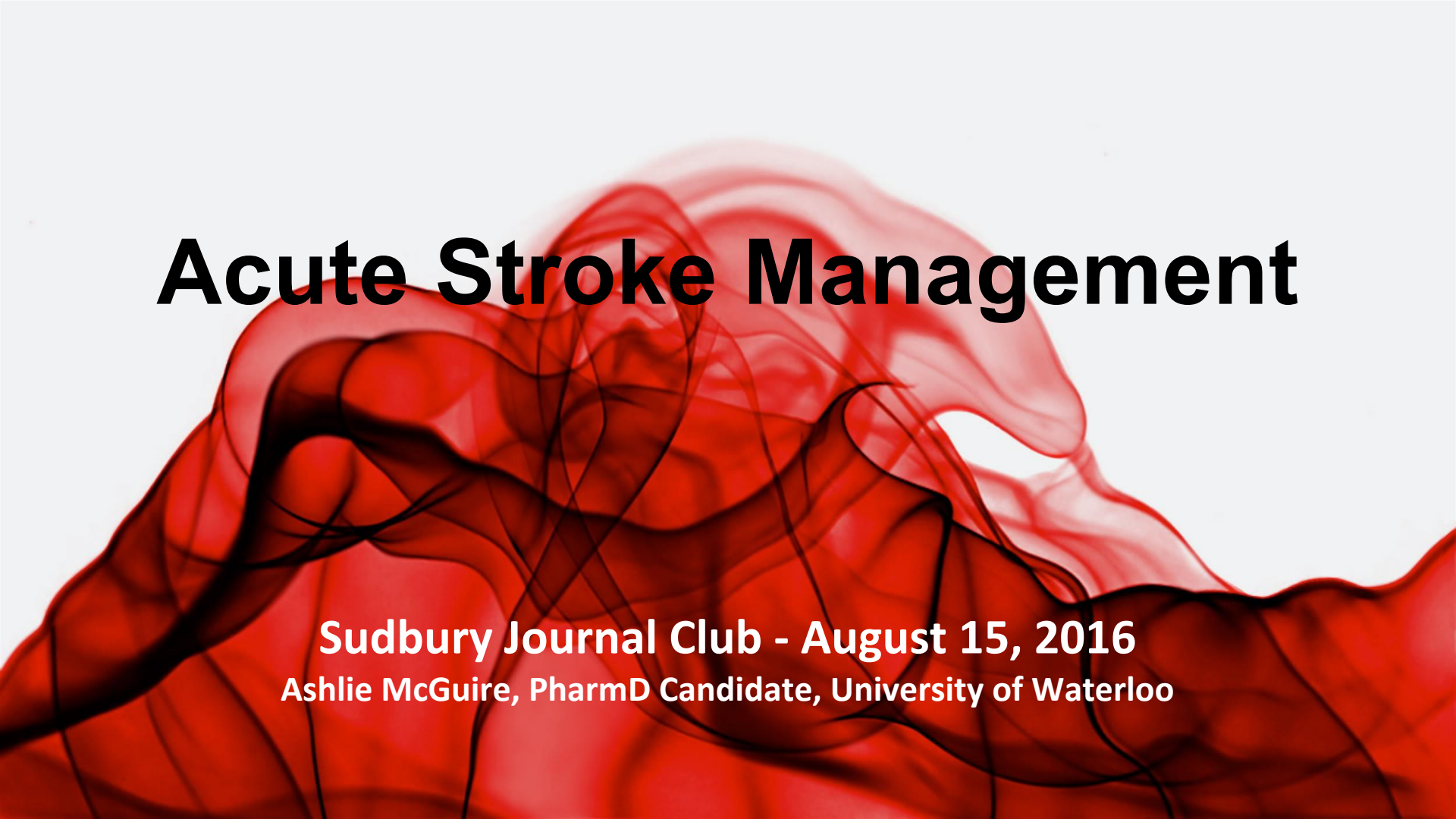


Acute Stroke Management

Sudbury Journal Club - August 15, 2016

Ashlie McGuire, PharmD Candidate, University of Waterloo

New Initiative!

The SJC will now be highlighting a charitable group in the community at every event.

A donation box will be at the entrance for SJC members, if they want to support these community groups.

Disclosures

Funds for this event are from an unrestricted educational grant

I have not received any payment for this presentation

Learning Objectives

- Review and differentiate the pathophysiology, epidemiology and general management pathways of ischemic versus hemorrhagic strokes
- Describe patients that are candidates to receive tPA during hyperacute ischemic stroke management
- Select appropriate antiplatelet therapy for secondary prevention of stroke
- Discuss VTE prophylaxis, restarting anticoagulation in stroke patients
- Optimize patient outcomes with appropriate pharmacological agents to reduce stroke recurrence and manage comorbid conditions

Defining Stroke

STROKE

Abrupt-onset focal neurologic deficit that lasts at least 24 hours and is of presumed vascular origin

TIA (Transient Ischemic Attack)

A TIA is the same, but lasts less than 24 hours and usually less than 30 minutes

In Canada, each year...

- Third leading cause of death
- 62,000 strokes and TIA admitted to ER
  - 1 every 9 minutes
- $20.9 billion/yr spent on health care and lost productivity due to stroke
- Stroke is predicted to increase due to aging population

Canadian Heart and Stroke Foundation Statistics. http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/k.34A8/Statistics.htm

CSBPR Continuum of Care

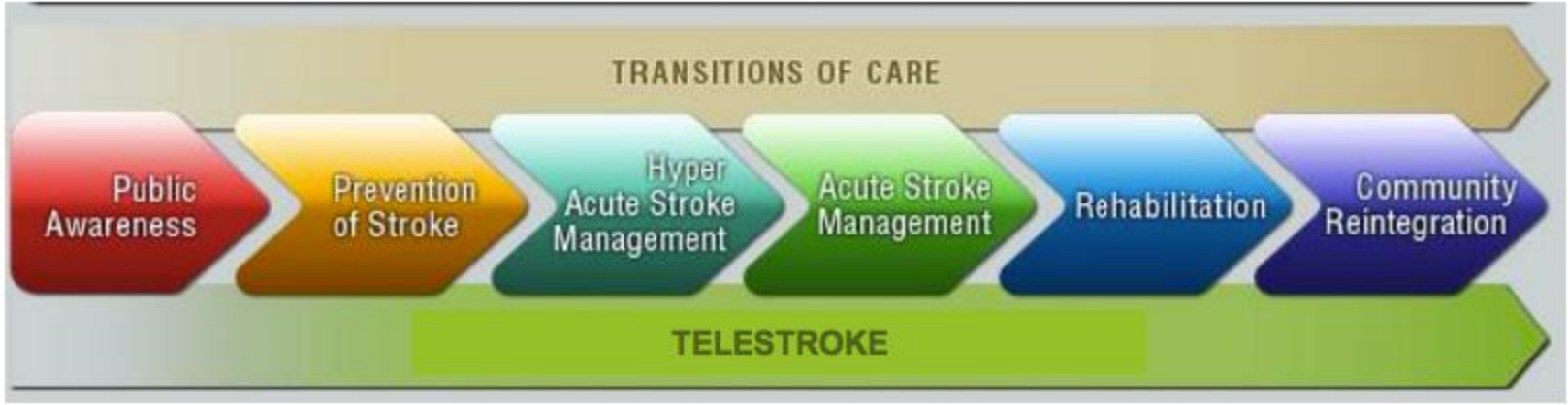


Figure 2.1: Canadian Stroke Best Practices Continuum of Care

Management: Hyperacute vs. Acute

Hyperacute care goals:

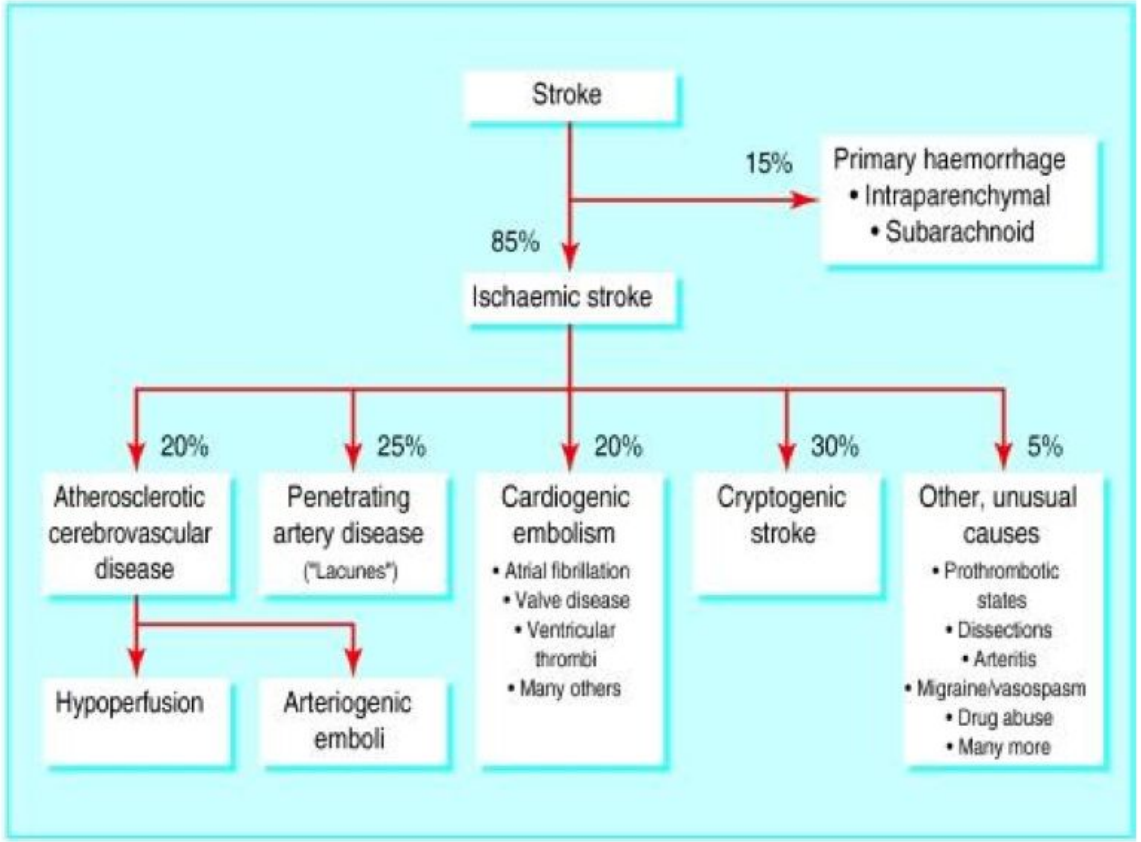
- Assessment, stabilization and treatment of stroke within first 48 hours
- Diagnose stroke type, create and execute treatment plan
- “Time = brain”

Acute care goals:

- Treatment, management and early recovery in the days following stroke onset
- Identify mechanism of stroke and prevent recurrence by reducing risk factors

CSBR: http://www.strokebestpractices.ca/wp-content/uploads/2010/10/Hyperacute-and-Acute-Stroke-Care-Definitions.pdf

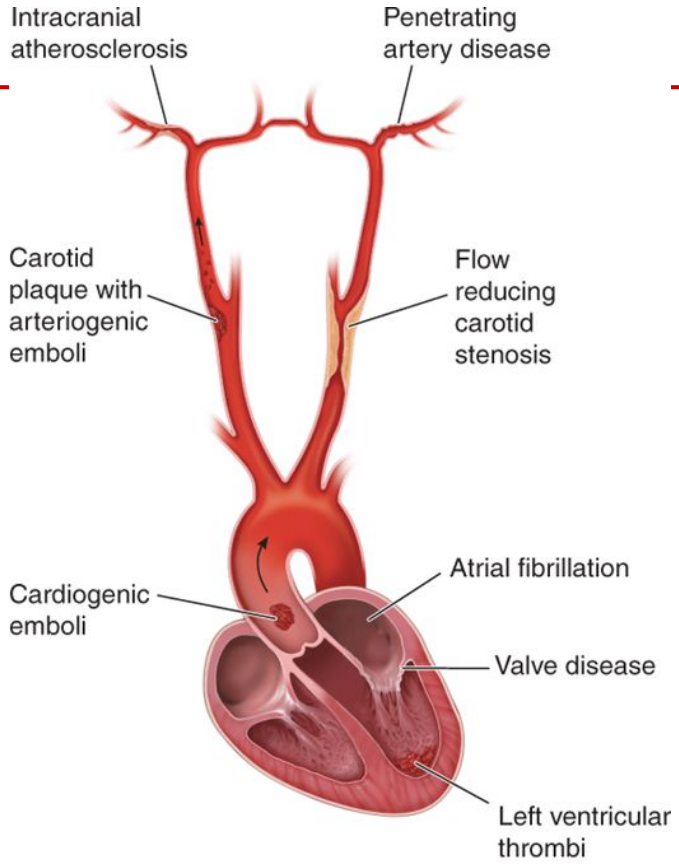
Types of Stroke



Albers GW et al. Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3 Suppl):483S-512S.

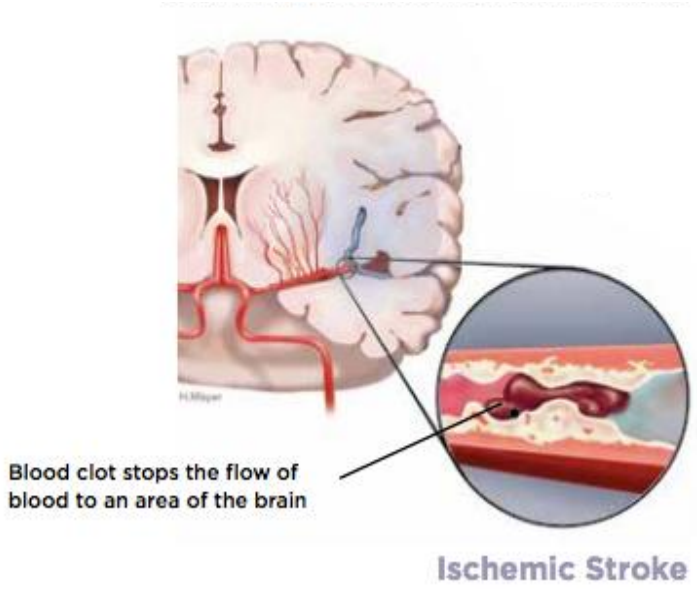
Ischemic stroke

- Most common type of stroke
- Embolism or thrombus occludes cerebral artery
- 20% of emboli arise from the heart
  - Afib, valve disease, clots
- Reduced blood flow causes infarction
- Tissue around the infarct core that is ischemic but has not died is the ‘penumbra’
  - May be salvaged
- “Time = brain”
- Complete appropriate interventions ASAP
- Control for underlying risk factors where possible



Ischemic stroke

- Most common type of stroke
- Embolism or thrombus occludes cerebral artery
- 20% of emboli arise from the heart
  - Afib, valve disease, clots
- Reduced blood flow causes infarction
- Tissue around the infarct core that is ischemic but has not died is the ‘penumbra’
  - May be salvaged
- “Time = brain”
- Complete appropriate interventions ASAP
- Control for underlying risk factors where possible

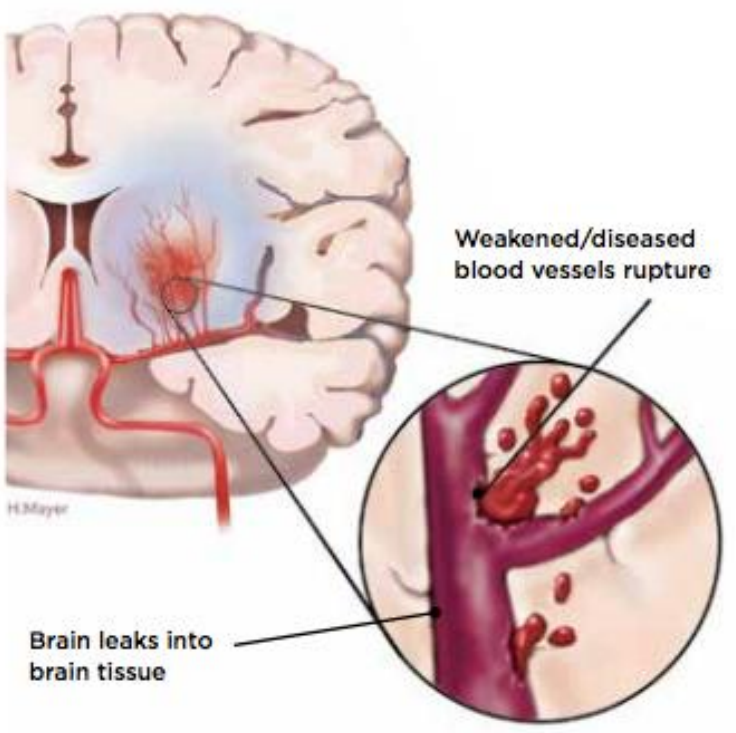


Non-modifiable	Modifiable risk factors	
Increasing age	Hypertension	Cholesterol
Male gender	Smoking	A.fib
Family history of Stroke/TIA	Obesity	Cardiac diseases
Race	Diabetes	Physical Inactivity

Chapter 10: Stroke. In Pharmacotherapy A Pathophysiological Approach. DiPiro.
Image: http://www.strokebestpractices.ca/wp-content/uploads/2016/01/TACLS-Chapter-2-Body-Structure.pdf

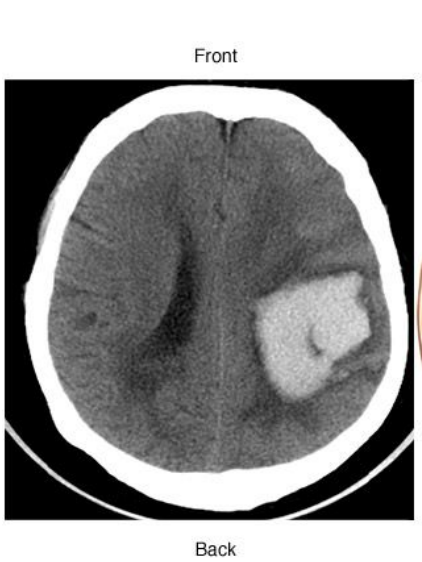
Hemorrhagic stroke

- About 15% of all strokes
- CT scan confirms diagnosis
- Broken blood vessel
  - Expanding hematoma
  - Compression of brain tissue
  - Subsequent ischemia
- Management includes:
  - Hemostasis
  - Reversal of anticoagulants, if required
  - Monitor intracranial pressure
  - Prevent seizures, DVT
  - Neurosurgical interventions



Hemorrhagic Transformation

- Ischemic stroke → hemorrhagic
- 5-6% of patients receiving IV tPA
- Most common within 12-24hrs
- Risk factors:
  - Size of infarct
  - Older age
  - Cardioembolic pathogenesis
- Delay treatment until patient is stable
- Treat as an ICH



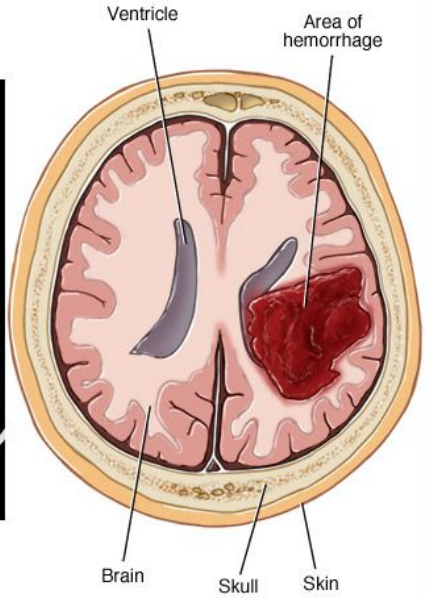


Image: http://www.mayoclinic.org/diseases-conditions/brain-avm/symptoms-causes/dxc-20129994

Determining stroke etiology

- Required to determine hyperacute treatment
- CT scan in hyperacute period to rule out active hemorrhage
- For example:
  - Cardiogenic emboli → anticoagulation to control A.fib
  - Carotid artery stenosis → endarterectomy, stenting
  - Thrombosis → antiplatelet treatment

Canadian Stroke Statistics

Canadian Stroke Network
Réseau canadien contre les accidents cérébrovasculaires

Figure 1. Stroke Occurrence by Age and Sex in Audit Patients, Canada 2008/2009

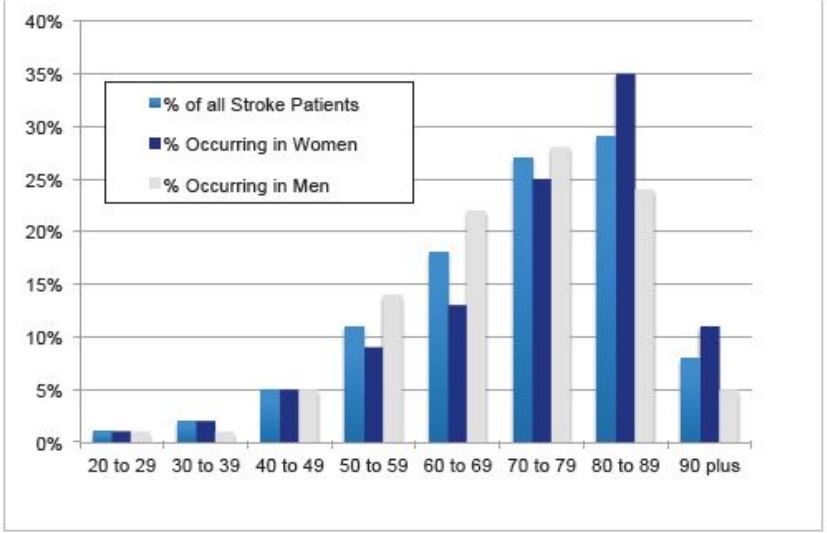


Table 4. Stroke Occurrence by Age and Stroke Type in Audit Patients, Canada 2008/2009

	Age Group								
Stroke Type	**Total**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**90+**
Ischemic Stroke	63%	56%	54%	54%	56%	61%	66%	66%	68%
Transient Ischemic Attack	17%	7%	7%	12%	14%	17%	18%	19%	18%
Intracerebral Hemorrhage	11%	17%	16%	11%	12%	12%	10%	10%	7%
Subarachnoid Hemorrhage	5%	16%	19%	20%	15%	6%	2%	1%	1%
Unable to Determine	4%	4%	4%	3%	3%	4%	4%	4%	6%
	100%	100%	100%	100%	100%	100%	100%	100%	100%

Report: The Quality of Stroke Care in Canada 2011. http://www.strokebestpractices.ca/wp-content/uploads/2011/06/QoSC-EN.pdf/. Accessed Aug.4, 20214

Canadian Stroke Statistics

Canadian Stroke Network

Réseau canadien contre les accidents cérébrovasculaires

Table 5. Medical History of Audit Patients, Canada 2008/2009

Medical History	% of Audit Patients with Risk Factor
Previous Stroke	22%
Previous Transient Ischemic Attack	13%
Hypertension	64%
Diabetes mellitus	24%
Current and Lifelong Smoker[23]	27%
Atrial Fibrillation	16%
Coronary Artery Disease	25%

Report: The Quality of Stroke Care in Canada 2011. http://www.strokebestpractices.ca/wp-content/uploads/2011/06/QoSC-EN.pdf/. Accessed Aug.4, 20214

Rates of stroke recurrence

Time frame	After TIA	After Stroke
30-days	4-8%	3-10%
1 year	12-13%	10-14%
5 years	24-29%	25-40%

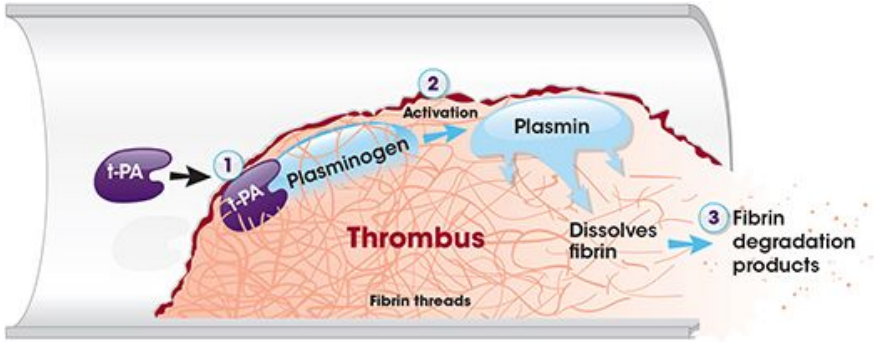
HEART & STROKE FOUNDATION

CANADIAN Stroke BEST PRACTICE RECOMMENDATIONS

Hyperacute Stroke Management

Reperfusion therapy

- Thrombolysis using recombinant-tissue plasminogen activator (r-tPA)
- Confirm stroke is of ischemic nature
- Strictly adhere to the criteria for use:
  - Time since event onset is <4.5hrs
  - Age >=18 years old
- Exclusion criteria:
  - Recent trauma, surgical procedures
  - Active bleeding
  - Anticoagulant use, or INR>1.7
  - Uncontrolled hypertension
  - Seizures



1 Recombinant t-PA (alteplase) binds to fibrin in thrombus 2 converts entrapped plasminogen to plasmin that 3 initiates local fibrinolysis.

Patient Case - D.T

62 year old man

PMH: Diabetes, hypertension, dyslipidemia, a.fib, history of DVT (resolved), no prior ACS or stroke, arthritis, GERD

Medications:
Metformin 1000mg po BID with meals
Amlodipine 5mg po daily
Simvastatin 10mg po daily
Esomeprazole 20mg po daily
Aleve 220mg po daily PRN pain
Apixaban 5mg po daily

Normal labs:
6'0, 190lbs
BP at home 150/90
HbA1C = 7.5 (June, 2016)
SCr 89, CrCl~ 87ml/min

Hyperacute treatment of D.T.

D.T has onset of right sided weakness at 6pm while eating dinner at home.

He arrives at HSN at 6:40 and ischemic stroke diagnosed by 7:30pm.

<u>Labs on admission to HSN:</u>
BP 175/95
CBC, lytes WNL
SCr 89, CrCl~ 87ml/min

Is D.T a candidate for tPA therapy?

To tPA, or not to tPA?

Agent	Guideline	In Theory	Comments
Apixaban	No	Maybe	• DOACs were not studied in pivotal trials • Antidotes not studied yet • May use if l**ast dose 24-48h**, normal **renal function**, **drug interactions** decreasing elimination (p-gp), 'labs normal' • Labs such as anti-Xa or ecarin levels are not widely used or available yet.
Rivaroxaban	No	Maybe	
Dabigatran	No	Maybe	
Warfarin	Maybe	Maybe	May use only if l**NR<1.7** & within **3hrs** of stroke onset
Aspirin	Yes	Yes	• 30-40% of patients in NINDS trial used aspirin • **Single antiplatelet agents** are acceptable • Lack of data on ticagrelor and prasugrel
Clopidogrel	Yes	Yes	
DAPT	No	Maybe	Not studied in pivotal trials. Likely higher risk for symptomatic ICH, however no mortality increase. Benefit may outweigh risk in some.

1. Pharmacist's Letter Document #290612: Alteplase (tPA) for Stroke in Patients Taking an Antithrombotic. June 2013. 2. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947. 3.Diedler J, Ahmed N, Sykora M, et al. Safety of Intravenous Thrombolysis for Acute Ischemic Stroke in Patients Receiving Antiplatelet Therapy at Stroke Onset. *Stroke*. 2010;41(2):288-294.

Clearance of DOACs

Table 3 **Last intake of drug before elective surgical intervention**

	Dabigatran		Apixaban–Edoxaban–Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl <15 mL/min	No official indication for use			
	There is no need for pre-operative bridging with LMWH/UFH			

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clinical impact.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. *Bayer Healthc Pharm Healthc Pharm Eur Hear J Adv Access*. 2016.

To tPA, or not to tPA?

At this point in time, AVOID initiating tPA in patients who:

- ✗ Take DOACs (apixaban, dabigatran, rivaroxaban) routinely
- ✗ Take warfarin, where INR > 1.7
- ✗ Have received heparin within last 48 hours

- ✓ May use tPA in patients with who were on aspirin or clopidogrel

Patient Case

D.T is not a candidate for tPA

- Has not missed any doses of his apixaban, is likely anticoagulated
- Risks outweigh benefit for administration

Hyperacute Blood Pressure Management

- Hyperacute BP management differs from acute and ongoing BP targets
- Management varies on whether the patient received thrombolytic treatment

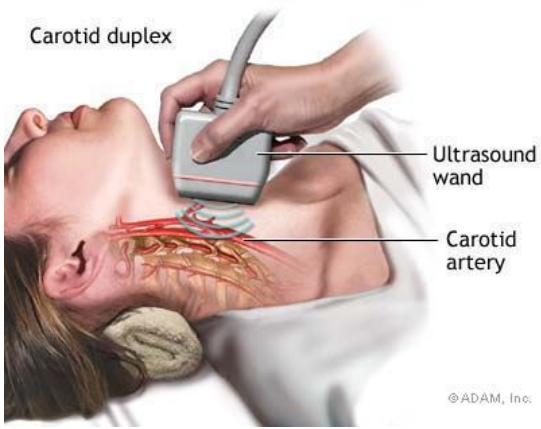
tPA received:

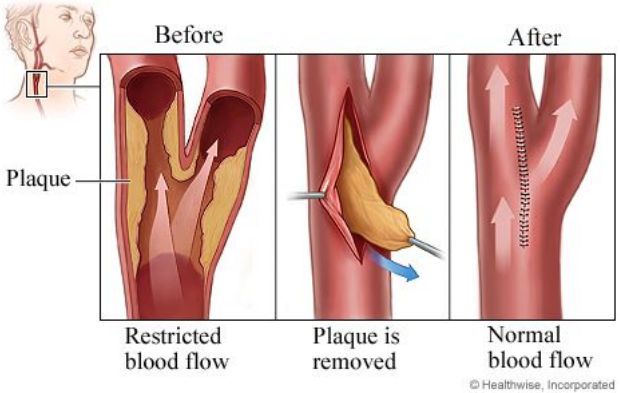
- Avoid blood pressure >185/110 mmHg to prevent intracranial hemorrhage
- Avoid significant blood pressure reduction, worsens ischemia and neuronal death

No tPA administered:

- Do not adjust blood pressure when <220/120 mmHg
- If blood pressure >=220/120, lower slightly by 15-25%.
- Avoid significant blood pressure reduction, worsens ischemia and neuronal death

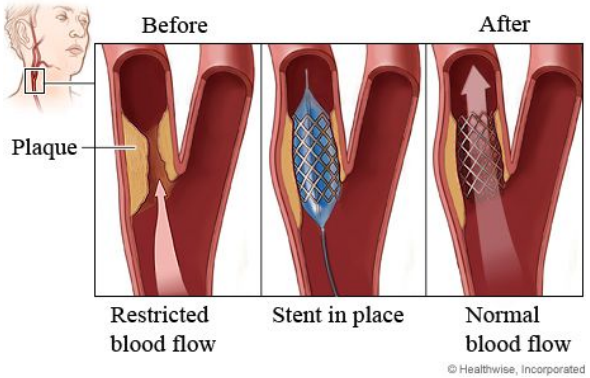
Interventions for Carotid Artery Stenosis





Carotid Endarterectomy (CEA)

Carotid Artery Stenting (CAS)



Images: http://www.nytimes.com/health/guides/disease/stroke-secondary-to-carotid-dissection/print.html ; https://myhealth.alberta.ca/Health/Pages/conditions.aspx?hwid=abp6220

Management of Intracranial Stenosis

Surgical removal of blockages

- **Carotid artery endarterectomy (CEA)**
  - ASA (81-325mg) prior to surgery, continued for 3 months.
  - Then continue with antiplatelet agent for secondary prevention
- **Carotid artery stenting (CAS)**
  - DAPT (ASA 325mg + Clopidogrel 75mg) for at least 30-days (CREST trial)
  - May continue for 6-12weeks, then drop down to aspirin alone
  - If DAPT not used, monotherapy with aspirin is more common

Medical management: (intracranial atherosclerosis)

- Stenosis 70-99%: DAPT for 90 days
- Stenosis 50-99%: ASA 325mg daily

Fairman RM. Carotid endarterectomy. UpToDate. Last updated February 24, 2016. Accessed August 14, 2016. Mohler ER, Fairman RM. Carotid artery stenting and its complications. UpToDate. Last updated May 3, 2016. Accessed August 12, 2016.

HEART & STROKE FOUNDATION

CANADIAN Stroke BEST PRACTICE RECOMMENDATIONS

Acute Stroke Management

Antiplatelet and Anticoagulation therapy

- Type of therapy depends on source of ischemic stroke
- Cardiogenic source:
  - Start on DOAC or warfarin - select agent based on patient factors
  - See SJC website for previous talk on selecting agents
    - http://www.sudburyjournalclub.com/uploads/1/2/8/9/12890496/not_another_afib_talk.final.pdf
- Non-cardiogenic source:
  - Initiate antiplatelet therapy, continue lifelong
  - Consider whether tPA, CEA, CAS was received to direct what to start, and when

Antiplatelet therapy

Guidelines indicate any of the following are appropriate options for management of non-cardioembolic ischemic stroke:

- Clopidogrel 75mg
- ASA 81mg
- Aggrenox (ASA 25mg + dipyridimole extended release [ERDP] 200mg)

Which do you choose?

How do you choose?

Overview of Guideline Recommendations

For management of non-cardioembolic ischemic stroke:

GUIDELINE	Aspirin	Clopidogrel	DAPT	ASA + ERDP	DOAC/ Warfarin
Canadian Stroke Best Practice Recommendations (CSBPR) 2014	✔	✔	X	✔	X
AHA/ASA 2013, 2014	✔	✔	X	✔	X
Chest 2012	✔	✔	N/A	✔	X
European Stroke Organisation (ESO), 2012	✔	✔	X	✔	X

(1) Casaubon LK, Boulanger J-M, Glasser E, et al. Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015. *Int J Stroke*. 2016;11(2):239-252. doi:10.1177/1747493015622461. (2) Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947. doi:10.1161/STR.0b013e318284056a. Accessed August 8, 2016 (3) Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236. doi:10.1161/STR.0000000000000024.

Limitations of Current Evidence

- Absence of head-to-head trials of agents
- Heterogeneous populations enrolled
  - Variable time to enrollment, duration, doses
- Composite endpoints reported in numerous trials
- Poor external validity
  - Applicability of study results to the population we are treating

Aspirin

- **Dose:** 80-325mg
  - Within 48hours: 160-325mg x 1 dose (some variability)
  - Lifelong: 81mg po daily

  * *If dysphagia or unable to tolerate PO meds, consider rectal administration*
- **Side effects**: GI bleeding
- **Guideline recommendations:**
  - As monotherapy for secondary prevention
  - Use as DAPT for 21 days after ischemic stroke

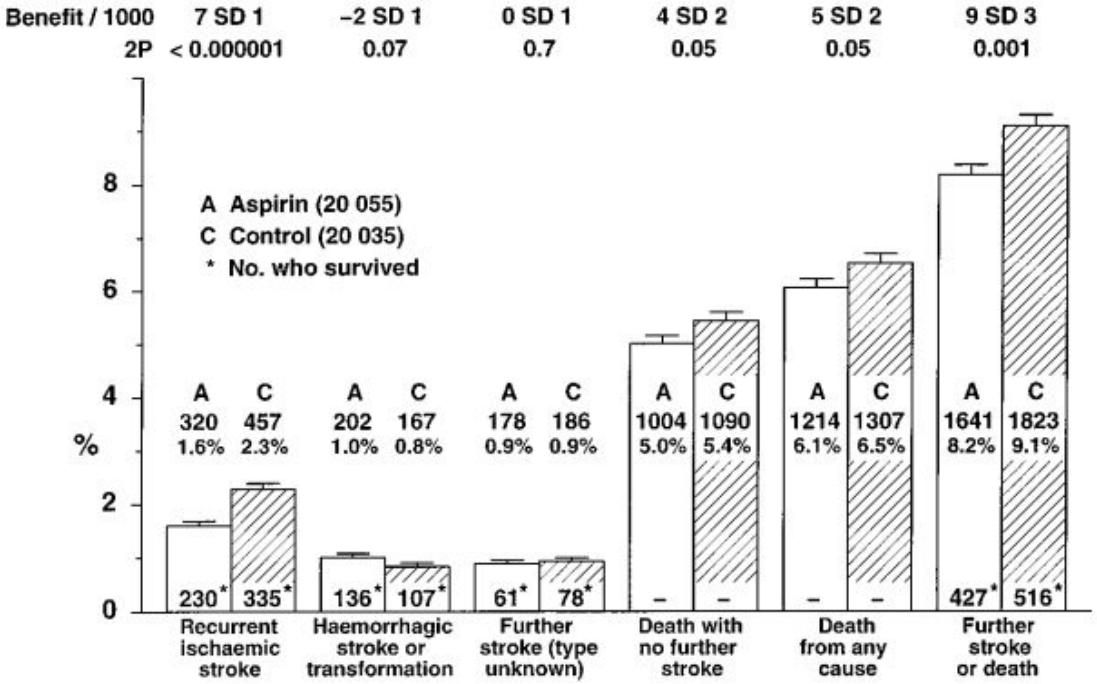
Start Aspirin within 24-48 hours of ischemic stroke

Long term ASA therapy

- 2002 Antithrombotic Trialists Collaboration (ATC) meta-analysis of 195 RCTs
  - 25% reduction in stroke, vs. placebo
  - Sub-analysis: patients with previous stroke - 36/1000 events over 29 months
- Recent Cochrane Review (Sandercrock et al., 2014)
  - 8 trials included, where treatment was ASA 160-325mg
    - 98% of the data was from two major trials from 1997: CAST and IST
  - Treatment with ASA:
    - Reduced odds of being dead or dependent at final follow-up: OR=0.95, p=0.01, NNT=79
    - Decreased risk of recurrent stroke: OR=0.77, p<0.0001, NNTB=140.
    - Associated with major extracranial hemorrhage: OR=1.69, 95% p<0.001. NNH=245.

Sandercock PA, Counsell C, Tseng M-C, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. In: Sandercock PA, ed. *Cochrane Database of Systematic Reviews*.

Benefit of Aspirin - CAST + IST trials



- Combined approx. 40,000 pts
- 2/1000 intracranial hemorrhage or hemorrhagic transformation
- 7/1000 significant reduction in stroke
- 4/1000 NS reduction in mortality

IST and CAST demonstrated that aspirin led to a reduction of 11 nonfatal strokes or deaths per 1,000 patients; NNT- 91.

Chen Z, Sandercock P, Pan H, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. *Stroke*. 2000;31(6):1240-1249.

Aspirin - General Practice Principles

- Low dose ASA is just as effective as high doses
  - Provides CV protection with fewer side effects
- Select as therapy in those with clopidogrel allergy
- May consider aspirin desensitization protocol for those with aspirin allergy
- Benefit over other agents:
  - Cost - inexpensive
  - Once daily
  - Relatively few side effects

Clopidogrel

- **Doses**
  - **Loading:** 300mg x1
  - **Maintenance:** 75mg po daily
- **Possible side effect:** GI discomfort, rash, diarrhea, neutropenia
- **Guideline recommendations:**
  - As monotherapy for secondary prevention
  - Use as DAPT for 21 days

Clopidogrel - Evidence

- Cornerstone trial: **CAPRIE, 1996** (clopidogrel 75mg vs. ASA 325mg)
- Benefits of Clopidogrel:
  - Lower annual ischemic stroke (5.32% vs. 5.83%, RRR 8.7%, p=0.043).
  - Lower GI bleed (2.0% vs. 2.7% P<0.05)
- No significant difference in ICH,
- Harms: Significant increase in rash, diarrhea with clopidogrel (p<0.05)
- Limitations:
  - Inclusion criteria for stroke patients: previous stroke 1 week - 6 months
  - High dose aspirin used
  - Limited reliability of subgroup analysis

Clopidogrel - General Practice Principle

- Importance of loading dose
- Select as therapy in those with aspirin allergy or intolerance
- Benefit over other agents:
  - Cost
  - Once daily
- Pharmacogenetics - CYP2C19 metabolism variability
- Perhaps a good option for those with peripheral vascular disease or history of MI or GI bleed (CAPRIE trial)

Stroke while on antiplatelet therapy

- Current thought process:
  - If stroked on ASA, choose plavix
  - If stroked on plavix, choose ASA
- Before switching, rule out causes of resistance:
  - Extrinsic: poor compliance, incorrect dosing, drug interactions
  - Intrinsic causes of resistance: pharmacogenetics (polymorphisms in CYP2C19)

Canadian guidelines indicate there is not enough evidence to guide management on antiplatelet selection if a patient has had a stroke on one

Recommend re-assessing and optimizing management of vascular risk factors

Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. doi:10.1111/ijs.12439.

Dual antiplatelet therapy

- ASA + Clopidogrel 75mg po daily
  - Variable doses of aspirin used in current evidence
- DAPT is commonly prescribed for treatment after CV events
- Canadian guidelines do not promote the use of DAPT post-stroke
  - Concerns about external validity of trial benefits
  - CHANCE trial, exclusively chinese population
- POINT trial - DAPT in a North American Population (recruitment phase)
- May be used in select ischemic stroke patient populations for specific duration

Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. doi:10.1111/ijs.12439.

DAPT Evidence

Trial	Treatment Options	Treatment Start	Duration	Benefit	Harms
CHANCE 2013	**Day 1-22:** DAPT vs ASA 75mg **Day 22-90:** Clopidogrel vs ASA 75mg	Within 24hrs	21 days	-Decreased stroke -NNT 29/ 90days	- NS increase in bleed or all-cause mortality
SPS3 2012	DAPT vs ASA 325mg	Within 2-180 days	3.4 years	-NS decrease in stroke/MI	- Major bleeding (NNH=32) - All-cause mortality (NNH=44)
FASTER 2007	DAPT vs ASA 81mg	Within 24hrs	90 days	-NS decrease in stroke	- Symptomatic bleeding (NNH=34)
MATCH 2004	DAPT vs. Clopidogrel 75mg	Within 3 months	18 months	-NS decrease in stroke, MI, vascular death or ischemic event	- Life-threatening bleed (NNH=50) - Major bleed (NNH=100) - Increased risk of ICH after 90 days

DAPT= clopidogrel 75mg + dose of ASA indicated in the trial's regimen.
NS= non significant, NNT=patients requiring treatment to prevent one poor outcome, NNH=patients exposed to treatment to cause harm

Adopted from: Kosar L, Koziol K, Martens A. April 2016. RxFiles Duation of DAPT and TT Online Extras. http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-DAPT-TT.pdf.
Koziol K, Merwe V Van der, Yakiwchuk E, Kosar L. Dual antiplatelet therapy for secondary stroke prevention. *Can Fam Physician*. 2016;62(8):640-645.

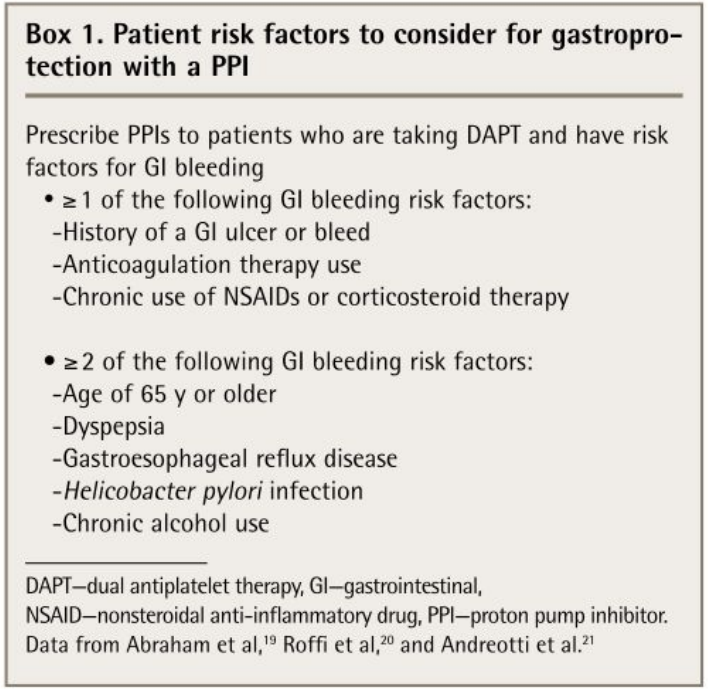
Aspirin + Clopidogrel

- ★ **Cautiously use for 21 days after ischemic stroke,** then single antiplatelet agent lifelong
- ★ Do not use long-term DAPT unless indicated:
  - Intracranial artery stenosis 70-99% (clopidogrel + high dose ASA for 90 days)
  - Coronary stenting after ACS
- ★ No significant decrease in ischemic stroke with DAPT
- ★ Increased occurrence of bleeding events when used beyond 90 days
- ★ Consider use of a PPI for duration of DAPT

(1) Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947. doi:10.1161/STR.0b013e318284056a. Accessed August 8, 2016 (2) Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236. doi:10.1161/STR.0000000000000024.

Proton Pump Inhibitors and Clopidogrel

- PPI gastroprotection or treatment of GERD
- Avoid using omeprazole or esomeprazole
- Pantoprazole safest selection
  - Ontario patients, >66 years old on plavix for MI
  - Use with pantoprazole did not impact reinfarction



Box 1. Patient risk factors to consider for gastroprotection with a PPI

Prescribe PPIs to patients who are taking DAPT and have risk factors for GI bleeding

- ≥1 of the following GI bleeding risk factors:
  - -History of a GI ulcer or bleed
  - -Anticoagulation therapy use
  - -Chronic use of NSAIDs or corticosteroid therapy
- ≥2 of the following GI bleeding risk factors:
  - -Age of 65 y or older
  - -Dyspepsia
  - -Gastroesophageal reflux disease
  - -*Helicobacter pylori* infection
  - -Chronic alcohol use

DAPT—dual antiplatelet therapy, GI—gastrointestinal, NSAID—nonsteroidal anti-inflammatory drug, PPI—proton pump inhibitor.
Data from Abraham et al,[19] Roffi et al,[20] and Andreotti et al.[21]

Koziol K, Merwe V Van der, Yakiwchuk E, Kosar L. Dual antiplatelet therapy for secondary stroke prevention. *Can Fam Physician*. 2016;62(8):640-645.

Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *Can Med Assoc J*. 2009;180(7):713-718.

Aspirin/Dipyridimole ER (Aggrenox)

- **Dose:** ASA 25mg/Dipyridamole ER 200mg po BID
- **Side effects:** headache
- **Guideline recommendations:**
  - Monotherapy for secondary prevention of ischemic stroke

- Primary evidence derived from two main trials: **ESPS-2 and ESPRIT**
  - No difference in mortality, bleeding risk
  - Benefit over aspirin, comparable to clopidogrel

Aspirin/ERDP - Evidence

Trial	Outcome	Safety (harms)	Comments
ESPS-2 N=6602 ASA vs. ERDP vs. ASA+ERDP vs. placebo	Re**duction in stroke or death:**: ● ASA alone: 13% ● ERDP alone: 15.4% ● ASA+ERDP: 23% (p=0.006)	● NS difference in major bleeds ● NS difference in death	**Limitations:** ● ASA only arm received only 25mg po BID
ESPRIT N=2739 ASA (30-325mg) vs ASA-ERDP	**Vascular mortality, non-fatal stroke, non-fatal MI, or non-fatal major bleeding:** NNT=33 over 3.5 years NNT=104 over 1 year	● NS difference in major bleeds ● NS difference in death ● Discontinuation due to headaches: NNH=16 over 2 years	**Limitations:** ● 89% of participants enrolled 1 week after stroke ● 30% of population was TIA ● 23% of pts were already using aspirin at time of event ● wide range of ASA doses used ● p-values not reported
PRoFESS N=20,332 Clopidogrel vs. ASA-ERDP	● NS difference in stroke ● ASA-ERDP did not meet pre-specified non-inferiority	ASA-ERDP, vs clopidogrel: ● Increase in hemorrhagic events ● More discontinuation	**Limitations:** ● Median enrolment after stroke: 15days ● Funded by Boehringer Ingelheim

Aspirin/ERDP - General Practice Principles

- Must use the manufactured combination product
  - Clinical benefit is not observed with immediate release dipyridamole
- Considerations
  - Most expensive antiplatelet
  - Twice daily dosing - compliance and pill burden
  - Side effects: 1 in 4 patients discontinued use due to headache
- Compared to aspirin alone:
  - Only prevents 1 additional event, per 100 patients treated
    - Events include: vascular death, MI or major bleed

Comparative costs of therapy

- Cost may be prohibitive to patients accessing each therapy equally
- May be a consideration when selecting which antiplatelet to select

Drug and dose	Cost/tablet*	Cost for 1 month (30-days)
Aspirin 81mg	OTC	<$3
Entrophen 325mg	$0.0280	$0.84
Clopidogrel 75mg po daily	$0.4735	$14.21
Aggrenox 25/200mg	$0.8746	$26.24

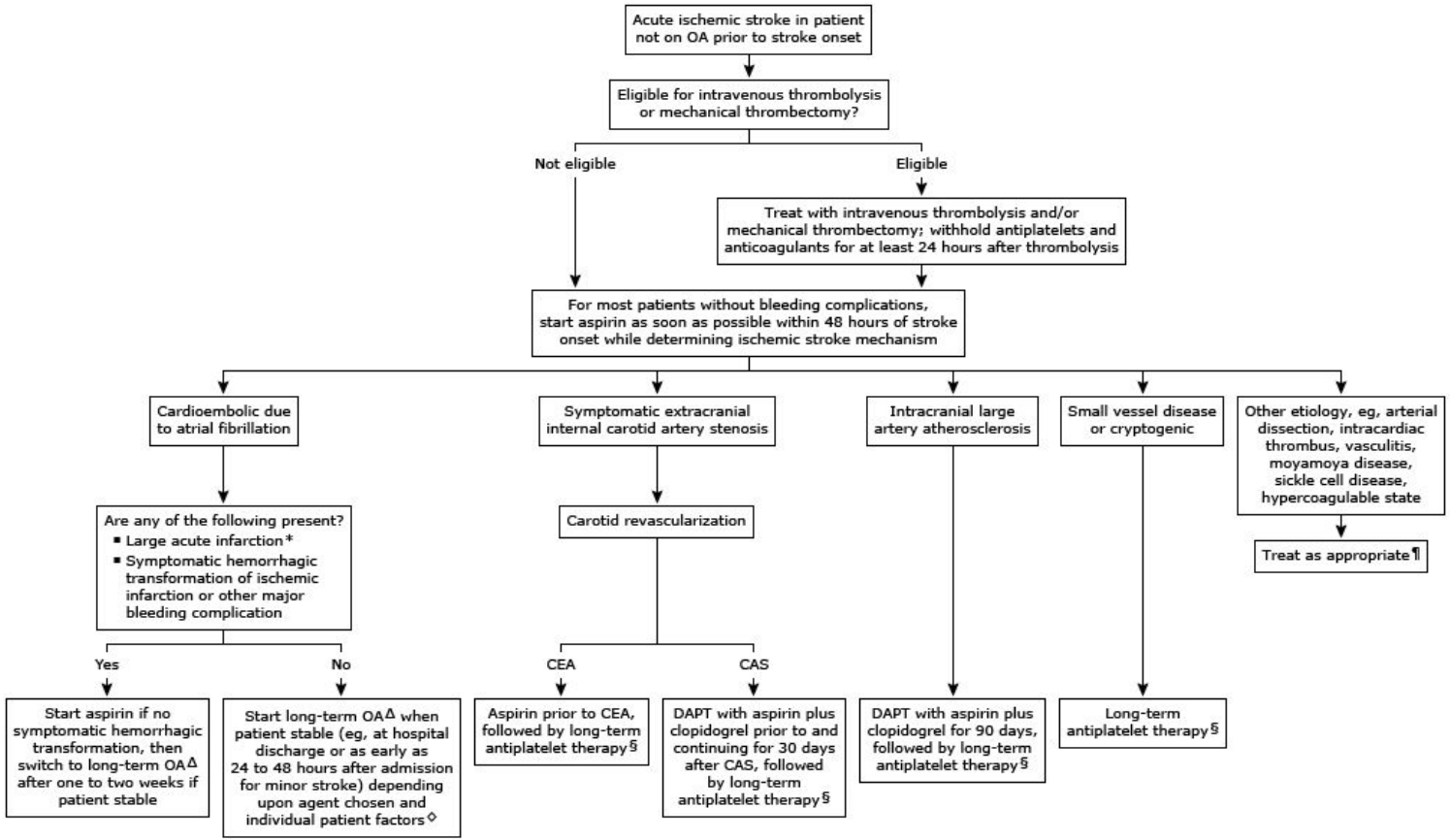
*ODB costs accurate as of Aug.4, 2016

https://www.formulary.health.gov.on.ca/formulary/. Accessed August 4, 2016.
RxFiles Oral Antiplatelet & Antithrombotic Agents: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf. Accessed Aug.4, 2016

Selecting an agent

- ASA/ERDP may provide additional benefit over ASA
- ASA/ERDP and clopidogrel are likely comparable
- ASA and Clopidogrel offer similar CV benefits

- Consider patient specific factors:
  - Cost
    - Aspirin is the most affordable agent
  - Compliance
    - Aggrenox requires twice daily dosing
    - Both aspirin and clopidogrel are once daily
  - Side effects
    - Aggrenox may be discontinued due to headache



Approach to antithrombotic therapy for acute ischemic stroke

Cucchiara BL, Messe SR. Antiplatelet therapy for secondary prevention of stroke. UpToDate. Last updated January 21, 2016. Accessed August 12, 2013

Patient Case D.T - continued

You are the pharmacist working on the floor where D.T is admitted. D.T has been stable for 30 hours.

Labs and vitals:
BP 145/88
Hgb 125, Plt 257, CrCl 75ml/min

Do you initiate VTE prophylaxis?
When do you initiate it?
What therapy do you choose?

A) Yes, place IPC devices on right away
B) Yes, start a heparin product right away
C) No, wait 48 hours before starting
D) This patient does not require VTE prophylaxis

Answer: **B**

Risk of VTE & Prophylaxis

- Highest risk is between 2-7 days after stroke
- Unrecognized PE are the cause of 13-25% of deaths, 2-4 weeks post-stroke
- Assess **ALL** patients for VTE risk within 24 hours
- Options:
  - Enoxaparin 40mg subQ daily
  - Heparin 5000units subQ BID
  - Intermittent pneumatic compression (IPC) devices
- If tPA was administered: Wait 24 hours to initiate enoxaparin or UFH
- Prophylaxis should be continued until the patient is mobile

Medical complications of stroke. UpToDate.
Casaubon LK, Boulanger J-M, Glasser E, et al. Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015. *Int J Stroke*. 2016;11(2):239-252.

VTE prophylaxis

- Patients at high risk of VTE are defined as:
  - Unable to move one or both limbs, or unable to move independently
  - History of VTE
  - Comorbid cancer
- Ischemic stroke patients with high VTE risk:
  - IPC should be applied within 24hrs of presentation.
    - If >24hrs, rule out DVT with ultrasound before applying IPC
  - Low molecular weight heparin or unfractionated heparin within 24-48h
- Hemorrhagic stroke patients with high VTE risk
  - May give LMWH or UFH after 2-4 days (LMWH preferred)
  - IPC device preferred if bleed risk remains high

VTE prophylaxis agents

- Enoxaparin is preferable to UFH in patients with normal renal function
  - **PREVAIL trial:** ischemic stroke patients within the last 48hrs
  - Enoxaparin 40mg daily vs. Unfractionated Heparin 500 units BID
  - 43% lower risk of DVT in patients who received Enoxaparin at 2-weeks
    - Enoxaparin 10% vs UFH 18% ($p<0.0001$)
  - No significant difference in bleeding events at 90-days
  - Benefits in preventing VTE observed at 1, 2 and 3 months
- Patients with CrCl<30ml/min, select UFH

Casaubon LK, Boulanger J-M, Glasser E, et al. Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015. *Int J Stroke*. 2016;11(2):239-252. doi:10.1177/1747493015622461.

VTE prophyalxis - IPC

- IPC is contraindicated in patients with:
  - Peripheral vascular disease
  - Peripheral edema
  - Leg ulceration or wounds
  - Dermatitis
- When using, monitor for:
  - Skin ulceration or barrier breakdown

Patient Case D.T. - continued

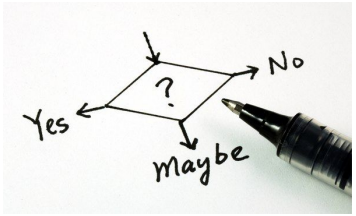
It has been 5 days since D.T. was admitted with a mild ischemic stroke.

He is starting to ambulate with assistance from the physiotherapist and discussions around discharge planning are underway.

A resident asks your opinion on whether they can re-start D.T.'s anticoagulant for A.fib.

When do you re-initiate D.T.'s anticoagulant for atrial fibrillation?

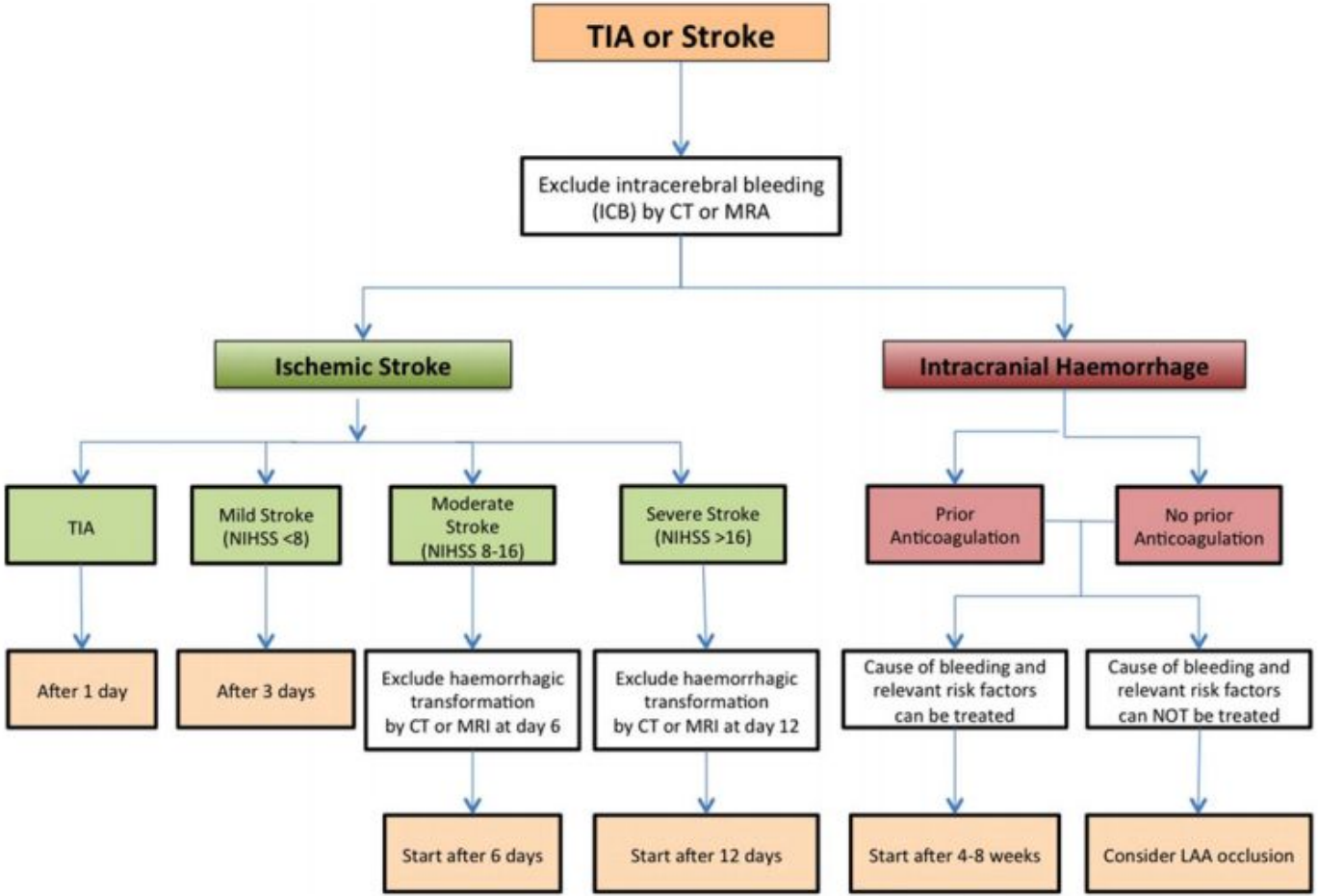
A) Today
B) Two weeks after the stroke
C) D.T.'s long-term anticoagulation should be re-assessed
D) Need more information



Atrial fibrillation

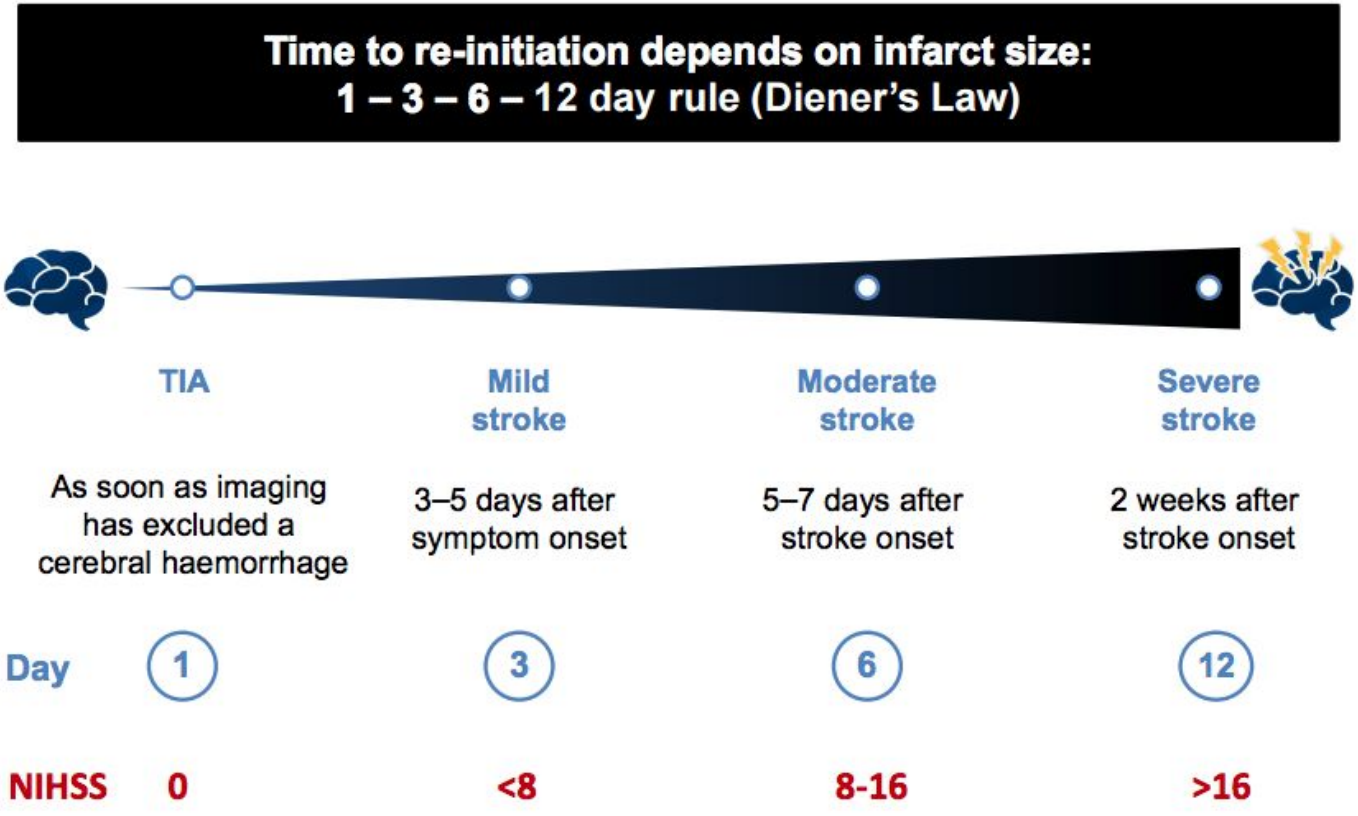
- Stroke recurrence due to Afib can be up to 8% in first two weeks post-stroke
- Balance risk of hemorrhagic transformation, with clot risk
- Preference for pharmacotherapy:
  - Use oral anticoagulants, over DAPT or aspirin alone.
  - Use of any DOAC is preferred over warfarin
  - In those who won't use anticoagulant, DAPT >ASA
- Can start 1-2 weeks, based on severity of the stroke

Guidelines: Chest 2012, CSBPR 2014.



Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. *Bayer Healthc Pharm Healthc Pharm Eur Hear J Adv Access*. 2016.

Re-starting anticoagulation after ischemic stroke



Patient D.T - answers

VTE prophyalxis

- High risk for DVT
- No evidence of hemorrhage on initial CT
- Enoxaparin is appropriate for him

When to re-start his anticoagulation?

- Mild stroke (~NIHSS<8), therefore re-start apixaban 5-7 days after stroke onset
- Ensure no hemorrhagic transformation
- Absence of any active bleeding

Re-starting antiplatelet and anticoagulants?

Agent to resume	Ischemic Stroke	Hemorrhagic Stroke
Single antiplatelet	Within 24hrs	Only start in those who have high ischemic risk and low ICH recurrence
DAPT	*Within 24-48hrs, for 21 days (or for other valid indications)	Unlikely to be beneficial for stroke unless there are other indications
Anticoagulation for Afib	*depends on stroke severity	*depends on patient factors, antidote use
Agents for VTE prophylaxis	Immediately-24hrs	48 hours if high risk (within 24hrs if IPC)

If patient received tPA, avoid re-starting any antiplatelet or anticoagulant within 24hrs

Wejdicks EF. The use of antithrombotic therapy in patients with an acute or prior intracerebral hemorrhage. UpToDate. Last updated April 1, 2014. Accessed August 14, 2016
Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. doi:10.1111/ijs.12439.

Continuity of care

Pharmacist's Role


LEARN THE SIGNS OF STROKE
FACE is it drooping?
ARMS can you raise both?
SPEECH is it slurred or jumbled?
TIME to call 9-1-1 right away.
ACT FAST BECAUSE THE QUICKER YOU ACT, THE MORE OF THE PERSON YOU SAVE.
© Heart and Stroke Foundation of Canada, 2014

How we are doing so far...

Canadian Stroke Network

Réseau canadien contre les accidents cérébrovasculaires

Table 12. Discharge Medications Prescribed to Audit Patients by Stroke Type, Canada 2008/2009

	% Prescribed an Antidepressant	% Prescribed an Antihypertensive	% Prescribed a Lipid Lowering Agent
All Patients with Stroke or Transient Ischemic Attack	**9%**	**71%**	**59%**
Ischemic Stroke	10%	76%	66%
Transient Ischemic Attack	10%	73%	60%
Intracerebral Hemorrhage	9%	68%	33%
Subarachnoid Hemorrhage	0%	0%	0%

Table 13. Antithrombotic Therapy for Audit Patients with Ischemic Stroke/TIA and Atrial Fibrillation, Canada 2008/2009

	% of Audit Patients with Ischemic Stroke/TIA and Atrial Fibrillation (n=5,229 patients)
% Receiving Antiplatelet Therapy	50%
% Receiving Anticoagulant Therapy	66%
% Receiving Either Antithrombotic Therapy	92%

Report: The Quality of Stroke Care in Canada 2011. http://www.strokebestpractices.ca/wp-content/uploads/2011/06/QoSC-EN.pdf/. Accessed Aug.4, 20214

Pharmacists optimizing care

- Complete a hospital discharge medscheck
- Ensure major risk factors for stroke recurrence are being treated & follow-up!
  - Hypertension
  - Diabetes
  - Smoking
  - Dyslipidemia
- Provide support, pharmacological options, strategies for success, follow-up
- Refer to other allied health and community resources if required

Furie KL & Rost NS. (2016) Overview of secondary prevention of ischemic stroke. UpToDate. Last Updated July 25, 2016. Accessed August 3, 2016

Pharmacist's Checklist:

A - Antiplatelet & A1C

B - Blood pressure

C - CV risk factors (smoking, diabetes, cholesterol)

D - Drugs & Diet

E - Exercise

Modified from: http://www.diabetes.ca/diabetes-and-you/complications/heart-disease-stroke.

Patient Case

Remember D.T?

- 62 year old male
- Type 2 diabetic
- Dyslipidemia
- Hypertension
- GERD
- Arthritis
- Atrial fibrillation
- Stressful desk job
- Drinks 10 alcoholic drinks/week
- Non-smoker
- Plays 1 round of golf each weekend

Medication

Metformin 1000mg po BID CC
Simvastatin 10mg po daily
Amlodipine 5mg po daily
Nexium 20mg po daily
Apixaban 5mg po BID
Aleve 220mg po daily PRN pain

Relevant Labs:

6'0, 190lbs (BMI=26.4)
HbA1C = 7.5 (June, 2016)
LDL= 3.0 mmol/L
Home BP~150/90 mmHg
SCr 89, CrCl~ 87ml/min

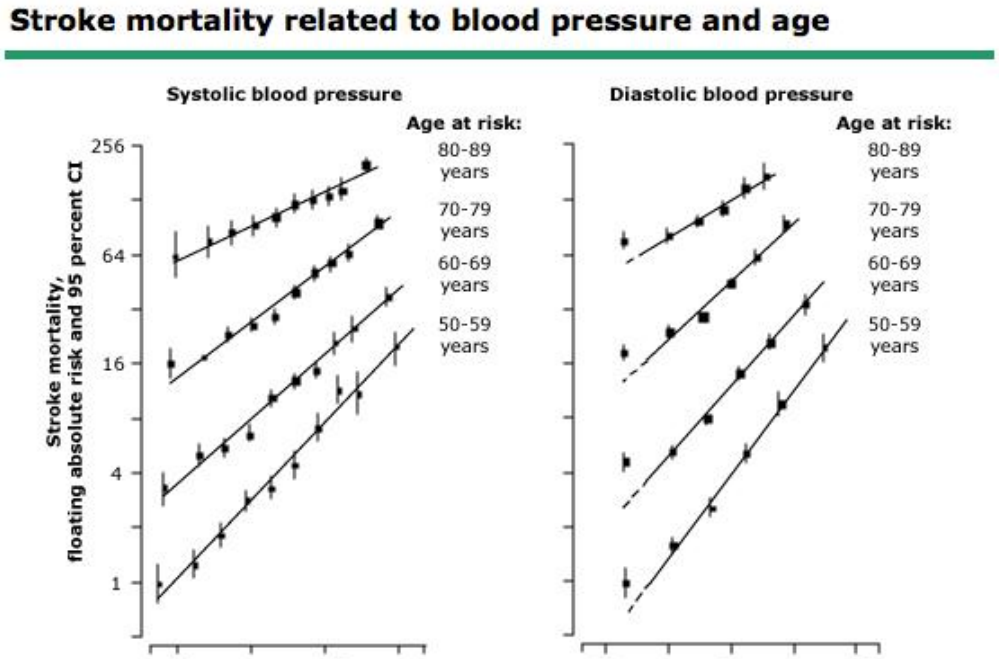
Which of the following steps should D.T. take?

To prevent stroke recurrence:

- ❑ Should target his blood pressure to <130/80 mmHg
- ❑ Achieve target blood pressure by increasing current medication dose first
- ❑ Start ezetimibe to better control his cholesterol
- ❑ Add on an SGLT2 inhibitor to his diabetic regimen
- ❑ Adopt the DASH (dietary approaches against hypertension) diet
- ❑ Stop drinking alcohol
- ❑ Start walking 45 minutes each night after work

Blood Pressure

- Hyperacute BP management differs from long-term secondary prevention
- Increases in SBP and DBP correlate with increasing stroke mortality
- BP lowering therapy shows a reduction in stroke recurrence, regardless of the patient's baseline



Preferred agents

- Lowering blood pressure manages the biggest risk factor of stroke
- If pre-existing hypertension, restart therapy 24hrs after stroke (if stable)
- 1st line agents: **ACE inhibitor + thiazide** (CHEP 2016, AHA 2014)
  - Add on additional agents in order to reach target blood pressures
  - Personalize therapy according to patient characteristics
- PROGRESS trial
  - Combination of Lisinopril 4mg + Indapamide 2.5mg
  - Reduced BP by 12/5 mmHg and stroke incidence decreased:
    - **Stroke RRR 28% over 4 years**
  - Benefit in both normotensive (136/79) and hypertensive (159/94) groups

1. Leung AA, Nerenberg K, Daskalopoulou SS, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can J Cardiol*. 2016;32:569-588. 2. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236.

Hypertension diagnosis

- Initiate antihypertensives in those who are newly diagnosed with hypertension
- Is there value in intensive BP targets (SBP <120 mmHg)?
  - SPRINT trial excluded patients with history of stroke
  - Increase in adverse effects
  - Pill burden and cost of extra medication to achieve targets
- Adhere to CHEP 2016 targets

CHEP 2016 targets

Population	Target range (mmHg)
Adults <80 years	<140/90
Adults >=80 years	SBP <150
Adults with diabetes	<130/80

(1) Leung AA, Nerenberg K, Daskalopoulou SS, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can J Cardiol*. 2016;32:569-588. (2) Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee.

Statin therapy

- Verify all stroke patients are on high-intensity statins
- CSBR 2015 recommends for ischemic stroke patients:
  - Achieve either 50% reduction in LDL, or target LDL <= 2.0 mmol/L
- Statins are not indicated to prevent hemorrhagic stroke
- Optimize statin doses before adding on ezetimibe to achieve LDL targets
- Statin-intolerant patients, try:
  - Lower-intensity regimen
  - A different statin
  - A drug holiday, then re-challenge

INTENSITY	STATIN OPTIONS
Low	Pravastatin 10–20 mg; lovastatin 10–20 mg; simvastatin 5–10 mg; atorvastatin 5 mg; rosuvastatin 2.5 mg
Moderate	Pravastatin 40–80 mg; lovastatin 40–80 mg; simvastatin 20–40 mg; atorvastatin 10–20 mg; rosuvastatin 5–10 mg
High	Atorvastatin 40–80 mg; rosuvastatin 20–40 mg

(1) Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. (2) Allan GM, Lindblad AJ, Comeau A, et al. Simplified lipid guidelines: Prevention and management of cardiovascular disease in primary care. *Can Fam physician Médecin Fam Can*. 2015;61(10):857-867, e439-e450.

Statin therapy

- SPARCL trial
  - Atorvastatin 80mg vs. placebo
  - Mean LDL levels reduced <2.0mmol/L on treatment
    - 1.9mmol/L (atorvastatin) vs. 3.3mmol/L (placebo)
  - Stroke recurrence reduced by 15% (NNT 5.3 over 4.9 years)
  - No change in overall mortality
  - Safety:
    - Increase in LFTs however no significant increase in myopathy (NNH=59)
    - Increase in hemorrhagic stroke (NNH= 112)

(1) Amarenco P Callahan A, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators BJ. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549. (2) Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee.

Glycemic Control

- Stroke risk increased 2-fold with diabetes
- Target HbA1C < 7
- Optimize therapy to align with patient values and daily regimen
- Consider agents with evidence to reduce CV outcomes (composite endpoints)

- Recent evidence:
  - Empagliflozin: (10mg or 25mg daily vs. placebo)
    - Death from CV causes, non-fatal stroke or MI reduced (NNT= 63 over 3.1 years)
    - Non-significant increase in fatal or nonfatal stroke (3.5 vs. 3.0%, p=0.26, HR 1.18)
  - Liraglutide: (1.8mg SubQ daily vs. placebo)
    - Death from CV causes, non-fatal stroke or MI reduced (NNT=53 over 3.8 years)
    - Non-significant decrease in non-fatal stroke (3.4% vs. 3.8%, p=0.3)

(1) Sharma M, Gubitz G. CDA Guidelines - Chapter 27: Management of Stroke in Diabetes. Canadian Diabetes Association Clinical Practice Guidelines. (2) Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):1-12. (3) Steven MP, Gilbert DH, Kirstine B-F, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *Dallas (SPM); Massachusetts Gen Hosp*. 2016;375(4):311-322.

Diet and Exercise

- Reinforce healthy eating habits to promote optimal control of diabetes, cholesterol and blood pressure.
  - Review carb counting and the importance of regular meals
- Minimize salt (<2g per day) and saturated fat intake
- increase potassium intake (new - CHEP 2016)
- Selection of appropriate meal replacements, supplements
- DASH diet, Mediterranean diet
  - Referral to dieticians (free via EatRight)
  - Outpatient diabetes education sessions

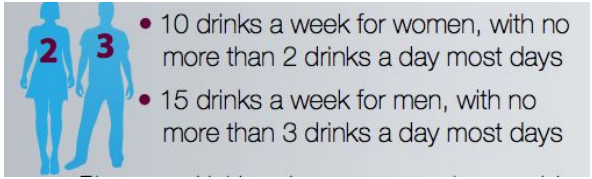
EatRight Ontario

1-877-510-510-2

(1) Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. (2) https://www.eatrightontario.ca/en/default.aspx

Diet and Exercise

- Motivate patients to get active
  - CSBR recommends 150 minutes of activity each week
  - Get moving at least 4 times/week, for more than 10 minutes
  - Suggest ways to track progress and adjust goals (ie. activity trackers, fitness logs)
- Help patients achieve health BMI (18.5 - 24.9 kg/m^2)
  - Reasonable and healthy weight loss goals
- Encourage patients to be mindful of alcohol intake
  - Canadian Low-Risk Alcohol Drinking Guidelines



"A drink"

Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. (2) Canada's Low-Risk Alcohol Drinking Guidelines (LRDG) http://www.ccsa.ca/Resource%20Library/2012-Canada-Low-Risk-Alcohol-Drinking-Guidelines-Brochure-en.pdf. Accessed August 13, 2016

Blood Pressure Benefits of Healthy Lifestyle

Cumulative actions contribute to a reduction in the largest risk factor for stroke

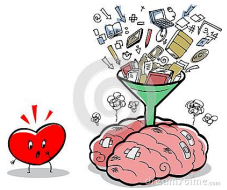
Action	Intervention	SBP/DBP (mmHg) Reduction
Reduced sodium intake	Maximum 1.8g/day	5.0 / 2.7.
Potassium supplementation	Intake of 1.9g/day	4.4 / 2.5
Weight loss	Per kg lost	1.1 / 0.9
Alcohol intake	Decrease drinks to 1-2 /day	3.9 / 2.4
Aerobic exercise	120-150 min/week	4.9 / 3.7
Diet improvements	DASH diet	11.4 / 5.5

Adapted from: Padwal R, Campbell N, Touyz RM, Canadian Hypertension Education Program. Applying the 2005 Canadian Hypertension Education Program recommendations: 3. Lifestyle modifications to prevent and treat hypertension. *CMAJ*. 2005;173(7):749-751.

Which of the following steps should D.T. take?

Yes	Should target his blood pressure to <130/80mmHg
No	Achieve target blood pressure by increasing current medication dose first
No	Start ezetimibe to better control his cholesterol
No	Add on an SGLT2 inhibitor to his diabetic regimen
Yes	Adopt the DASH diet
No	Stop drinking alcohol
Maybe	Start walking 45 minutes each night after work

Practice Pearls



Ischemic Stroke

- ★ Wait 24h after tPA to initiate *any* antiplatelet or anticoagulant for any indication
- ★ Select a single antiplatelet agent that is tailored to the patient
  - Consider applicability of evidence, cost, compliance, side effects
- ★ If DAPT is prescribed for ischemic strokes, therapy should be 21 days
- ★ Only use anticoagulants when indicated for ischemic strokes of cardioembolic origin, or appropriate indications
- ★ Start VTE prophylaxis for eligible ischemic stroke patients within 24h
  - ICP for patients with high bleed risk;
  - Otherwise Enoxparin > UFH (unless CrCl<30ml/min)

Practice Pearls

- ★ Treat blood pressure preferentially with ACE inhibitors and diuretic, to target of <140/90 (<130/80 for diabetics)
- ★ Use high intensity statins to reduce LDL by 50% of to target of <2.0 mmol/L
- ★ Optimize glycemic control to target A1C<7
- ★ Promote healthy lifestyle, diet and exercise habits
- ★ Encourage use of PPI for gastroprotection and reduced use of NSAIDs for minimizing GI bleeds

References

- Chutinet A, Furie KL, Barnett HJM. Antiplatelet therapy. In: Stroke Prevention, Treatment and Rehabilitation. Spence D & Barnett HJM (eds). 2012. McGraw Hill. pp.98-118
- Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947. doi:10.1161/STR.0b013e318284056a. Accessed August 8, 2016
- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236. doi:10.1161/STR.0000000000000024.
- Leung AA, Nerenberg K, Daskalopoulou SS, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can J Cardiol*. 2016;32:569-588. doi:10.1016/j.cjca.2016.02.066.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):1-12. doi:10.1056/NEJMoa1504720.
- Steven MP, Gilbert DH, Kirstine B-F, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *Dallas (SPM); Massachusetts Gen Hosp*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.
- Sharma M, Gubitz G. CDA Guidelines - Chapter 27: Management of Stroke in Diabetes. Canadian Diabetes Association Clinical Practice Guidelines. http://guidelines.diabetes.ca/executivesummary/ch27. Published 2013.
- Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *Can Med Assoc J*. 2009;180(7):713-718. doi:10.1503/cmaj.082001.

References

- Coutts SB, Wein TH, Patrice Lindsay M, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014 and on behalf of the Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. doi:10.1111/ijs.12439.
- Karam JG, Loney-Hutchinson L, McFarlane SI. High-Dose Atorvastatin After Stroke or Transient Ischemic Attack: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. *J Cardiometab Syndr*. 2008;3(1):68-69. doi:10.1111/j.1559-4572.2008.07967.x.
- Furie KL & Rost NS. (2016) Overview of secondary prevention of ischemic stroke. UpToDate. Last Updated July 25, 2016. Accessed August 3, 2016
- Kaplan NM & Townsend RR (2016) Antihypertensive therapy to prevent recurrent stroke or transient ischemic attack. UpToDate. Last updated March 21, 2016. Accessed August 3, 2016
- Kosar L, Koziol K, Martens A. April 2016. RxFiles Duation of DAPT and TT Online Extras. http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-DAPT-TT.pdf.
- Allan GM, Lindblad AJ, Comeau A, et al. Simplified lipid guidelines: Prevention and management of cardiovascular disease in primary care. *Can Fam physician Médecin Fam Can*. 2015;61(10):857-867, e439-e450.
- Chen Z, Sandercock P, Pan H, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. *Stroke*. 2000;31(6):1240-1249. doi:10.1161/01.STR.31.6.1240.
- Diedler J, Ahmed N, Sykora M, et al. Safety of Intravenous Thrombolysis for Acute Ischemic Stroke in Patients Receiving Antiplatelet Therapy at Stroke Onset. *Stroke*. 2010;41(2):288-294. doi:10.1161/STROKEAHA.109.559724.Accessed August 8, 2016
- Pharmacist's Letter Document#290612. June 2013. Alteplase (tPA) for Stroke in Patients Taking an Antithrombotic. Accessed August 8, 2016

References

- Koziol K, Merwe V Van der, Yakiwchuk E, Kosar L. Dual antiplatelet therapy for secondary stroke prevention. *Can Fam Physician*. 2016;62(8):640-645.
- Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. *Bayer Healthc Pharm Healthc Pharm Eur Hear J Adv Access*. 2016. doi:10.1093/eurheartj/ehw058.
- Casaubon LK, Boulanger J-M, Glasser E, et al. Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015. *Int J Stroke*. 2016;11(2):239-252. doi:10.1177/1747493015622461.
- Canada's Low-Risk Alcohol Drinking Guidelines (LRDG) http://www.ccsa.ca/Resource%20Library/2012-Canada-Low-Risk-Alcohol-Drinking-Guidelines-Brochure-en.pdf. Accessed August 13, 2016
- Padwal R, Campbell N, Touyz RM, Canadian Hypertension Education Program. Applying the 2005 Canadian Hypertension Education Program recommendations: 3. Lifestyle modifications to prevent and treat hypertension. *CMAJ*. 2005;173(7):749-751. doi:10.1503/cmaj.050186.
- Wejdicks EF. The use of antithrombotic therapy in patients with an acute or prior intracerebral hemorrhage. UpToDate. Last updated April 1, 2014. Accessed August 14, 2016
- Albers GW et al. Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3 Suppl):483S-512S.

Questions?

Supplemental Information

NIH Stroke Scale

Table 3.2. National Institutes of Health Stroke Scale (maximum = 42)

Response	(Score)	Response	(Score)
Level of consciousness		Motor arm (left and right)	
alert	(0)	no drift	(0)
drowsy	(1)	drift before 10 seconds	(1)
stuporous	(2)	falls before 10 seconds	(2)
coma	(3)	no effort against gravity	(3)
		no movement	(4)
Response to level of consciousness questions*		Motor leg (left and right)	
answers both correctly	(0)	no drift	(0)
answers one correctly	(1)	drift before 5-10 seconds	(1)
answers neither correctly	(2)	falls before 5-10 seconds	(2)
		no effort against gravity	(3)
		no movement	(4)
Response to level of consciousness commands†		Ataxia	
obeys both correctly	(0)	absent	(0)
obeys one correctly	(1)	one limb	(1)
obeys neither	(2)	two limbs	(2)
Pupillary response		Sensory	
both reactive	(0)	normal	(0)
one reactive	(1)	mild	(1)
neither reactive	(2)	severe loss	(2)
Gaze		Language	
normal	(0)	normal	(0)
partial gaze palsy	(1)	mild aphasia	(1)
total gaze palsy	(2)	severe aphasia	(2)
		mute or global aphasia	(3)
Visual fields		Facial palsy	
no visual loss	(0)	normal	(0)
partial hemianopsia	(1)	minor paralysis	(1)
complete hemianopsia	(2)	partial paralysis	(2)
bilateral hemianopsia	(3)	complete paralysis	(3)
Dysarthria		Extinction/inattention	
normal	(0)	normal	(0)
mild	(1)	mild	(1)
severe	(2)	severe	(2)

* Level of consciousness questions: "How old are you?" "What month is this?"

† Level of consciousness commands: "Squeeze my hand" (using nonparetic hand), "Close your eyes."

<4 = Good prognosis ... No tPA ... 4-20 = mild to moderate ... ideal tPA ... >20 = severe deficit ... No tPA

http://www.midatlanticneurology.com/scan/nih_stroke_scale.jpg

Criteria for tPA

Exclusion criteria for those presenting <3hrs of stroke:

- Evidence of intracranial hemorrhage on noncontrast head CT
- Only minor or rapidly improving stroke symptoms
- High clinical suspicion of subarachnoid hemorrhage even with normal CT
- Active internal bleeding (e.g., GI/GU bleeding within 21 days)
- Known bleeding diathesis, including but not limited to platelet count <100,000/mm^3 (<100 × 10^{12}/L)
- Patient has received heparin within 48 hours and had an elevated APTT
- Recent use of anticoagulant (e.g., warfarin) and elevated PT (>15 seconds)/INR
- Intracranial surgery, serious head trauma, or previous stroke within 3 months
- Major surgery or serious trauma within 14 days
- Recent arterial puncture at noncompressible site
- Lumbar puncture within 7 days
- History of intracranial hemorrhage, arteriovenous malformation, or aneurysm
- Witnessed seizure at stroke onset
- Recent acute myocardial infarction
- SBP >185 mm Hg or DBP >110 mm Hg at time of treatment

Criteria for tPA

Exclusion criteria for those presenting between 3-4.5 hrs:

- Age greater than 80 years
- Current treatment with oral anticoagulants
- NIH Stroke Scale Score >25 (severe stroke)
- History of both stroke and diabetes

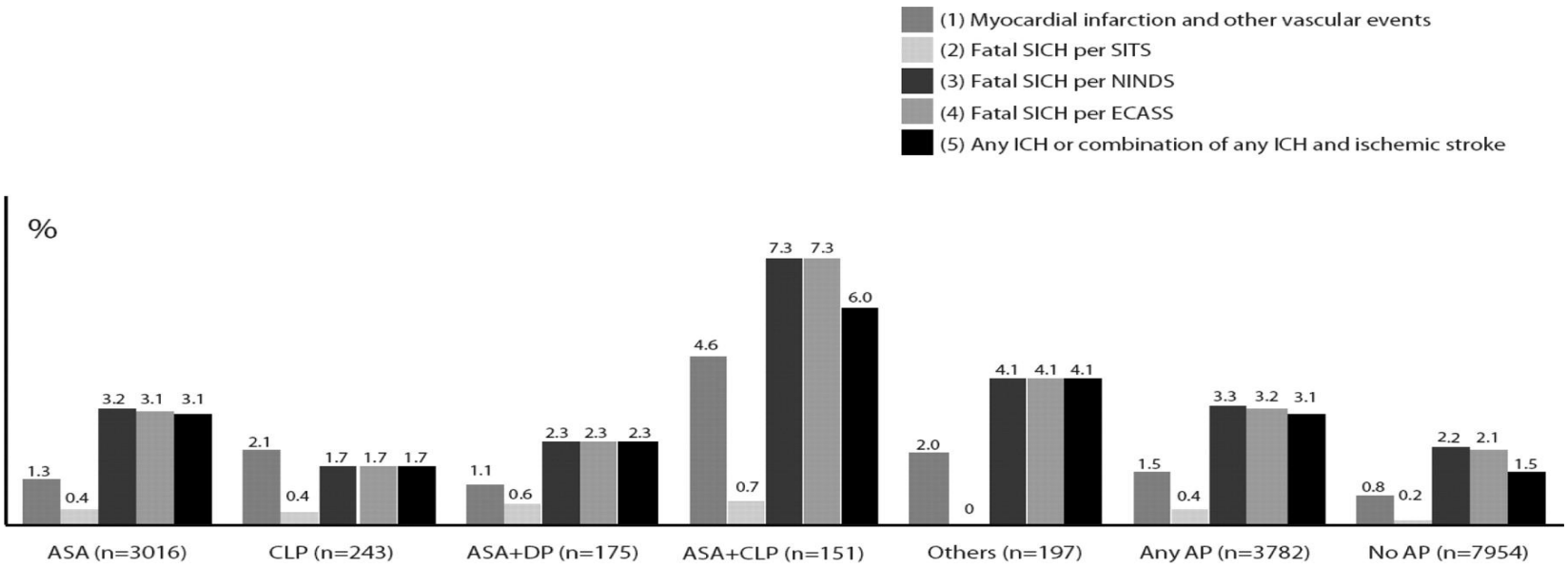
Duration of DAPT

	DAPT coronary stent	TRIPLE THERAPY AF + stent*	DAPT cerebrovascular
Phase I: Initial Therapy **The specialist will select the intended duration of therapy, & will specify if therapy is to be extended.** Initial prescription is usually for:	Clopidogrel + ASA or Prasugrel + ASA or Ticagrelor + ASA x 12 months	Warfarin + Clopidogrel + ASA x 1 to 6 months rarely up to 12 months	Clopidogrel + ASA (single antiplatelet therapy also still an option) x 21 days for ischemic stroke x 90 days for intracranial stent
Phase II: Step Down **Once the intended duration is complete, therapy should be stepped down as directed by the specialist.**	ASA x life-long DAPT may be extended up to 30 months see inside	Warfarin + Clopidogrel (warfarin + ASA or DAPT also an option) up to 12 months post stent then Warfarin x life-long	single antiplatelet x life-long
Tipping Point for Benefit vs Harm: **When DAPT or TRIPLE THERAPY extends beyond the recommended duration, the balance between benefit & harm shifts.**	8 fewer myocardial infarctions 6 more major bleeds per 1,000 patients treated/year with potentially 2 more deaths [1]		ISCHEMIC STROKE 21 days of DAPT ↓ risk of stroke in a Chinese population CHANCE DAPT >90 days ↑ risk of major bleeds & all-cause mortality MATCH, SPS3

*Preferred agents for triple therapy are listed. See inside chart for other options.

http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT%20and%20Triple%20Therapy%20Newsletter%20and%20Chart.pdf

Figure 2. Causes of death, indicated as percentage of subgroup.



Jennifer Diedler et al. Stroke. 2010;41:288-294