Carotid stenosis</td>
<td>1.3%</td>
</tr>
<tr>
<td>Transient monocular blindness</td>
<td>2.2%</td>
</tr>
<tr>
<td>TIA</td>
<td>3.7%</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>6.1%</td>
</tr>
<tr>
<td>Major stroke</td>
<td>9.0%</td>
</tr>
</tbody>
</table>


Risk factors include DM1: 27% vs 8%; HR 3.32


Recurrent Stroke in the Young (15-49yo + 10y): DM1 40.9%, DM2 29.7%, nonDM 12.0% (roughly 1.5x for all vascular events) (REF: http://www.neurology.org/content/76/21/1831.abstract)

**Delirium**

(REF: Neurology March 15, 2011 vol. 76 no. 11 993-999; http://www.neurology.org/content/76/11/993.abstract)

11.8% develop delirium <1wk

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting cognitive decline</td>
<td>2.6</td>
</tr>
<tr>
<td>Infection</td>
<td>3.4</td>
</tr>
<tr>
<td>R side stroke</td>
<td>2.0</td>
</tr>
<tr>
<td>Anterior/Large vessel</td>
<td>3.4</td>
</tr>
<tr>
<td>NIHSS (high vs low tertile)</td>
<td>15.1</td>
</tr>
<tr>
<td>Brain atrophy (high vs low tertile)</td>
<td>2.7</td>
</tr>
</tbody>
</table>

“Delirium was associated w/a worse outcome in terms of duration of hospitalization, mortality, & functional outcome.”


Avoid: Haldol, ativan, opiates, nifedipine, alpha-blockers

**Depression**

Studied: TCAs, fluoxetine (FLAME trial), citalopram, escitalopram

Most have benefit on cog/motor behaviors w/o a clear relationship to antidepressive effects. Also trials are sometimes not rigorous in outcomes (positive or adverse).


RCT: fluoxetine, nortriptyline, placebo x12 wks

Short course of antidepressant had strangely late effect

No clear relationship of depressive scores to survival

Nortriptyline contraindicated for cardiac conduction abnormality or MI <3mo

Fluoxetine contraindicated for ICH

(REF: http://ajp.psychiatryonline.org/cgi/content/full/160/10/1823)

Anxiety


Fatigue:


Death/Autopsy


Non-acute evaluation

MRI: Diffusion to confirm stroke (Diffusion bright, ADC dark). Identify hemorrhage, mass lesion, or acute infarct (performance measure)

Follow-up CT: To look for hypodensity c/w w/stroke

Cardiac evaluation

EKG

Holter

TTE w/agitated saline for PFO, R-to-L shunts, thrombi, Left atrium & ventricle sizes, spontaneous echo contrast

If TTE neg & high pre-test probability & findings will change management, consider TEE for arch, septum, thrombi, & valves

May help guide antithrombotic choice, i.e. anticoagulation
Echo: TTE w/bubble or agitated saline: r/o cardioembolic source, paradoxical stroke. If neg but septic emboli still a possibility, consider TEE. 71% healthy volunteers may have R-to-L shunt (PFO 38%, pulm AVM 28%, both 5%). (REF: Chest 2010 Aug; 138:264. http://dx.doi.org/10.1378/chest.09-2797)

TransCranial Dopplers (TCDs)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>HITS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native cardioembolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inf Endocarditis</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>LVaneurysm</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Cardiac thrombus</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Dilated CM</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Valve disease</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td>77</td>
<td>58</td>
</tr>
<tr>
<td>Porcine</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>Homografts</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Carotid Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic stenosis</td>
<td>46</td>
<td>52</td>
</tr>
<tr>
<td>Asymptomatic stenosis</td>
<td>54</td>
<td>7</td>
</tr>
</tbody>
</table>

Other
Syphillis: VDRL, RPR, ELISA
Lumbar puncture for unusual stroke?

Prognosis

Prognosis by Stroke Syndrome
Initial NIHSS vs. 3mo

<table>
<thead>
<tr>
<th>NIHSS</th>
<th>Dead</th>
<th>Poor</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>1%</td>
<td>3%</td>
<td>15%</td>
<td>80%</td>
</tr>
<tr>
<td>4-6</td>
<td>2%</td>
<td>10%</td>
<td>25%</td>
<td>63%</td>
</tr>
<tr>
<td>7-10</td>
<td>4%</td>
<td>18%</td>
<td>32%</td>
<td>46%</td>
</tr>
<tr>
<td>11-15</td>
<td>9%</td>
<td>36%</td>
<td>34%</td>
<td>22%</td>
</tr>
<tr>
<td>16-22</td>
<td>18%</td>
<td>40%</td>
<td>25%</td>
<td>17%</td>
</tr>
<tr>
<td>23</td>
<td>34%</td>
<td>48%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>GOS</td>
<td>&gt;2</td>
<td>1-2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Barthel</td>
<td>&lt;12</td>
<td>12-20</td>
<td>19-20</td>
<td></td>
</tr>
</tbody>
</table>

Excellent: Glasgow Outcome Scale 1 & Barthel Index 19-20; Good: GOS 1-2 & BI 12-20; Poor: all other combos


Early NIHSS vs. poor outcome at 3mo

Poor outcome: mod sev disability (unable walk w/o assist & unable to do own bodily needs w/out assist), sev disability or death (mRS >3)

Pres: NIHSS >17 + AFib = PPV 96%

24h: NIHSS >22 = PPV 98%

7-10d: NIHSS >16 = PPV 92%

<½ had poor outcomes if criteria not met
Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100

A

![Graph showing intercranial hemorrhage (% any type) vs. SPAN-100 negative vs. positive with p=0.062 and p=0.004](image)

B

![Graph showing composite favorable outcome (%) vs. SPAN-100 negative vs. positive with p=0.75](image)

Stroke Prognostic Instrument II (SPI-II)

CHF +3, DM +3, Prior Stroke +3, Age >70 +2, Index Stroke (rather than TIA) +2, HTN +1, CAD +1

<table>
<thead>
<tr>
<th>Pts</th>
<th>Stroke/Death /2y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-3</td>
</tr>
<tr>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Med</td>
<td>4-7</td>
</tr>
<tr>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>High</td>
<td>8-15</td>
</tr>
<tr>
<td></td>
<td>31%</td>
</tr>
</tbody>
</table>


Rates of stroke or death by 1y: 8.2%, 24.5%, and 35.6% (REF: Navi. Validation of the Stroke Prognostic Instrument-II in a large, modern, community-based cohort of ischemic stroke survivors. Stroke. 2011 Dec;42(12):3392-6. PMID: 21960582. http://stroke.ahajournals.org/content/42/12/3392.long)

ASTRAL Score

Post-tPA Prognosis: DRAGON Score

Predicting Hemorrhage After Thrombolysis (HAT) Score
H/o DM or glu>200mg/dL: +1
NIHSS: 20 +2, 16-19 +1
CT MCA hypodense: 1/3 +2, <1/3 +1

HAT associated w/worse 3mo outcome (tPA & placebo)
iScore


Symptomatic ICH after tpa: SEDAN Score


Crossed leg sign

Crossed leg sign <15d indicates a favorable outcome after severe stroke (REF: http://www.neurology.org/content/77/15/1453.full

1y: mRS (2.9 vs 5.1, p < 0.001), BI (71.3 vs 49.2; p = 0.045) better in the crossed leg group

“Anti-orthostatic” response

Significant BP rise on sit/stand: OR for mRS 0-1 @3mo 7.95


Initial DWI vs. 24h DWI vs. 90d FLAIR

Recannalization affects change from initial to 24h DWI

24h DWI & predicts 90d FLAIR


30d mRS -> 90d mRS

<table>
<thead>
<tr>
<th>Progression 30d-&gt;90d</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 pts better</td>
<td>6%</td>
</tr>
<tr>
<td>1 pt better</td>
<td>27%</td>
</tr>
<tr>
<td>Same mRS</td>
<td>53%</td>
</tr>
<tr>
<td>1 pt worse</td>
<td>11%</td>
</tr>
<tr>
<td>2 pts worse</td>
<td>3%</td>
</tr>
</tbody>
</table>

(REF: Neurology 2010;75:688-692)

4yr outcome

78.1% felt not completely recovered

Sig predictors: age & acute disability


Aphasia


Neglect

Investigational: Rotigotine patch post R MCA strokes (dopaminergic agonist) w/domperidone (for peripheral nausea ppx)

Driving

Road Sign Recognition, Compass, & TMT B (REF: http://www.neurology.org/content/76/8/747.abstract)

Race

"Overall in-hospital mortality was lower for black pts than for white pts (5.0% vs 7.4%; P < 0.001), as was all-cause mortality at 30 days (6.1% vs 11.4%; P < 0.001) & 1 year (16.5% vs 24.4%; P < 0.001). ... After adjustment for the probability of dying in the hospital, black pts w/stroke were more likely to receive life-sustaining interventions (OR, 1.22 [CI, 1.09 to 1.38]) but less likely to be discharged to hospice (OR, 0.25 [CI, 0.14 to 0.46])." (REF: http://www.annals.org/content/154/3/152.abstract)

Brain Natriuretic Peptide (BNP)

- BNP: Associated w/cardiac emboli. Death OR 1.75. Good Outcome at 6mo OR 0.64


Rehab

No clear benefit to robot-assisted therapy (REF: http://www.nejm.org/doi/full/10.1056/NEJMoa0911341)


Readmission

Rehosp reason: infection (28%), recurrent stroke (18%), CV (10%) (REF: http://www.neurology.org/content/76/5/438.full)

Palliative Care

Death

Small vessel disease poorer prognosis

Causes: 35% Brain (usually recurrent stroke), Cardiac (40% SVD, 27% nonSVD), Cancer (14%), Infection (5%), Trauma (3%)

(REF: http://www.neurology.org/content/76/8/734.full)

Secondary Prevention


(REF: http://stroke.ahajournals.org/cgi/content/full/39/5/1647)


Performance Measures: At d/c: Statin (if LDL-c >100, not measured, or already on lipid med), Antiplatelet agent, Anticoagulation.

Smoking: Stopping smoking has been observed to decrease stroke risk at 5 years by 50% (REF: JAMA 1995 Jul 12;274(2):155-60).

Alcohol: Heavy drinker -> 0. Men 2/d, Women 1/d. Do not counsel to start drinking

Obesity: independent risk factor, most studied for primary prevention

Physical activity: if possible, 30min (break a sweat) 1-3/wk. If w/disability, supervision on initiation

Compliance

75.5% pts at 3mo cont taking all secondary prevention meds prescribed at d/c

Likelier to take all: fewer med classes, older, PMH, less severe stroke, having insurance, working status, understanding why meds prescribed & how refill, increased quality of life, financial hardship, geographic region, hospital size


High rates may be maintained at 90d if measures initiated at hospital discharge (REF: Stroke. 2004 Dec; 35(12):2879-83. In-hospital initiation of secondary stroke prevention therapies yields high rates of adherence at follow-up. PMID: 15514170. http://stroke.ahajournals.org/content/35/12/2879.long)

Common Ischemic Stroke Mechanisms
Large Artery Atherosclerosis


Extracranial Carotid Stenosis

(REF: http://content.onlinejacc.org/cgi/reprint/j.jacc.2010.11.006v1.pdf)


Carotid Endarterectomy (CEA)

Benefit on ipsilateral strokes for symptomatic carotid stenosis >70% (REF: NASCET, ECST, VA Cooperative Study Program)


<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean f/u</th>
<th>Surgery</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECST</td>
<td>3 y</td>
<td>2.8%</td>
<td>16.8%</td>
</tr>
<tr>
<td>NASCET</td>
<td>2.7 y</td>
<td>9%</td>
<td>26%</td>
</tr>
<tr>
<td>VACS</td>
<td>11.9 mo</td>
<td>7.9%</td>
<td>25.6%</td>
</tr>
</tbody>
</table>

No benefit for <50%


Unclear gender effect or impact of age 80

<table>
<thead>
<tr>
<th>Recurrent stroke</th>
<th>CS+</th>
<th>CS-</th>
</tr>
</thead>
<tbody>
<tr>
<td>3d</td>
<td>5.6% (2/36)</td>
<td>0.4% (1/278)</td>
</tr>
<tr>
<td>7d</td>
<td>5.6% (2/36)</td>
<td>0.7% (2/278)</td>
</tr>
<tr>
<td>14d</td>
<td>8.3% (3/36)</td>
<td>1.8% (5/278)</td>
</tr>
</tbody>
</table>


Carotid Artery Stenting (CAS)

Higher short-term risk of stroke & death w/stenting than CEA.

MI risk may be lower w/stenting than CEA.

Long-term outcomes (>30-120 d) may be similar (REF: CREST. NEJM. 2010 May 27; 362(21))


**CEA vs CAS by Age**

MI risk may be lower w/stenting than CEA.

For any stroke or death within 120d


**EC/IC Bypass**

STA-MCA bypass for symptomatic athero of ICA or MCA

Increased short term M&M, no clear long term benefit

**Carotid Occlusion**


Pts: "AICAO causing hemispheric symptoms <120d & hemodynamic cerebral ischemia by ipsilateral increased O$_2$ extraction fraction by PET"

Intervention: STA-ICA bypass

<table>
<thead>
<tr>
<th></th>
<th>30d</th>
<th>2y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>14.4%</td>
<td>21.0%</td>
</tr>
<tr>
<td>Surgery</td>
<td>14.4%</td>
<td>21.0%</td>
</tr>
<tr>
<td>Med</td>
<td>2.0%</td>
<td>22.7%</td>
</tr>
</tbody>
</table>

**Extracranial Vertebral Stenosis**

May want to consider revascularization procedure in pts who have symptoms despite max med therapy


**Intracranial Atherosclerosis**

High risk of subsequent stroke (~>10%/y) w/o clearly beneficial therapy

Almost 2x risk of hemodynamic symptoms (w/position/orthostatic, effort, or -antiBP med), even higher risk stroke


**Anticoagulation**
“The only subgroup that appeared to fare better with warfarin were the patients with basilar artery stenosis. However, there was no difference in the rates of ischemic stroke in the territory of the symptomatic basilar artery between the treatment groups.” (REF: Kasner. Warfarin vs aspirin for symptomatic intracranial stenosis: subgroup analyses from WASID. Neurology. 2006 Oct 10;67(7):1275-8. PMID: 17030766. http://www.neurology.org/content/67/7/1275.long)

“Patients w/intracranial stenosis who fail antithrombotic therapy are not at higher risk of stroke than those who do not fail antithrombotic therapy. Given our finding that pt ON & OFF antithrombotic therapy are both at high risk for stroke in the territory, intracranial stenting trials should not be limited to just those who fail antithrombotic therapy.” (REF: Stroke. 2009 Feb;40(2):505-9. PMID: 19095991)

BP, stroke, and intracranial arterial stenosis


Stenting


30d stroke or death: Angioplasty + stent 14.7% vs Med 5.8%, 1y 20.0% A+S vs 12.2% Med

Also no benefit over ~2y


Pending: VISSIT Intracranial Stent Study for Ischemic Therapy: focus on balloon mouted stents, hypoperfusion (sten?) vs. artery-to-artery embolus (aggressive antithrombotic?)
Ischemic Preconditioning

May be helpful but in 1 study not ITT analysis, high exclusion after randomization, mild fx, & limited info about stenosis


Cardiac Embolism

20% of ischemic strokes: nonvalvular AF ½, valvular HD ¼, LV mural thrombus 1/3


Atrial Fibrillation (AFib)


Epidemiology

>75K strokes/yr 2/2 AF in US
Etiology

Electrophysiological abnormalities

- Enhanced automaticity (focal AF)
- Conduction abnormality (reentry)

- Atrial pressure elevation

- Mitral or tricuspid valve disease

- Myocardial disease (primary or secondary, leading to systolic or diastolic dysfunction)

- Semilunar valvular abnormalities (causing ventricular hypertrophy)

- Systemic or pulmonary hypertension (pulmonary embolism)

- Intracardiac tumors or thrombi

- Atrial ischemia

- Coronary artery disease

Inflammatory or infiltrative atrial disease

- Pericarditis

- Amyloidosis

- Myocarditis

- Age-induced atrial fibrotic changes

Drugs

- Alcohol

- Caffeine

Endocrine disorders

- Hyperthyroidism

- Pheochromocytoma

Changes in autonomic tone

- Increased parasympathetic activity

- Increased sympathetic activity

Primary or metastatic disease in or adjacent to the atrial wall

Postoperative

- Cardiac, pulmonary, or esophageal

- Congenital heart disease
Neurogenic
Subarachnoid hemorrhage
Nonhemorrhagic, major stroke
Idiopathic (lone AF)
Familial AF

Evaluation

H&P
Presence & nature of symptoms associated w/AF
Clinical type of AF (first episode, paroxysmal, persistent, or permanent)
Onset of the first symptomatic attack or date of discovery of AF
Frequency, duration, precipitating factors, & modes of termination of AF
Response to any pharmacological agents that have been administered
Presence of any underlying heart disease or other reversible conditions (e.g., hyperthyroidism or alcohol consumption)

EKG
Rhythm (verify AF)
LVhypertrophy
P-wave duration & morphology or fibrillatory waves
Preexcitation
Bundle-branch block
Prior MI
Other atrial arrhythmias
To measure & follow the R-R, QRS, & QT intervals in conjunction w/antiarrhythmic drug therapy

TTE
Valvular heart disease
LA & RA size
LVsize & function
Peak RV pressure (pulmonary hypertension)
LVhypertrophy
LA thrombus (low sensitivity)
Pericardial disease
Blood tests: TFT, renal, LFT
For a first episode of AF, when the ventricular rate is difficult to control

Additional testing
Six-minute walk test
If the adequacy of rate control is in question
Exercise testing
If the adequacy of rate control is in question (permanent AF)
To reproduce exercise-induced AF
To exclude ischemia before treatment of selected pts w/a type IC antiarrhythmic drug
Holter monitoring or event recording
If diagnosis of the type of arrhythmia is in question
As a means of evaluating rate control
Transesophageal echocardiography
To identify LA thrombus (in the LA appendage)
To guide cardioversion
Electrophysiological study
To clarify the mechanism of wide-QRS-complex tachycardia
To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
To seek sites for curative ablation or AV conduction block/modification
Chest radiograph, to evaluate
Lung parenchyma, when clinical findings suggest an abnormality
Pulmonary vasculature, when clinical findings suggest an abnormality

Anticoagulation

Warfarin

<table>
<thead>
<tr>
<th>Annual Risk</th>
<th>Placebo</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>4.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>


(REF: 2011 ACCF/AHA/HRS Focused Update on the Management of pt w/Atrial Fibrillation. http://circ.ahajournals.org/cgi/content/full/123/1/104)

(REF: ACC/AHA/ESC 2006 Guidelines for the Management of pt w/Atrial Fibrillation. http://circ.ahajournals.org/cgi/content/full/114/7/e257)


Elderly

<table>
<thead>
<tr>
<th>Annual Risk</th>
<th>Warfarin</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, ICH, systemic embolus</td>
<td>1.8%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Extracranial Hemorrhage</td>
<td>1.4%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>


Falls causing SDH?: Elderly persons who fall have ~1.81 falls/y. Risk of SDH must be 535x to outweigh warfarin benefit ~ 535/1.81 = 296 falls/y. But may develop other injuries (REF: Man-Son-Hing. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999 Apr 12;159(7):677-85. PMID: 10218746. http://archinte.ama-assn.org/cgi/content/full/159/7/677)


Bridging
Heparin to LMWH: Shut off heparin, wait 30-60min (90 if last PTT > 110), then start LMWH
No need for heparin bridge in new onset nonvalvular AFib (REF: Chest 2008; 133:546S).


INRRange

Efficacy ~ significantly for INR<2

No data to indicate increasing INR provides additional protection

Higher INR associated w/increased risk of bleeding, esp INR>4

Warfarin, short term: dissection, venous thrombosis: 3-6 mo, goal INR 2-3, 3-4.5 for prosthetic valves.


Self-monitoring may be safer and more efficacious


Antiplt Therapy

RR `21%


<table>
<thead>
<tr>
<th>ACTIVE-A</th>
<th>ASA</th>
<th>ASA + clop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>3.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.3%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>


Adding clopidogrel to ASA (if can not do warfarin), may be of benefit (trend) if considering relative weight of events (REF: Ann Intern Med. 2011 Nov 1;155(9):579-586. Net Clinical Benefit of Adding Clopidogrel to Aspirin Therapy in pt w/Atrial Fibrillation for Whom Vitamin K Antagonists Are Unsuitable. PMID: 22041946. http://www.annals.org/content/155/9/579.full)

Anticoag + Antiplt
Adding aspirin does not modify stroke risk, increases bleed risk (REF: Lancet 1996 Sep 7;348(9028):633-8)

Retrospective Review (REF: Arch Intern Med 2010 Sep 13; 170:1433)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Bleed rate/pt yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA + clopidogrel + warfarin</td>
<td>15.7%</td>
</tr>
<tr>
<td>Clopidogrel + warfarin</td>
<td>13.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Hazard Ratio vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>0.93</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1.66</td>
</tr>
<tr>
<td>ASA + clopidogrel</td>
<td>1.66</td>
</tr>
<tr>
<td>ASA + warfarin</td>
<td>1.83</td>
</tr>
<tr>
<td>Clopidogrel + warfarin</td>
<td>3.08</td>
</tr>
<tr>
<td>ASA + clopidogrel + warfarin</td>
<td>3.70</td>
</tr>
</tbody>
</table>


Direct Thrombin inhibitors

Dabigatran


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabi 110mg</th>
<th>Dabi 150mg</th>
<th>Warfarin</th>
<th>D110: p vs W</th>
<th>D150: p vs W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke: Hemorrhagic</td>
<td>0.12</td>
<td>0.10</td>
<td>0.38</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke: Ischemic or nos</td>
<td>1.34</td>
<td>0.92</td>
<td>1.20</td>
<td>0.35</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.75</td>
<td>3.64</td>
<td>4.13</td>
<td>0.13</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Approved for higher dose only (REF: http://healthpolicyandreform.nejm.org/?p=14213)


(REF: Ezekowitz. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol. 2007 Nov 1;100(9):1419-26. PMID: 17950801.)


RE-LY Inclusion

AFib +

h/o Stroke, TIA, systemic embolism

EF <40%

HF (NYHA 2)

Age 75

Age 65 + DM, CAD, HTN

Factor Xa inhibitors

Apixaban


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>D150: p vs W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke: Hemorrhagic</td>
<td>0.24</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke: Ischemic or nos</td>
<td>0.97</td>
<td>1.05</td>
<td>0.42</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.52</td>
<td>3.94</td>
<td>0.047</td>
</tr>
</tbody>
</table>
Apixaban vs ASA (AVERROES, NCT00496769)

Rivaroxaban


May be reversible by prothrombin complex concentrate (PCC), unlike direct thrombin inhibitors (dabigatran)


Expected in 2011: Global Study to Assess the Safety & Effectiveness of DU-176b versus Standard Practice of Dosing w/Warfarin in pts w/Atrial Fibrillation (EngageAFTIMI48, NCT00781391), in which 2 doses of edoxaban, 30 mg & 60 mg, each administered once daily, are being compared w/warfarin.

Comparisons


Left atrial appendage (LAA) occlusion

Noninferior to warfarin w/fewer bleeds (90% pts stop warfarin). Increased adverse events (esp pericardial effusion 5%).


Anticoagulation Timing


Risk of early recurrent embolism? 2/123 <7d (REF: TOAST: cardioembolic, placebo) vs. 5% <14d in IST (REF: IST), 5% in CAST (REF: CAST), 8% in HAEST (REF: HAEST). Higher risk of recurrence in previous cardioembolic studies (REF: [http://archneur.ama-assn.org/cgi/reprint/43/1/71])

In selected low-risk pts, early anticoagulation (heparin -> warfarin, <1d-1wk) for cardioembolic/AFib strokes can lead to 1.5% symptomatic hemorrhagic transformation (vs. 10.9% in high-risk pts) (REF: Eur Neurol. 2010;64(4):193-200. Symptomatic hemorrhagic transformation & its predictors in acute ischemic stroke w/atrial fibrillation. PMID: 20714158. [http://web.ebscohost.com/ehost/pdfviewer/pdfviewer?sid=5c89a904-1503-4e01-85b2-1d16a6c38190%40sessionmgr11&vid=2&hid=21])


Early Anticoagulation Trials

CES: early heparin (n=24, 5 large infarcts, avg 32 hr): no recurrent embolism or hemorrhagic infarction on repeat CT ~6.3d; delayed heparin (n=21, 8 large infarcts): 2 asymptomatic hemorrhagic transformation, 2 recurrent emboli, 3 deaths (REF: Stroke. 1983 Sep-Oct;14(5):668-76. Immediate anticoagulation of embolic stroke: a randomized trial. Cerebral Embolism Study Group. PMID: 6362091. [http://stroke.ahajournals.org/content/14/5/668.full.pdf])

TOAST: IV LMWH <24h x7d: increase in serious ICH 2.2% vs. 0.6%; no significant difference in favorable outcomes at 7d & 3mo (REF: JAMA. 1998 Apr 22-29;279(16):1265-72. Low molecular weight heparinoid, ORG 10172 (danaparoid), & outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. PMID: 9565006. [http://jama.ama-assn.org/content/279/16/1265.full])

IST: open trial cross of early heparin x14d (0k, 5k IU bid, or 12.5k IU bid) ± ASA 300mg. Table shows early events (<14d), no effect at 6mo

<table>
<thead>
<tr>
<th></th>
<th>w/AFib</th>
<th>H 12.5k</th>
<th>H 5k</th>
<th>No Heparin</th>
<th>p (H/No H)</th>
<th>ASA</th>
<th>No ASA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>2.3%</td>
<td>3.4%</td>
<td>4.9%</td>
<td>&lt;0.01</td>
<td>3.3%</td>
<td>4.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>2.8%</td>
<td>1.3%</td>
<td>0.4%</td>
<td>&lt;0.001</td>
<td>1.4%</td>
<td>1.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or non-fatal stroke</td>
<td>18.8%</td>
<td>19.4%</td>
<td>20.7%</td>
<td>19.8%</td>
<td>19.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>w/out AFib</th>
<th>Heparin</th>
<th>No Heparin</th>
<th>p</th>
<th>ASA</th>
<th>No ASA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>8159</td>
<td>8105</td>
<td>8097</td>
<td>8167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>2.9%</td>
<td>3.6%</td>
<td>&lt;0.05</td>
<td>2.7%</td>
<td>3.8%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.1%</td>
<td>0.4%</td>
<td>&lt;0.0001</td>
<td>0.8%</td>
<td>0.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or non-fatal stroke</td>
<td>10.3%</td>
<td>10.3%</td>
<td>9.6%</td>
<td>11.0%</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Rhythm control

Typically poorly responsive to antiarrhythmics, which have adverse fx


<table>
<thead>
<tr>
<th></th>
<th>AFFIRM (n=2027)</th>
<th>Rhythm (n=2033)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus at 5y</td>
<td>?</td>
<td>62.6%</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>&gt;85%</td>
<td>~70%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>25.9%</td>
<td>26.7%</td>
<td>0.08</td>
</tr>
<tr>
<td>Torsades</td>
<td>0.2%</td>
<td>0.8%</td>
<td>0.007</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>5.5%</td>
<td>7.1%</td>
<td>0.79</td>
</tr>
<tr>
<td>Cranial Bleed</td>
<td>1.9%</td>
<td>2.1%</td>
<td>ns</td>
</tr>
<tr>
<td>MI</td>
<td>4.9%</td>
<td>6.1%</td>
<td>0.60</td>
</tr>
</tbody>
</table>


(REF: Chest. 2004 Aug;126(2):476-86. Rate control vs rhythm control in pt w/nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. PMID: 15302734. http://chestjournal.chestpubs.org/content/126/2/476.long)


Dronedarone

400mg bid


Amiodarone
Catheter Ablation


Rate control

Prognosis


![Graph showing stroke and mortality rates](http://circ.ahajournals.org/cgi/content/full/114/7/e257)

AFib + Sepsis

<table>
<thead>
<tr>
<th></th>
<th>Sepsis w/AFib</th>
<th>Sepsis w/o AFib</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital stroke</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>56%</td>
<td>39%</td>
</tr>
</tbody>
</table>

(REF: http://jama.ama-assn.org/content/306/20/2248.short)

Initially healthy women w/New-onset AFib

(REF: http://jama.ama-assn.org/content/305/20/2080.full)

<table>
<thead>
<tr>
<th>Event</th>
<th>No incident AF</th>
<th>Incident AF</th>
<th>HR</th>
<th>No pAF</th>
<th>Incident pAF</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>33711</td>
<td>1011 (2.9%)</td>
<td>2.1%</td>
<td>1539</td>
<td>656 (64.9% of AF)</td>
<td>1.5</td>
</tr>
<tr>
<td>Death</td>
<td>2.1% (1539)</td>
<td>10.8% (63)</td>
<td>~2</td>
<td>2.0% (1539/34066)</td>
<td>7.2% (28/656)</td>
<td>~1.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>560/33711</td>
<td>47/1011</td>
<td>4.17</td>
<td>572/34066</td>
<td>23/656</td>
<td>3.09</td>
</tr>
<tr>
<td>CHF</td>
<td>252/33711</td>
<td>83/1011</td>
<td>14.67</td>
<td>258/34066</td>
<td>29/656</td>
<td>4.52</td>
</tr>
<tr>
<td>MI</td>
<td>472/33711</td>
<td>24/1011</td>
<td>3.14</td>
<td>479/34066</td>
<td>15/656</td>
<td>2.81</td>
</tr>
</tbody>
</table>

AFib/Stroke Prediction

Cardiac factors increasing thromboembolic risk: LVdysfunction, left atrial size, mitral annular calcification, spontaneous echo contrast, LA thrombus (REF: Stroke. 2011 Jan 4;42(1):227-76. Guidelines for the prevention of stroke in pt w/stroke or transient ischemic attack. PMID: 20966421. http://stroke.ahajournals.org/content/42/1/227.long)


CHADS2-Vasc: CHF, HTN, Age (65-74 = +1, 75=>2), Stroke/TIA/VTE x2, Vascular Hx, DM, Female (REF: http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk)

<table>
<thead>
<tr>
<th>Risk scheme</th>
<th>Formula</th>
<th>Low risk</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>Event/pt-y</td>
<td>Risk/100 pt years (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS2 (2001)</td>
<td>CHF, HTN, Age75, DM, Stroke/TIA x2</td>
<td>0</td>
<td>1-2</td>
<td>3-6</td>
</tr>
<tr>
<td>CHADS2 Revised</td>
<td>0</td>
<td>1</td>
<td>2-6</td>
<td></td>
</tr>
<tr>
<td>Framingham (2003)</td>
<td>Age 10, F 6, SBP 4, DM 5, Stroke/TIA 6</td>
<td>0-7</td>
<td>8-13</td>
<td>14-31</td>
</tr>
<tr>
<td>NICE guidelines (2006)</td>
<td>Age &lt;65 w/o embolism, HTN, DM, or other risk factors</td>
<td>Age 65 w/o risk factors; age &lt;75 w/HTN, DM, or vascular disease</td>
<td>Prev embolism; age 75 w/HTN, DM, or vascular disease; valve disease or HF; &quot;LVon echo</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA/ESC guidelines (2006)</td>
<td>No risk factors</td>
<td>1 risk factor: age 75, HTN, DM, HF, or &quot;LVfunction</td>
<td>Prev embolism; mitral stenosis; prosthetic valve; 2 or more of: age 75, HTN, DM, HF, or &quot;LVfunction</td>
<td></td>
</tr>
<tr>
<td>ACCP guidelines (2006)</td>
<td>Age 75 w/o risk factors</td>
<td>1 risk factor: age &gt;75, HTN, DM, or &quot;LVfunction ±HF</td>
<td>Prev embolism; 2: age &gt;75, HTN, DM, or &quot;LVfunction ±HF</td>
<td></td>
</tr>
<tr>
<td>Rietbrock modified (2008)</td>
<td>Age 6, female, DM, h/o Stroke/TIA 6</td>
<td>Na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>CHA2DS2-VASc (2009)</td>
<td>CHF, HTN, Age65+, 75 x2, DM, Stroke/TIA/VTE x2, Female, Vasc disease</td>
<td>0</td>
<td>1</td>
<td>2-9</td>
</tr>
</tbody>
</table>


Elderly (age > 75 y)

<table>
<thead>
<tr>
<th>Score</th>
<th>Event/pt-y</th>
<th>Risk/100 pt years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>7/505</td>
<td>1.39 (0.56-2.86)</td>
</tr>
<tr>
<td>2</td>
<td>27/607</td>
<td>4.45 (2.95-6.41)</td>
</tr>
<tr>
<td>3</td>
<td>13/248</td>
<td>5.24 (2.82-8.80)</td>
</tr>
<tr>
<td>4</td>
<td>4/115</td>
<td>3.48 (0.96-8.67)</td>
</tr>
<tr>
<td>5</td>
<td>3/36</td>
<td>8.57 (1.80-23.06)</td>
</tr>
<tr>
<td>6</td>
<td>0/2</td>
<td>0 (0-84.19)</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>6/284</td>
<td>2.11 (0.77-4.60)</td>
</tr>
<tr>
<td>3</td>
<td>10/529</td>
<td>1.89 (0.91-3.48)</td>
</tr>
<tr>
<td>4</td>
<td>24/359</td>
<td>6.69 (4.28-9.95)</td>
</tr>
<tr>
<td>5</td>
<td>8/197</td>
<td>4.06 (1.75-8.01)</td>
</tr>
<tr>
<td>6</td>
<td>6/110</td>
<td>5.45 (2.00-11.87)</td>
</tr>
<tr>
<td>7</td>
<td>0/31</td>
<td>0 (0-11.90)*</td>
</tr>
<tr>
<td>8</td>
<td>0/5</td>
<td>0 (0-73.78)*</td>
</tr>
</tbody>
</table>
Bleeding Scores

Note: CHADS2 also correlates with bleed risk (REF: Risks for Stroke, Bleeding, & Death in pt w/Atrial Fibrillation Receiving Dabigatran or Warfarin in Relation to the CHADS2 Score: A Subgroup Analysis of the RE-LY Trial. Ann Intern Med 2011;155 660-667. http://www.annals.org/cgi/content/abstract/155/10/660)

HAS-BLED: HTN (SBP>160), Abnormal Liver (cirrhosis, bilirubin >2, AST/ALT x3) or Renal (Cr>2.6), Stroke, Bleed, Labile INR (<60% therapeutic), Elderly (Age 65), Drugs/Alcohol (REF: http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk)


ATRIA Risk Score

Anemia (Hgb <13 in M, <12 in F) +3, CKD/GFR<30 +3, Age 75 +2; HTN +1, Prior bleeding +1

<table>
<thead>
<tr>
<th>ATRIA score</th>
<th>Derivation %</th>
<th>Validation %</th>
<th>Combined %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0–3)</td>
<td>131/18,094 0.72</td>
<td>75/9,071 0.83</td>
<td>206/27,166 0.76</td>
</tr>
<tr>
<td>Intermediate (4)</td>
<td>44/1,623 2.71</td>
<td>18/746 2.41</td>
<td>62/2,369 2.62</td>
</tr>
<tr>
<td>High (5–10)</td>
<td>132/2,205 5.99</td>
<td>61/1,147 5.32</td>
<td>193/3,353 5.76</td>
</tr>
</tbody>
</table>


GI Bleed

Warfarin: 3.21 vs. placebo, 1.92 vs. ASA

Warfarin + ASA: 4.72 vs. ASA, 2.66 vs. warfarin

ASA: vs. placebo: 3.23 (p>0.05)

ASA + clopidogrel: 1.93 vs. ASA

Dabigatran: 1.30 vs. warfarin


Artificial Heart Valves

(REF: http://content.onlinejacc.org/cgi/content/full/48/3/e1)

(REF: http://www.americanheart.org/presenter.jhtml?identifier=3004542)


* Risk factors: AFib, prior thromboembolism, LV dysfunction, hypercoag state

Recomendations for Medical Therapy in the Prevention of Systemic Embolization

(REF: http://circ.ahajournals.org/cgi/reprint/114/5/e84)

Class I: There is evidence and/or general agreement that antithrombotic therapy in indicated in pt w/mechanical heart valves in the following settings:
Warfarin for INR 2-3:
1. Aortic valve replacement (AVR) w/bileaflet mechanical or Medtronic Hall valves if no risk factors* are present.

Warfarin for INR 2.5-3.5:
1. AVR w/bileaflet mechanical or Medtronic Hall valves if risk factors* are present.
2. AVR w/Starr-Edwards or disc valves other than Medtronic Hall if no risk factors* are present.
3. Mitral valve replacement (MVR) w/any mechanical valve.

ASA:
1. After AVR or MVR in pt who cannot take warfarin, at a dose of 75 to 325 mg/day.
2. At a dose of 75 to 100 mg/day in addition to warfarin in all pt w/mechanical valves & in pt w/biological valves who have risk factors*.

Class IIa: The weight of evidence or opinion is in favor of the usefulness of antithrombotic therapy in pt w/mechanical heart valves in the following settings:
In the first three months after AVR, warfarin for INR 2.5-3.5

Class IIb: The weight of evidence or opinion is less well established for the usefulness of antithrombotic therapy in pt w/mechanical heart valves in the following setting:
In high-risk pt in whom aspirin cannot be used, clopidogrel (75 mg/day) or warfarin for INR 3.5-4.5

Other recs
Pt w/unexplained stroke/TIA w/bioprosthetic: can consider warfarin for INR 2-3
Pt w/stroke w/mech valve: warfarin for INR 2.5-3.5


Native Valve Disease


Rheumatic Mitral Valve Disease
Rheumatic Mitral Valve + Previous Embolus -> 30-65% recurrent embolism (60-65% <1y, most <6mo)
Mitral valvuloplasty does not seem to eliminate the risk of thromboembolism
Anticoag supported by multiple observational studies (LAA thrombus can disappear)

Mitral Valve Prolapse
Most common form of valve disease in adults
Framingham Heart Study has failed to clearly identify an increased risk of stroke
No randomized trials have addressed the efficacy of antithrombotic therapies for this specific subgroup of stroke or TIA patients.
Mitral Annular Calcification

Sometimes associated with significant mitral regurgitation and is an uncommon nonrheumatic cause of mitral stenosis.

Thrombus has been found at autopsy on heavily calcified annular tissue, and echogenic densities have been identified in the LV outflow tract in patients with MAC who experience cerebral ischemic events.

Spicules of fibrocalcific material may embolize from the calcified mitral annulus.

In a cohort study of American Indians, MAC was found to be a strong risk factor for stroke.

No relevant data comparing the safety and efficacy of anticoagulant therapy versus antiplatelet therapy in patients with TIA or stroke.

Aortic Valve Disease

Clinically detectable systemic embolism in isolated aortic valve disease due to microthrombi or calcific emboli.

In the absence of associated mitral valve disease or AF, systemic embolism in patients with aortic valve disease is uncommon.

No randomized trials of selected patients with stroke and aortic valve disease exist.

Patent Foramen Ovale

R-to-L shunt: PFO or pulmonary AVM

15-25% adults, 2-3% isolated atrial septal aneurysm

<table>
<thead>
<tr>
<th>RR stroke</th>
<th>&lt;55yo</th>
<th>&gt;55yo</th>
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<tbody>
<tr>
<td>PFO</td>
<td>3.10</td>
<td>1.27</td>
</tr>
<tr>
<td>ASA</td>
<td>6.14</td>
<td>3.43</td>
</tr>
<tr>
<td>PFO+ASA</td>
<td>15.59</td>
<td>5.09</td>
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</table>


Stroke + PFO = ASA “reasonable”, insufficient data on anticoagulation or closure.


PFO Closure


Post Myocardial Infarction (MI)

w/o reperfusion therapy: intracardiac thrombus ~1/3 of pts <2wk s/p ant MI (~ w/large infarct of LV apex)

LV thrombus s/p MI -> 10% stroke (~3mo)

Unclear how thrombolysis helps this

Acute inferior & ant MI -> heparin & warfarin ~ stroke 3% -> 1%

Anticoag "thrombus formation by >50%"

If MI -> LV mural thrombus & stroke = anticoag w/warfarin (INR 2-3) 3mo

CardioMyopathy/Heart Failure (HF)
-10% of pt w/ischemic stroke have LVEF 30%

No clear current recommendations for antitp vs. anticoag

Early prospective trials (warfarin, ASA, placebo/clopidogrel): Heart Failure Long-Term Antithrombotic Study (HELAS), Warfarin/Aspirin Study in Heart Failure (WASH)

Warfarin & Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial: warfarin vs. ASA vs. clop: terminated 2/2 low enrollment, but no clear difference w/1587 pts


Anterior MI is an inconsistent risk factor with unclear management


Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial

LVEF 35% w/NSR (w/out AF, mechanical prosthetic heart valve, or other indication for anticoag) (REF: http://clinicaltrials.gov/ct2/show/NCT00041938). INR 2-3.5.

HR for ischemic stroke 0.52 favoring warfarin (1.36 events/100py vs. 0.72), no sig diff in ICH (0.12 vs. 0.05/100py) or death (6.63 vs. 6.52/100py). Possibly has overall effect >3y for primary composite of ischemic stroke, ICH, death. Inc major bleeds w/warfarin (1.78 vs. 0.87/100py)


Perioperative Stroke/Neuro Complications

Coronary Artery Bypass Graft (CABG)


Stroke
Predicting Stroke & Encephalopathy post CABG (REF: http://archneur.ama-assn.org/cgi/reprint/59/9/1422.pdf)


Revised Cardiac Risk Index

High risk surgical procedure? (intraperitoneal, intrathoracic, suprainguinal vascular)

h/o Ischemic Heart disease? (h/o MI, h/o +ETT, angina, nitrates, pathologic Q waves)

h/o CHF (h/o CHF, pulm edema, PND, B rales or S3, CXR showing pulm vascular redistribution)

h/o TIA or stroke

h/preop bx w/insulin

preop Cr>2 mg/dl

Risk ofmajor cardiac event:

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>Risk</th>
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<tbody>
<tr>
<td>0</td>
<td>I</td>
<td>0.4%</td>
</tr>
<tr>
<td>1</td>
<td>II</td>
<td>0.9%</td>
</tr>
<tr>
<td>2</td>
<td>III</td>
<td>6.6%</td>
</tr>
<tr>
<td>3</td>
<td>IV</td>
<td>11%</td>
</tr>
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</table>


Non Cardiac risk calculator


Surgical Moratlity Probability Model (S-MPM): 9pt, 30d

ASA physical status (I/Healthy=0, II/Mild systemic disease=2, III/severe sys dis=4, IV/severe sys dis constant threat to life=5, V/will not survive w/out operation=6)
Emergency status (nonemergent=0, emergent=1)

Surgery risk class (low=0, int=1, high-risk=2)

<table>
<thead>
<tr>
<th>S-MPM</th>
<th>0-4</th>
<th>5-6</th>
<th>7-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.34%</td>
<td>5.27%</td>
<td>7.98%</td>
</tr>
<tr>
<td>Mortality</td>
<td>&lt;0.5%</td>
<td>1.5-4%</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>

Seizures


Neuropsych Decline

Usually w/neuropsych testing

Difficulty of control comparison for prev studies

Usual risk factors (pt & postop)

Most pts have impaired cog pre-surgery (20-46%)

Short-term: “No substantive differences” for CABG vs. non-bypass cardiac interventions. Usually resolve 1-3mo, except subj memory

Long-term: 41% lower at 5y than baseline, but non-randomized
All outcomes


Preventative Measures

If asymptomatic CAS >70%, likely better to do CEA pre or w/CABG rather than delay until later


Preoperative Question Examples

Is any additional neurologic investigation suggested prior to the operation?

Is any additional specific treatment of the neurologic disease needed prior to surgery?

Is any specific postoperative monitoring of the neurologic disease recommended?

Are there any specific recommendations for perioperative administration of neurologic medications?

Is any additional consultation related to the neurologic disease needed before surgery?

Are there any other specific perioperative issues related to the patient’s neurologic disease or its treatment?

Is there a neurologic contraindication to the proposed procedure?

Infective Endocarditis (IE)

(REF: http://circ.ahajournals.org/content/111/23/e394.full)
Presentation

Bacteremia/fungemia, active valvulitis, peripheral emboli, immunologic vascular phenomena

Classic peripheral stigmata may be missing in acute or RH endocarditis

In pts w/neurologic complications of IE, stroke may be the first sign in 47% of cases. Also meningitis 16%, toxic encephalopathy 20%, Headache 13%, ICH 7%, Abscess 2% (REF: Arch Intern Med. 2000 Oct;160(18):2781-7. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. PMID: 11025788. http://archinte.ama-assn.org/cgi/content/full/160/18/2781)

Workup

BCx: 80-90% sens pre antibiotics, ¯35-40% after

Echo: TEE first if prosthetic valves, "possible IE", or complicated IE [paravalvular abscess]; TTE first in other pts. Agreement by echo higher for veg & site (97+%) than characteristics

ESR/CRP: CRP 96% sensitive, ESR 72% in small series (REF: Infection. 1997 Mar-Apr;25(2):82-5. C-reactive protein is more sensitive than erythrocyte sedimentation rate for diagnosis of IE. PMID: 9108181)

U/A&sed: microscopic hematuria

Duke Criteria


Major criteria

BCx+ for IE

Typical microorganism for IE

Viridans streptococci

Streptococcus bovis

HACEK group: Haemophilus spp, Actinobacillus actinomycet comitants, Cardiobacterium hominis, Eikenella spp, & Kingella kingae

Staphylococcus aureus

Community-acquired enterococci, in the absence of a primary focus

BCx for Coxiella burnetii or antiphase 1 IgG titer >1:800

Persistent BCx+ of microorganism consistent w/IE

2 BCx >12h apart

3 BCx

Majority of 4 BCx, 1h apart

Endocardial involvement (Echo + for IE)

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material (no alternative explanation)

Abscess

New partial dehiscence of prosthetic valve

New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria

Predisposition: predisposing heart condition or IVDU

Fever: >38°C (100.4°F)
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway’s lesions

Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, rheumatoid factor

Microbiological evidence: BCx+ but does not meet a major criterion

**Definite IE**

**Pathologic criteria**

Microorganism: demonstrated by culture or histo in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess OR

Pathologic lesions: vegetation or intracardiac abscess, confirmed by histo showing active endocarditis

**Clinical criteria**

2 major criteria OR

1 major & 3 minor criteria OR

5 minor criteria

**Possible IE**

1 major criterion & 1 minor criterion OR

3 minor criteria

**Rejected IE**

Firm alternate diagnosis for manifestations of endocarditis OR

Resolution of manifestations of endocarditis, w/antibiotic therapy 4d OR

No pathologic evidence of IE at surgery or autopsy after antibiotic therapy 4d

Does not meet criteria for possible IE, as above

**Noninfectious endocarditis**

Sterile valvular vegetations form & embolize

Mitrval valve most often affected

Valvular regurgitation predominant functional abnormality

Antiphospholipid syndrome: autoimmune disorders, SLE,

Neoplasia: atrial myxoma, marantic endocarditis, neoplastic disease, carcinoid

Autoimmune: rheumatic carditis, systemic lupus erythematosus, polyarteritis nodosa, Behçet’s disease

Postvalvular surgery: thrombus, stitch, or other postsurgery changes

Misc: eosinophilic heart disease, ruptured mitral chordae, myxomatous degeneration

**Physical Exam**

**Splinter Hemorrhages**

Splinter hemorrhages, linear reddish-brown lesions, are seen in the nail bed of this patient w/bacterial endocarditis due to group B streptococcus.
Janeway Lesions

“A Janeway lesion (arrow) occurred on the palm in this patient with bacterial endocarditis due to Streptococcus bovis. These lesions are macular, blanching, nonpainful, and are located on the palms and soles.”

Osler’s Nodes

“Osler’s nodes are tender papulopustules located on the pulp of the finger in a patient with bacterial endocarditis caused by Staphylococcus aureus.”

Roth Spots

Exudative, edematous hemorrhagic lesions of the retina

IE Emboli
Systemic embolization 22-50%, up to 65% of events CNS, >90% in MCA

Timing: most <2-4 wks of antibio (13 -> <1.2/1000 pt-days), 2nd peak 15-30wk (nonhealin veg)

Organisms: Staph aureus (esp aggressive ischemic & hemorrhagic; esp w/prosthetic valves), Candida, HACEK, Abiotrophia

Risks: mitral veg 25%, aortic 10%, -veg size, large veg (>1cm diameter) on anterior mitral leaflet

Surgery: specific to pt, benefit greatest early when embolic rates highest & predictors of complicated course present (ie, recurrent embolization; CHF; aggressive, antibiotic-resistant organisms; or prosthetic valve IE)

**Mycotic Aneurysms**

Pathophys: Septic embolization to arterial vasa vasorum or intraluminal space -> through intima & vessel wall. Likelier at impacting branching points (esp distal MCA bifurcations). Intracranial > visceral > limbs

Epi: 1.2-5% of cases, possibly underestimated (~50% strep, ~10% staph aureus), 20% multiple

Significance: Intracranial Mycotic Aneurysms (ICMA): 20-40% neuro complications, mortality 60% (30% unruptured, up to 80% ruptured, >50% if proximal, similar if multiple)

Presentation: nonspecific, mass lesion, embolic events, leak -> mild meningeal irritation, sudden SAH/IPH

Screening: not warranted in absence of signs/symptoms, indicated w/HA, abnl LP, focal signs/symps

Imaging: MRA/CTA 90-95% sens & spec, but “for 5mm aneurysms: possible for screen or f/u. If high suspicion: conventional cerebral angio (classically most sens)

Prognosis: 52% resolve, 29% ~ size, 19% - size, 10% new

Management: single distal IMCA -> frequent imaging, treat by excision/endo if enlarges/bleeds. Multiple/proximal: monitor closely, less amenable to excision

CV Surgery: address more severe problem, consider bioprosthetic valve to minimize anticoag, ideally delay CV surg 2wk after CNS event (stroke, bleed, repair)

**Treatment/Antibiotics**

2 sets of BCx q24-48h until neg

Start counting from 1st day after tx that BCx neg

Give agents at the same time for synergy

Postop course/choice depends on prosthetic valve


**Anticoagulation**

Controversial, particularly in mechanical valve endocarditis (generally consider discontinuing w/Staph aureus + embolus). No clear benefit for native valve (REF: Stroke. 2011 Jun;42(6):1797-8. Anticoagulation should not be used in most pt w/stroke w/infective endocarditis. PMID: 21546485. [http://stroke.ahajournals.org/content/42/6/1797.full](http://stroke.ahajournals.org/content/42/6/1797.full))

Trend towards more bleeding even w/ASA (routine use not recommended) (REF: J Am Coll Cardiol. 2003 Sep 3;42(5):775-80. A randomized trial of aspirin on the risk of embolic events in pt w/infective endocarditis. PMID: 12957419. [http://content.onlinejacc.org/cgi/content/full/42/5/775](http://content.onlinejacc.org/cgi/content/full/42/5/775))

Many bleeds may be caused by hemorrhagic transformation of infarcts rather than mycotic aneurysms

**Surgery**

For large vegetations, severe valvular insufficiency, abscess cavities or pseudoaneurysms, valvular perforation or dehiscence, decompensated heart failure

Individualized input w/cardiologist & surgeon

Higher op mortality w/CHF, but pt w/IE + CHF -> surgery = mortality < medical therapy (as high as 51% mortality) vs. 2-3% reinfection
Consider surgical intervention for fungal IE, infection with aggressive antibiotic-resistant bacteria or bacteria that respond poorly to antibiotics, left-sided IE caused by Gram-negative bacteria such as S marcescens & Pseudomonas species, persistent infection with positive blood cultures after 1 week of antibiotic therapy, or 1 or more embolic events during the first 2 wk of antimicrobial therapy.

Benefit of surgery is greatest in the early phase of IE, when embolic rates are highest & other predictors of a complicated course (eg, recurrent embolization & prosthetic valve endocarditis) are present (REF: Association Between Valvular Surgery & Mortality Among pt w/Infective Endocarditis Complicated by Heart Failure. http://jama.ama-assn.org/content/306/20/2239.full)


**Followup**

Echo near end of tx

Med fx: vestibular, auditory, & nephrotoxicity from aminoglycosides, leukopenia & thrombocytopenia from -lactams & vancomycin, & nephrotoxicity from vancomycin & gentamicin

IVDA program

S. bovis: colonoscopy for malignancy or mucosal lesions

Perivalvular extension/abscess: ECG (new AV block: PPV 88%, 45% sens), TTE detection 18-63%, TEE sens 76-100%, 95% spec

Spleenic abscess: Persistent or recurrent bacteremia, fever, or sepsis -> abd CT/MRI (spec & sens 90-95)

Dental eval

Reinfection

CHF = greatest impact on prognosis, esp acute aortic regurgitation

Diarrhea/C.diff

**REFs**


**Arterial Dissection**

Definition

Tear between arterial intima & media in a high pressure system

Separation of layers of arterial wall

Leads to artery-to-artery embolism or stenosis->occlusion of affected vessel

May be cervical/extracranial or extend intracranial/intradural

May form pseudoaneurysms causing thrombi or SAH (intracranial vertebrobasilar)

Epidemiology


10-25% of stroke in young/middle age

Carotid: 2.5-3/100k, Women ~40y? or Older Men?

Vertebral: 1-1.5/100k, no clear sex difference

More common in Sep-Nov

Pathophysiology

Intimal tear -> Intramural hematoma -> stenosis or dilation
Extracranial-Intracranial: Mobility? Vulnerability?

Dissection -> stroke 2/2 thromboembolism > hemodynamic compromise

Spontaneous: 50%

Trauma: whiplash, coughing, direct strike (need not be severe)

Intracranial: possibly less 2/2 trauma, more 2/2 cocaine

Abnormality or neural crest cells?


Connective tissue disorders: fibromuscular dysplasia (FMD), Ehlers-Danlos (type IV), Marfan syndrome, osteogenesis imperfecta, autosomal dominant polycystic kidney disease, alpha-1-antitrypsin deficiency (REF: www.genereviews.org)

Pseudoaneurysm: leakage outside the arterial wall, contained by surrounding tissues (aka dissection hematoma)


Other vessels: intracranial aneurysms, widened aortic root, arterial redundancies (e.g., coils, kinks, and loops), increased arterial distensibility. Renal, cutaneous lentigines, congenitally bicuspid aortic valve

(REF: Netter's Pediatrics)

Clinical manifestations

May have warning attacks, signs may fluctuate x min-h, be gradual or thunderclap

Starts ~2-3 cm distal to bulb, usually not past petrous temporal bone. Tapers early, dilates distally


Headache (60-95%; unilat, frontotemp), neck pain (~25%): nonthrobbing, usually around eye, sometimes more local. May experience rapid & marked relief after steroids

Median to other symptoms ~4d

Unilateral Horner's (<50%): Decreased pupil size (miosis), drooping upper eyelid (ptosis), ±decreased sweating (due to sympathetic plexus around ECA?)

Cranial nerve palsies (12%): hypoglossal most common

Pulsatile tinnitus (25%)

Less common: cervical bruit, transient vision loss, facial numbness

Ischemia (50-95% prior to more imaging): TIAs over internal carotid distribution -> hemispheric stroke (20% have stroke w/out warning signs)

Vertebral

~80% Extracranial, ~10% Extra->Intracranial, ~10% Intracranial

Start: Prevertebral/V1 20%, pars transversaria/V2 35%, atlas loop/V3 34%, intracranial/V4 11%

Stenosis & aneurysms C1-C2

Headache (70%): occipital. Median to other symptoms ~1 wk

Neck pain (50%): on same side as dissection. Median to other symptoms ~2 wk

Ischemic symptoms (>90%, preimaging): Mostly stroke, TIA less frequent.

Vertigo (lateral medullary syndrome)

Dizziness, vertigo, veering to one side, imbalance (cerebellum)

Diplopia & dysarthria (pons, midbrain)

Central cervical spinal cord infarct (ant spinal art)

Hemianopia (embolus to PCA)

**Intracranial**

Fluctuating symptoms w/unilateral cranial pain

MCA: retro-orbital

Basilar: occipital

Vertebral: occipital + supraorbital

**Multiple**


**Aortic**

Nutshell: sudden/severe pain, CXR w/wide aorta/mediastinum, pulse/BP diffs. More varied neuro findings

Severe pain (sens 90%), sudden onset (sens 84%); absence LR- 0.3
Exam: HTN 49%, diastolic murmur 28%, pulse deficits/BP diff 31% (LR+ 5.7), focal neuro 17% (LR+ >6.6)

CXR: sens 90%, LR- 0.3

(REF: RCE: Does This Patient Have an Acute Thoracic Aortic Dissection?)

**Workup**


MRI/A: ischemia/dissection (stenosis, double lumen), w/T1 fat saturation protocol

Head CT: r/o bleed, aneurysm

CTA: from aortic arch to Circle of Willis

Ultrasound: may help detect

Conventional angio for intracranial dissection

**Treatment**

Usual tx anticoag: heparin -> warfarin x3-6 mo, then if resolving by imaging, lifelong antiplt


If recurrent ischemic events: consider continuing anticoag

If continued recurrent stroke on anticoag: consider endovascular reopening/stent (intracranial may have higher bleeding risk)

If not endovascular candidate: consider surgery (10-12% stroke/death)

If intradural: No anticoagulation, just aspirin/antiplt (decreased vessel thickness, increased bleeding risk & severity)

Consider steroids for pain

**Prognosis**

**Death <5%**


Stenosis: 90% resolve. Occlusion: 2/3 recannalize. Aneurysms: 1/3 decrease. Change <2-3mo, rarely >6mo

**Relative to Stroke**


Stroke at presentation: ¼ die, ½ seriously impaired vs. other study ~¾ good functional recovery?!


**Recurrent Dissection**

Usually in another artery: 2% x1mo -> 1%/yr. Usually greater chance recurrence in another artery, higher rate w/family history.


Aneurysms
Extracranial aneurysms usually do not rupture.
Pseudoaneurysms usually do not need repair.

Reversible Cerebral Vasoconstriction Syndrome (RCVS)


Transient Ischemic Attack (TIA)

Definition
A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, w/o acute infarction.

Now defined by lack of neuroimaging findings, rather than duration (previously <24h).

(REF: Stroke. 2009;40:2276)

Other brain factors such as leukoaraiosis may help determine the clinical duration of an event (REF: Arsva. Severity of leukoaraiosis determines clinical phenotype after brain infarction. Neurology. 2011 Jul 5;77(1):55-61. PMID: 21700580. http://www.neurology.org/content/77/1/55.abstract)

Epidemiology
USincidence 200,000-500,00/y, prevalence 2.3% (REF: Stroke. 2009;40:2276)

Risk factors same as stroke (eg: age, men, ATAm>Hispanic>White)

Pathophysiology
Large Artery, low-flow TIA
Associated w/stenotic lesions, often at vessel bifurcation (ICAsiphon)
Usually short-lived (min), stereotyped, occur up to several times / day
Posterior circulation does not often involve recurrent symptoms

Cardioembolic TIA
PFO, Left atrial clot, Aortic arch atheroma, Valve disease, Atrial septal aneurysm/defect
Caused by emboli from a discrete source – i.e., thrombus, plaque. May produce emboli, resulting in ischemia.
Typically last hr, Symptoms vary according to area. Can be large or small.

Lacunar / small vessel TIA
Stenosis of small perforating vessels off MCA / basilar. Brief, stereotyped clinical symptoms & signs, suggests liphyalinosis

Presentation
Transient brain, retinal, or spinal cord ischemia

"60% of events were <1 hr; 71% were <2 hr, only 14% were >6 hr." (REF: Stroke. 2007; 38: 463)

Transient Monocular Blindness (amaurosis fugax)

Evolves swiftly: 5-30 sec

Horizontal shade falling (or rising) smoothly over visual field until eye completely but painlessly blind

Clears slowly and uniformly

Sometimes wedge shape loss, sudden gen blur, or, rarely, a gray or bright light

Usually more stereotyped than hemispheric TIA

(REF: Adams & Victor, 8th ed)


NASCET: If Hemisphere Symptoms: 6:1, Retinal symptoms: 1:4

NASCET: By Contralateral events: Original Hemispheric: 4:1, Original Retinal: 1:1


ABCD2 score predicts risk of stroke

Age 60 = +1

BP 140/90 = +1

Clinical TIA: Focal weak = +2, Speech impair = +1

Duration: 60 min = +2, 10-59 = +1

DM = +1

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<th>Risk of ischemic stroke</th>
<th>2 d</th>
<th>90 d</th>
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</thead>
<tbody>
<tr>
<td>ABCD2 6</td>
<td>8%</td>
<td>18%</td>
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<tr>
<td>ABCD2 = 4-5</td>
<td>4%</td>
<td>10%</td>
</tr>
<tr>
<td>ABCD2 = 2-3</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>ABCD2 = 0-1</td>
<td>0%</td>
<td></td>
</tr>
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</table>

(REF: Lancet. 2007 Jan 27;369(9558):283-92; http://dx.doi.org/10.1016/S0140-6736(07)60150-0)

TIA factors that predict DWI+

Motor symptoms, not history, aphasia, or clinical scores

(REF: http://stroke.ahajournals.org/cgi/content/full/40/6/2229)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal DWI (n=68)</th>
<th>Positive DWI (n=67)</th>
<th>All Cases (n=135)</th>
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<tr>
<td>Risk factors</td>
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<td></td>
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<tr>
<td>Age, y±SD</td>
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<td>69.8±10.7</td>
<td>68.7±11.5</td>
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<td>42 (61.8)</td>
<td>39 (58.2)</td>
<td>81 (60.0)</td>
<td>0.673</td>
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<tr>
<td>Hypertension</td>
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<td>46 (68.7)</td>
<td>90 (66.7)</td>
<td>0.626</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>16 (23.5)</td>
<td>16 (23.9)</td>
<td>32 (23.7)</td>
<td>0.962</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (25.0)</td>
<td>17 (25.4)</td>
<td>34 (25.2)</td>
<td>0.960</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>6 (8.8)</td>
<td>10 (14.9)</td>
<td>16 (11.9)</td>
<td>0.273</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (17.6)</td>
<td>10 (14.9)</td>
<td>22 (16.3)</td>
<td>0.669</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>2 (2.9)</td>
<td>3 (4.5)</td>
<td>5 (3.7)</td>
<td>0.680</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>23 (33.8)</td>
<td>25 (37.3)</td>
<td>48 (35.6)</td>
<td>0.672</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (8.8)</td>
<td>8 (11.9)</td>
<td>14 (10.4)</td>
<td>0.553</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster TIA</td>
<td>13 (19.1)</td>
<td>24 (35.8)</td>
<td>37 (27.4)</td>
<td>0.030</td>
</tr>
<tr>
<td>Aphasia</td>
<td>24 (35.3)</td>
<td>12 (17.9)</td>
<td>36 (26.7)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>16 (26.5)</td>
<td>32 (47.8)</td>
<td>50 (37.0)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>DWI -</td>
<td>DWI +</td>
<td>Sn</td>
<td>Sp</td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>ABCD2 0-3</td>
<td>0/178</td>
<td>2/30</td>
<td>100%</td>
<td>85.6%</td>
</tr>
<tr>
<td>ABCD2 4-7</td>
<td>3/495</td>
<td>36/200</td>
<td>92.3%</td>
<td>71.2%</td>
</tr>
</tbody>
</table>

**MRI/DWI <24h helps predict 90d risk of disabling stroke**

(REF: [http://stroke.ahajournals.org/cgi/content/full/40/10/3252](http://stroke.ahajournals.org/cgi/content/full/40/10/3252))


(REF: [http://cip.martinos.org/cip.php](http://cip.martinos.org/cip.php)) (REF: [http://stroke.ahajournals.org/cgi/content/full/40/1/181](http://stroke.ahajournals.org/cgi/content/full/40/1/181))
CT defined stroke is not as sensitive as MRI (intermediate to above curves?)


Negative DWI predicts recurrent transient symptoms, but not stroke

Pt can still have poor functional prognosis
Differential

Stroke (Ischemic or Hemorrhagic), seizure, syncope, complex migraine, conversion

Mass lesions on CT in 5% of cases (REF: South Med J. 1986; 79: 804–807)

Workup


AHA recommends admission for pts w/ABCD2  3 or uncertainty that workup can be completed w/in 2 days or evidence indicating event was caused by focal ischemia (REF: Stroke. 2009;40:2276)

Consider also admitting pt w/ worsening symptoms, sx > 1 hr, stenosis, known AFib / hypercoag state

For low risk pts, unclear whether workup should be as in or outpt (rapid clinic <3d) (REF: Stroke. 2011 Jul;42(7):1839-43. 2 ACES: Transient Ischemic Attack Work-Up as Outpatient Assessment of Clinical Evaluation & Safety. PMID: 21617143. http://stroke.ahajournals.org/content/42/7/1839.full)

Workup similar to stroke: Neuroimaging (ideally MRI w/DWI <24h, Vascular imaging, Cardiac: EKG/Holter /Echo, Labs)

15% of pts may have no DWI restriction but perfusion deficits (REF: Kleinman. Automated Perfusion Imaging for the Evaluation of Transient Ischemic Attack. Stroke. 2012 Apr 3. PMID: 22474058. http://stroke.ahajournals.org/content/43/6/1556.abstract)

Management

Management similar to secondary stroke prevention (above).

Aspirin, or if on aspirin consider increase vs other antiplt agent. (performance measure for noncardioembolic stroke)

Anticoagulation if atrial fibrillation (performance measure)

Statin therapy

BP control

Neurovascular evaluation

Major Risk Factors/Comorbidities

Hypertension (HTN)

Screen 18yo (REF: http://www.annals.org/content/147/11/783; http://www.annals.org/content/147/11/787)

Stroke risk

SBP 120-129 or DBP 80-84: RR 1.22 (0.95-1.57)

SBP 130-139 or DBP 85-89: RR 1.79 (1.49-2.16)
Age specific relevance of BP to stroke:

![Graph showing systolic and diastolic blood pressure against stroke mortality](image)

### Classification

<table>
<thead>
<tr>
<th>BP Class</th>
<th>SBP</th>
<th>DBP</th>
<th>Initial Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
<td>w/ compelling indications</td>
</tr>
<tr>
<td>PreHTN</td>
<td>120-139</td>
<td>80-89</td>
<td>w/ compelling indications</td>
</tr>
<tr>
<td>HTN St1</td>
<td>140-159</td>
<td>90-99</td>
<td>Thiazide, consider ACEi, ARB, BB, CCB</td>
</tr>
<tr>
<td>HTN St2</td>
<td>160</td>
<td>100</td>
<td>Thiazide + ACEi, ARB, BB, CCB</td>
</tr>
</tbody>
</table>


### Primary Prevention


### Secondary Prevention

HTN: Goal SBP 120-139, "BP 6 mmHg "stroke risk 40% (REF: Lancet 1990 Apr 7;335(8693):827-38)

Benefit appears independent of a previous formal HTN diagnosis


Treatment by patient type

Elderly Pts


First-line: low-dose thiazides & long-acting Ca channel blockers (dihydropyridines)
Also first-line: ACEi or ARBs
Consider: sustained release isosorbide dinitrate (SBP > DBP)
Defer beta-blockers: may be worse for stroke prevention (esp smokers)
Avoid orthostatic hypoBP

Age

Younger: ACEi or ARB > beta-blocker > all others

Race

Black: thiazide or CCB

Sex

Women similar to men
(REF: http://www.uptodate.com/contents/essential-hypertension-in-women?source=search_result&selectedTitle=1~150)

DM

Thiazides, ACEi/ARB, CCB less clear, BB may mask hypoglycemia.
ACEi + CCB may be better than ACEi + HCTZ

Acute management post-stroke

“Auto-regulate” x24-48h
JNC7 report: maintain BP at intermediate levels (~160/100) until neurologically stable

After 1 wk or when neurologically stable, can initiate more aggressive tx for secondary prevention

Special circumstances: - ICP, edema, ongoing ischemia, vasospasm, postop, B carotid stenosis

Home BP meds: case-by-case adjustment to avoid hypoBP, rebound/excess HTN, MI


Stenosis, BP and stroke risk

Most dangerous for bilateral carotid stenosis


Drugs


Beta blockers
Metoprolol vs Labetalol


Conversion

Metoprolol

Esmolol

Labetalol

Atenolol

Carvedilol

Propranolol

Dose, onset, duration, metabolites

The following doses are equivalent to carvedilol 12.5mg BID

- acebutolol 100mg BID, metoprolol 50mg BID, propranolol 40mg BID
- atenolol 50mg daily, metoprolol SR 100mg daily, propranolol LA 80mg daily
- bisoprolol 5mg daily, nadolol 80mg daily, sotalol 80mg BID
- labetolol 100mg BID, pindolol 5mg BID, timolol 5mg BID

(REF: http://www.bcguidelines.ca/pdf/heart_failure_appendix_b.pdf)

ACE Inhibitors

Conversion

<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>ACE Ratio</th>
<th>10mg of quin/lisin =</th>
</tr>
</thead>
<tbody>
<tr>
<td>ramipril: quinapril</td>
<td>1:4</td>
<td>2.5 mg ramipril</td>
</tr>
<tr>
<td>captopril: quinapril</td>
<td>5:1</td>
<td>50 mg captopril</td>
</tr>
<tr>
<td>benazepril: quinapril</td>
<td>1:1</td>
<td>10 mg benazepril</td>
</tr>
<tr>
<td>fosinopril: quinapril</td>
<td>1:1</td>
<td>10 mg fosinopril</td>
</tr>
<tr>
<td>moexipril: quinapril</td>
<td>1:1.5</td>
<td>7.5 mg moexipril</td>
</tr>
<tr>
<td>enalapril: quinapril</td>
<td>1:2</td>
<td>5 mg enalapril</td>
</tr>
<tr>
<td>lisinopril: quinapril</td>
<td>1:1</td>
<td>10 mg lisinopril</td>
</tr>
</tbody>
</table>


Dyslipidemia

Epidemiology and stroke risk


Epi results may be due to lumping ICH & various ischemic stroke (REF: http://www.neurology.org/content/63/10/1868.long)

Some suggestions that lower cholesterol is associated w/lower ischemic stroke risk but higher ICH (REF: http://www.nejm.org/doi/full/10.1056/NEJM198904063201405)

Benefit may be greatest in atherosclerotic strokes (large artery athero & lacunar)
Low HDL & high LDL increase carotid atherosclerosis; controlling with statin decreased carotid wall thickening (REF: Circulation 1998 May 12;97(18):1784-90)

Therapeutic effects may be driven most by statins or rather by overall lipid lowering (REF: http://archinte.ama-assn.org/cgi/content/full/163/6/669)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes</td>
<td>0.79</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fatal strokes</td>
<td>0.94</td>
<td>0.37</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.90</td>
<td>ns</td>
</tr>
</tbody>
</table>

(REF: http://stroke.ahajournals.org/cgi/content/full/35/12/2902)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin</th>
<th>Control</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed ischemic strokes</td>
<td>2.8%</td>
<td>3.4%</td>
<td>0.81</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2%</td>
<td>0.2%</td>
<td>1.05</td>
<td>ns</td>
</tr>
</tbody>
</table>


Prior use of statins

(REF: http://stroke.ahajournals.org/cgi/content/full/40/7/2581)

(REF: http://www.neurology.org/content/76/18/1581.long)

**Primary Prevention**

"It may be most appropriate to view lipid lowering therapy with statins as an intervention that can reduce relative cardiovascular risk by ~20 to 30% regardless of baseline LDL-C… The absolute benefit of treatment will be proportional to the underlying absolute risk… We suggest treatment with a moderate dose of a statin (eg, 40 mg of lovastatin, pravastatin, or simvastatin, or 20 mg of atorvastatin)" (REF: http://www.uptodate.com/online/content/topic.do?topicKey=lipiddis/11971)

"Statins Have No Benefit on All-Cause Mortality in High-Risk Primary Prevention" (REF: http://archinte.ama-assn.org/cgi/content/abstract/170/12/1024)

ATP III Guidelines: (REF: Circulation 2002; 106:3143; http://circ.ahajournals.org/cgi/reprint/106/25/3143): Primary CHD risk is low when LDL <130

**Pts w/0-1 risk factors (goal LDL <160):**

<table>
<thead>
<tr>
<th>LDL levels</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL 130</td>
<td>Lifestyle mods</td>
</tr>
<tr>
<td>LDL 160-189</td>
<td>Drugs optional when LDL 160-189 but consider w/&gt;standard risk factor</td>
</tr>
<tr>
<td>LDL 190</td>
<td>Strongly consider drugs</td>
</tr>
</tbody>
</table>

**Pts w/2 risk factors: Lifestyle mods for all**

<table>
<thead>
<tr>
<th>10yr Hard CHD risk:</th>
<th>&lt;10% (&lt;1%/yr)</th>
<th>10-20%</th>
<th>&gt;20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL 160</td>
<td>Drug</td>
<td>Drug</td>
<td>Drug</td>
</tr>
<tr>
<td>LDL 130</td>
<td>Lifestyle</td>
<td>Lifestyle -&gt; Drug</td>
<td>Drug</td>
</tr>
<tr>
<td>LDL 100</td>
<td>Lifestyle</td>
<td>Lifestyle -&gt; Drug</td>
<td></td>
</tr>
</tbody>
</table>

**Proposed modifications of ATP III by the National Cholesterol Education Program (NCEP)**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>LDL goal (mg/dL)</th>
<th>LDL for lifestyle mod</th>
<th>LDL to consider drugs (goal 30-40% decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD, PAD, AAA, CVD, DM 10 yr risk &gt;20%</td>
<td>&lt;100, optional &lt;70 in very high risk</td>
<td>100</td>
<td>100 (fibrate for hypertrig or nicotinic acid for HDL&lt;40 mg), &lt;100 consider drugs</td>
</tr>
<tr>
<td>Moderately high risk: 2 risk factors 10 yr risk = 10-20%</td>
<td>&lt;130, optional &lt;100</td>
<td>130</td>
<td>130, 100 consider drugs</td>
</tr>
<tr>
<td>Moderate risk: 2 risk factors 10 yr risk &lt;10%</td>
<td>&lt;130</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor 10 yr risk &lt;10%</td>
<td>&lt;160</td>
<td>160</td>
<td>190, 160 consider drugs</td>
</tr>
</tbody>
</table>

Risk factors: age (M45, F55), smoking, BP 140/90, CHD first degree relative (M<55, F<65), HDL<40. If HDL60, -1 risk factor

Risk calculators

Framingham Risk Score for men (REF: http://www.uptodate.com/online/content/topic.do?topicKey=cardcalc/6141); for women (REF: http://www.uptodate.com/online/content/topic.do?topicKey=cardcalc/5718)

UKNICE (National Institute for Health & Clinical Excellence): pts w/10y risk of CVD 20% should be treated w/statins: UK Primary Cardiovascular Risk Calculator (REF: http://www.patient.co.uk/showdoc/40000133/)

**Secondary Prevention**

“Persons w/established CHD should receive intensive LDL-lowering therapy. The goal of therapy in persons w/established CHD should be LDL cholesterol <100 mg/dL.” (REF: Circulation 2002; 106:3143; http://circ.ahajournals.org/cgi/reprint/106/25/3143)

**SPARCL**


Secondary prevention s/p stroke/TIA w/o known CHD

Dx: Ischemic stroke or TIA (<24h) or (Hemorrhagic stroke & “at risk for ischemic stroke or CHD”).

Pts: Ambulatory, LDL 100-(160:190)
Exclusion: AFib, Cardioembolism, SAH

Time: 1-6 months after event to start med

Meds: Atorvastatin 80mg (n=2365) vs Placebo (n=2366)

Primary outcome: Stroke (nonfatal or fatal)

Could use open label statins (25.4% placebo, 11.4% atorvastatin)

NNT over 5 years to prevent 1 stroke: 46, Major CV event: 29

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atorvastatin</th>
<th>Placebo</th>
<th>Unadjust p</th>
<th>Adjust HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal stroke</td>
<td>11.2</td>
<td>13.1</td>
<td>0.14</td>
<td>0.84</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>1</td>
<td>1.7</td>
<td>0.04</td>
<td>0.57</td>
</tr>
<tr>
<td>TIA</td>
<td>6.5</td>
<td>8.8</td>
<td>0.04</td>
<td>0.74</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>1.7</td>
<td>1.6</td>
<td>0.90</td>
<td>1.00</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.8</td>
<td>3.5</td>
<td>0.001</td>
<td>0.51</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>9.2</td>
<td>11.6</td>
<td>&lt;0.05</td>
<td>0.78</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>2.3</td>
<td>1.4</td>
<td>&lt;0.05</td>
<td>1.66</td>
</tr>
<tr>
<td>Death</td>
<td>9.1</td>
<td>8.9</td>
<td>0.77</td>
<td>1.00</td>
</tr>
<tr>
<td>LDL</td>
<td>61.3</td>
<td>133.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>52.1</td>
<td>51.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>111.5</td>
<td>145.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFTs &gt;3xULN x2</td>
<td>2.2</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td>0.1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heart Protection Study (HPS)


Dx: Nondisabling ischemic stroke 63%, TIA 46%, CEA or carotid angio 10%

Pts w/cerebrovascular dz (n=3280), or other vascular disease (CAD, PAD, DM, HTN; n=17256)

Exclusion: Not hemorrhagic stroke, no CV event <6mo + etc

Enrolled at ~4.3y after stroke/TIA

F/u: ~5y

Meds: simvastatin 40mg vs placebo (+antioxidant vitamins)

LDL 131 -> -39 mg/dL

Data on stroke prevention for pts w/h/o cerebrovascular disease was weaker than cardiovascular disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke: Severe/fatal</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>3.4</td>
<td>3.5</td>
<td>ns</td>
</tr>
</tbody>
</table>
Lifestyle modifications

LDL-lowering diet, weight reduction, & increased physical activity

Medical therapy

Just because a med changes a cholesterol number does not mean it changes outcomes (several examples, including ACCORD lipids). (REF: The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010 Mar 14; [e-pub ahead of print]. [http://dx.doi.org/10.1056/NEJMoa1001282])

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Serum LDL cholesterol</th>
<th>Serum HDL cholesterol</th>
<th>Serum triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td>15 to 30%</td>
<td>0 to slight increase</td>
<td>No change*</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>10 to 25%</td>
<td>15 to 35%</td>
<td>25 to 30 percent</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>20 to 60%</td>
<td>5 to 10%</td>
<td>10 to 33 percent</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>10 to 15%</td>
<td>15 to 25%</td>
<td>35 to 50 percent</td>
</tr>
<tr>
<td>Fenofibrate (micronized form)</td>
<td>6 to 20%</td>
<td>18 to 33%</td>
<td>41 to 53 percent</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td>17%</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Neomycin</td>
<td>20 to 25%</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>4 to 49%</td>
<td>5 to 9%</td>
<td>23 to 45 percent</td>
</tr>
<tr>
<td>Drug class</td>
<td>Dose</td>
<td>Dosing</td>
<td>Major side effects &amp; drug interactions</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>--------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td><strong>Statins (HMG CoA reductase inhibitors)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lovastatin</strong></td>
<td>20-80 mg/day</td>
<td>Take w/evening meal. BID if dose &gt;20 mg/day.</td>
<td>Headache; nausea; sleep disturbance; elevations in hepatocellular enzymes &amp; alkaline phosphatase. Myositis &amp; rhabdomyolysis, primarily when given w/gemfibrozil or cyclosporine; myositis is also seen w/severe renal insufficiency (CrCl &lt;30 mL/min). Lovastatin, atorvastatin, rosuvastatin, &amp; simvastatin potentiate effect of warfarin &amp; all but rosuvastatin raise digoxin levels; these interactions not seen w/pravastatin or fluvastatin.</td>
</tr>
<tr>
<td><strong>Pravastatin</strong></td>
<td>10-80 mg/day</td>
<td>Take at bedtime.</td>
<td></td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>5-80 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fluvastatin</strong></td>
<td>20-80 mg/day 80 mg SR/day</td>
<td>BID if dose &gt;40 mg/day.</td>
<td></td>
</tr>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>10-80 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rosuvastatin</strong></td>
<td>5-40 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gemfibrozil</strong></td>
<td>600 mg BID</td>
<td>30 to 60 min before meals.</td>
<td>Potentiates warfarin action. Absorption of gemfibrozil diminished by bile acid sequestrants.</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>14-5 mg/day</td>
<td>Micronized taken w/meals. Use lower doses w/renal insufficiency.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16-20 mg/day</td>
<td>Skin rash, gastrointestinal (nausea, bloating, cramping) myalgia; lowers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>blood cyclosporine levels; potentially nephrotoxic in cyclosporine treated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pts. Avoid in pts w/CrCr &lt;30 mL/min.</td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>1-12 g/day</td>
<td>Given w/meals. Start w/100 mg BID &amp; titrate to 500 mg TID. After 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>weeks, check lipids, glucose, liver function, &amp; uric acid. Increase dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>as needed.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostaglandin-mediated cutaneous flushing, headache, warm sensation, &amp;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pruritus; hyperpigmentation (particularly in intertriginous regions);</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>acanthosis nigricans; dry skin; nausea; vomiting; diarrhea; &amp; myositis.</td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>4-24 g/day</td>
<td>Take within 30 min of a meal. A double dose w/dinner produces same</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>lipid-lowering effect as BID dosing.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea, bloating, cramping, &amp; constipation; elevations in hepatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>transaminases &amp; alkaline phophatase. Impaired absorption of fat soluble</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>vitamins, digoxin, warfarin, thiazides, -blockers, thyroxine, &amp; phenobarbital.</td>
<td></td>
</tr>
<tr>
<td>Colestipol</td>
<td>5-30 g/day</td>
<td>Take w/meals QD or divided BID</td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>3.75 g/day</td>
<td>Similar</td>
<td></td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>10 mg/day</td>
<td>Increased transaminases in combination w/statins</td>
<td></td>
</tr>
<tr>
<td>Neomycin</td>
<td>1 g BID</td>
<td>Ototoxicity; nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td>Probucol</td>
<td>50-100 mg BID</td>
<td>Loose stools; eosinophilia; QT prolongation; angioneurotic edema.</td>
<td></td>
</tr>
</tbody>
</table>

Relative LDL-lowering Efficacy

<table>
<thead>
<tr>
<th>% LDL-C</th>
<th>Atorva</th>
<th>Fluvatin</th>
<th>Pitavastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>40 mg</td>
<td>1 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38%</td>
<td>10 mg</td>
<td>80 mg</td>
<td>2 mg</td>
<td>40 mg or 80 mg</td>
<td>40 mg</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>41%</td>
<td>20 mg</td>
<td>4 mg</td>
<td>80 mg</td>
<td>80 mg</td>
<td>5 mg</td>
<td>40 mg</td>
<td></td>
</tr>
<tr>
<td>47%</td>
<td>40 mg</td>
<td></td>
<td></td>
<td>10 mg</td>
<td>80 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55%</td>
<td>80 mg</td>
<td></td>
<td></td>
<td></td>
<td>20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Myopathy

If muscle symptoms, check CK. If >10x upper limit of nl, then d/c statin (REF: Am J Cardiol. 2006 Apr 17; 97(8A):89C-94C. PMID: 16581336)

CKD

(REF: http://www.uptodate.com/contents/statins-actions-side-effects-and-administration?source=search_result&selectedTitle=1%7E150#H27)


Pravastatin may be safer than other statins (REF: Ann Intern Med. 2003;138(2):98. PMID: 12529091)

ICH


Triglycerides

(REF: http://circ.ahajournals.org/content/123/20/2292.full)

<table>
<thead>
<tr>
<th>Level mg/dL</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>Normal</td>
</tr>
<tr>
<td>150-199</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200-499</td>
<td>High</td>
</tr>
<tr>
<td>500</td>
<td>Very high</td>
</tr>
</tbody>
</table>

The association of TriG w/vascular disease is not clear after adjusting for “standard risk factors & for HDL-C & non-HDL-C”.

Gemfibrozil
VA-HIT: h/o CHD, <74 yo, HDL40, LDL140, TriG300 -> MI & CHD death

Data from the Helsinki Heart Study, a randomized primary prevention trial in dyslipidemic men, showing the incidence of coronary events at five years according to the baseline serum triglyceride concentration & the LDL-to-HDL cholesterol ratio. The risk was markedly increased in pts w/both a triglyceride concentration above 2.3 mmol/L [200 mg/dL] & an elevated LDL-to-HDL ratio. A beneficial effect of gemfibrozil to lower the incidence of coronary events was limited to this group.

Niacin
Niacin ER (+ simvastatin) improves lipids (HDL, LDL, Trig) but does not seem to prevent vascular events & may increase the risk of stroke (REF: AIM-HIGH. http://www.nejm.org/doi/full/10.1056/NEJMoa1107579)

But THRIVE trial still pending (REF: http://www.ctsu.ox.ac.uk/~thrive/)

May be similar to ILLUMINATE (REF: Effects of torcetrapib in pt at high risk for coronary events. N Engl J Med 2007 Nov 5; http://dx.doi.org/10.1056/NEJMoa706628)

**Omega 3 fatty acids**


No clear benefit for secondary prevention (REF: ?)


**CETP Inhibitors**

Evacetrapib: raises HDL, lowers LDL, even in addition to statin. Outcomes not yet determined (REF: Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination w/Statins on HDL & LDL Cholesterol: A Randomized Controlled Trial. JAMA. 2011; 306:2099-2109. http://jama.ama-assn.org/content/306/19/2099.abstract)

Also dalcetrapib, anacetrapib

**Monoclonal antibody to proprotein convertase subtilisin/kexin type 9**

(REF: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2812%2961771-1/fulltext)

(REF: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2812%2961770-X/fulltext)

**What should we measure?**

**Lipoprotein(a) (Lp(a))**

Independent risk factor based on 24 cohort studies

No clear target goals

Therapy: Estrogen & niacin. Reduce levels, but unclear clinical impact

Apolipoprotein B & A-I, lipoprotein(a), lipoprotein-associated phospholipase A2


**Diabetes**

DM: DM1 associated w/4x stroke risk, DM2 w/2x stroke risk (REF: Diabetes Care. 2007 Jul;30(7))

Adequate glycemic control may mitigate some risks

Aggressive glucose control may be riskier, eg HbA1c <6% vs. 7-7.9% = HR death 1.22, stroke 1.06 (REF: ACCORD)


Metformin as a primary agent prevents more vascular disease than sulfonylureas (REF: http://annals.org/article.aspx?articleID=1309945)


**Hypercoagulable states**

**Antiphospholipid Syndrome**

(REF: http://www.uptodate.com/contents/diagnosis-of-the-antiphospholipid-syndrome?source=search_result&selectedTitle=1~150)

**Epidemiology**

1-6.5%, higher in elderly & pt w/lupus

Association w/stroke strongest for <50yo

Anticardiolipin: 9.7% ischemic stroke pts, 4.3% controls

WARSS/APASS: APL antibodies 40.7% of stroke pts: low titer, no sig effect


**Laboratory**

Antibodies x2 / 6wks (<5y prior to clinical manifestation)


Anticardiolipin antibody (IgG or IgM >40 until GPL or >99 percentile)

Anti-2 glycoprotein-I (IgG or IgM >99th percentile)

**Pathophysiology**

Autoantibodies to negatively charged cell membrane phospholipids

**Clinical**
Venous, arterial, or small vessel thrombosis (unequivocal evidence in any tissue or organ)

Morbidity w/pregnancy (unexplained death 10wk gestation; 1 premature birth <34wk because of preeclampsia or placental insufficiency; 3 spontaneous abortions <10wk)

Thrombocytopenia: plt usually 50-140k, does not preclude thrombosis

Livedo Reticularis


Treatment

WARSS/APASS: warfarin (INR 1.4-2.8) vs. ASA 325mg

Event rate 22.2% for APL+ vs. 21.8% APL-

No diff warfarin vs. ASA


Other Hypercoag states

Protein C or S deficiency
Antithrombin III deficiency
Hyperhomocysteinemia

Activated protein C resistance/Factor VLeidenmutation Arg506Gln (heterozygous = mild)

Prothrombin gene mutation (G20210A) (heterozygous = mild)

High plasma levels of Factor VIII (mild)
Methylenetetrahydrofolate reductase (MTHFR) C677T mutation

Homocysteine
Factor VIII

Von Willebrand factor

Plasminogen activator inhibitor-1

Endogenous tissue plasminogen activator activity

(REF: Stroke.2011; 42: 1158-1192 http://stroke.ahajournals.org/content/42/4/1158.full)

Antithrombotic Therapy

Anticoagulation

Coagulation Cascade
Low Molecular weight heparin

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Prophylactic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>Lovenox</td>
<td>40mg daily</td>
<td>1mg/kg q12h (or 1.5mg/kg q24h)</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>5000 units daily</td>
<td>200 units/kg q24h</td>
</tr>
</tbody>
</table>

Careful if GFR < 30ml/min

Heparin-Induced Thrombocytopenia (HIT)

4Ts scoring system

4T <4 = low risk

<table>
<thead>
<tr>
<th>4Ts category</th>
<th>2 points</th>
<th>1 point</th>
<th>0 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Pit count fall &gt; 50% and plt nadir 20</td>
<td>Pit count 30%-50% or plt nadir 10-19</td>
<td>Pit count fall &lt; 30% or plt nadir &lt; 10</td>
</tr>
<tr>
<td>Timing of plt count fall</td>
<td>Clear onset days 5-10 or plt fall 1 day (prior heparin exposure within 30 days)</td>
<td>Consistent with days 5-10 fall, but not clear (eg, missing plt counts); onset after day 10; or fall 1 day (prior heparin exposure 30-100 days ago)</td>
<td>Pit count 4 days without recent exposure</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous unfractionated heparin bolus</td>
<td>Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)</td>
<td>None</td>
</tr>
</tbody>
</table>


Direct thrombin inhibitors

Dabigatran, Ximelagatran (voluntarily withdrawn from the European market & further development was terminated because of severe liver toxicity reported in clinical trials (Anon, 2006)), Bivalrudin

AntiPlatelet/ASA


(REF: USPTF, http://www.annals.org/content/150/6/396.full)
Young: do not encourage ASA for CV prevention (M<45, F<55)

M 45-79: ASA when potential benefit on MI > potential harm on GIB

F 55-79: ASA when potential benefit on ischemic stroke > potential harm on GIB

Old (>80y): Evidence insufficient to assess benefits & harms for CV prevention

Hemorrhage


Primary Prevention

Rate of major bleeding/1000 person-year: never ASA=3.60, current ASA 5.58

“Of note, the use of statins was associated with a significant reduction of both gastrointestinal (IRR, 0.65; 95% CI, 0.60-0.71) and intracranial (IRR, 0.69; 95% CI, 0.64-0.74) bleeding.”

Secondary Prevention

ASA for secondary prevention reduces stroke risk from 2.54% to 2.08% per year (REF: Lancet. 2009 May 30;373(9678):1849-60).


Adding dipyrimidole may slightly reduce stroke risk further (REF: Stroke. 2008 Apr;39(4):1358-63) but greatly increases bleed risk.

There may be a benefit to using ASA + clopidogrel after minor stroke or TIA in first few days (REF: Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial. http://www.nejm.org/doi/full/10.1056/NEJMoa1215340).

Clopidogrel may be better than ASA for pts w/PVD (REF: Lancet 1996 Nov 16;348(9038):1329-39).


Discontinuation of ASA (nonadherence) -> 40% increase Stroke/TIA (REF: http://www.neurology.org/content/76/8/740.abstract)

There may be residual plt reactivity following antiplt loads for ACS (REF: http://jama.ama-assn.org/content/306/11/1215.full)

Clopidogrel & CYP2C19 Genotype: lower levels of metabolism to create active metabolites, decreased plt inhibition, lower risk of bleeding, but no clear impact on CV events (REF: http://jama.ama-assn.org/content/306/24/2704.abstract)

Ticlodipine: Canadian American Ticlopidine Study (CATS), Ticlopidine Aspirin Stroke Study (TASS), African American Antiplatelet Stroke Prevention Study. Associated w/TTP

Other agents: triflusal, cilistazol, sarpogrelate

Comparing antiplatelet agents

ASA vs clopidogrel (CAPRIE): rates of stroke not statistically significantly different for the secondary stroke pts: "7.15% in the clopidogrel group compared w/7.71% in the aspirin group (RRR, 7.3%; 95% CI, –6% to 19%; P=0.26)"

ASA vs ASA/dipy (ESPS-1, ESPS-2, ESPRIT): overall maybe a benefit to ASA/dipy, but these studies all used weird doses of these drugs, had problems in data quality per reviews, & were open label (ESPRIT).

Clopidogrel vs ASA/dipyridamole (PROFESS): "results failed to show that aspirin/dipyridamole was not inferior to clopidogrel." "recurrent stroke occurred among 9.0% of participants assigned to aspirin/dipyridamole compared w/8.8% assigned to clopidogrel (HR, 1.01; 95% CI, 0.92 to 1.11)"
"Unfortunately, there have been no clinical trials to indicate that switching antiplatelet agents reduces the risk for subsequent events." (REF: Furie. Guidelines for the prevention of stroke in pt w/stroke or transient ischemic attack. Stroke. 2011 Jan;42(1):227-76. PMID: 20966421. http://stroke.ahajournals.org/content/42/1/227.full)

Comparing ASA vs. Warfarin


Aspirin in DM


ASA lowered risk coronary events 9%, stroke 15% (p=ns both)

Excess GIB risk = 1-5/1000 pts/year

<table>
<thead>
<tr>
<th>Rec (ASA 75-162mg)</th>
<th>10y CVD risk</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasonable</td>
<td>&gt;10%, no risk of bleeding</td>
<td>M&gt;50, F&gt;60 w/one additional major risk factor (smoking, HTN, dyslipid, FH, albuminuria)</td>
</tr>
<tr>
<td>Might be considered</td>
<td>5-10%</td>
<td>Young w/risk factors or older without</td>
</tr>
<tr>
<td>Should not be recommended</td>
<td>&lt;5%</td>
<td>M&lt;50, F&lt;60, no other risk factors</td>
</tr>
</tbody>
</table>

Measuring Plt Reactivity