Clinical Cases in Secondary Stroke Prevention

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Jacqui Herbert, BScPhm, ACPR

Clinical Pharmacist – Stroke Rehabilitation

Toronto Rehabilitation Institute, UHN

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I have no financial disclosures or conflicts of interest to report

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Learning Objectives

1. In the context of clinical cases:
   a. Review ischemic stroke risk factors, etiologies, and workup
   b. Review major trial outcomes in stroke
   c. Determine appropriate secondary ischemic stroke prevention including considerations for antithrombotic therapy, lipid-lowering therapy, and hypertension management
2. Apply the above knowledge to patient cases to make appropriate clinical decisions

Background

Stroke: term used to describe an abrupt-onset focal neurological deficit that lasts at least 24 hours and is of presumed vascular origin[1]

- Location of the injury determined through imaging studies of the brain (i.e. CT, MRI)
- NIH Stroke Scale (NIHSS) can help quantify impairment from stroke (0-42)

Stroke survivors are at high risk of recurrent stroke, often more severe and disabling than index event[2]

Optimal secondary prevention of stroke requires rapid diagnosis and treatment including prompt identification of the underlying cardiovascular cause[2]

Focus of today's workshop will be cases of **ischemic stroke** prevention beyond the acute phase

1. Fagan S, Hess D. Stroke. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill; 2014: 354.
2. Hankey, G. Secondary stroke prevention. *Lancet Neurol* 2014; 13: 178–94.

Secondary Stroke Prevention

Antithrombotic therapy

- Antiplatelet therapy
- Anticoagulant therapy

Lipid management

Hypertension management

- Acute phase
- Long-term

Diabetes management

Case 1:

Harry is a 54 year old male patient in ER. He woke up with new left arm weakness and left facial droop (last seen well last night at 22:00). CT head was initially negative; MRI confirmed R lacunar infarct.

Past Medical History:
- None known, no GP

Current Medications:
- None

Social History:
- Drinks approximately 20-25 alcoholic drinks per week
- Smokes 1 ppd x 30 years

What medications should be started for appropriate secondary stroke prevention?

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- Weight 88 kg
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- TTE: Normal LV/RV size and function, no obvious thrombus, no significant valvular pathology
- CTA head/neck: Diffuse atherosclerosis without significant stenosis

NIHSS = 3

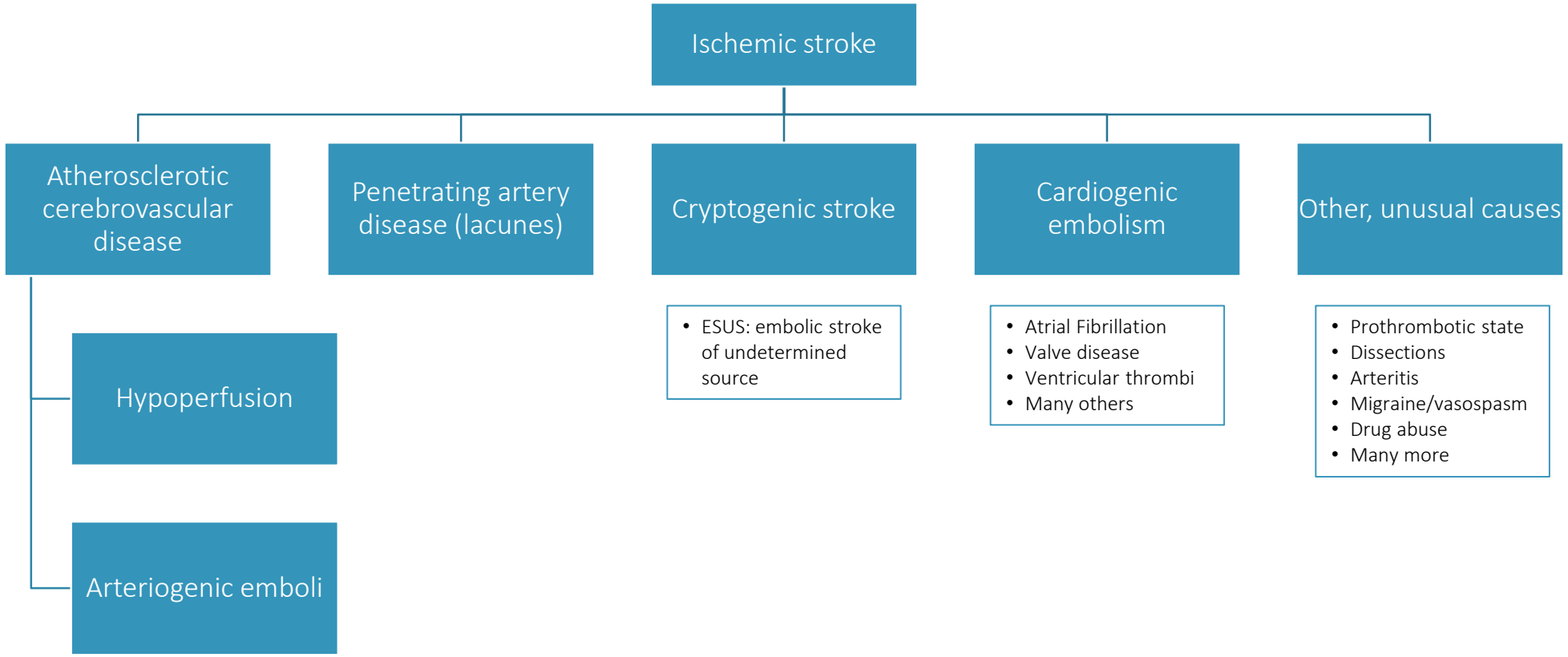
What medications should be started for appropriate secondary stroke prevention?

Polling question: most appropriate antithrombotic therapy for Harry right now?

A. Acetylsalicylic acid (ASA)
B. Clopidogrel
C. ASA and Dipyridamole
D. A, B, or C
E. DAPT – ASA + Clopidogrel x 21-30 days, then SAPT with either agent
F. DAPT – ASA + Clopidogrel x 90 days, then SAPT with either agent
G. Oral anticoagulation

Step one: Determine etiology

Ischemic stroke etiology



Fagan S, Hess D. Stroke. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill; 2014: 354

Ischemic Stroke Workup

Brain imaging

- CT or MRI

Vascular imaging (including carotid imaging)

- CTA or MRA from aortic arch to vertex or carotid ultrasound

12-lead ECG + additional cardiac rhythm monitoring

- For patients being investigated for embolic stroke, ECG monitoring for >24H recommended to detect paroxysmal AF (Holter monitor)
- For patients being investigated for embolic stroke whose short-term ECG monitoring does not reveal AF but cardioembolic mechanism is suspected, prolonged ECG monitoring for at least 2 weeks is recommended in selected patients

Laboratory investigations

- CBC, electrolytes, aPTT, INR, SCr, troponin, hemoglobin A1C, lipid panel

Transthoracic echocardiogram (TTE)

- To assess for valvular abnormalities, visualize thrombus if present, detect wall motion abnormalities
- Bubble study to assess for intraatrial shunt indicating atrial septal defect or patent foramen ovale

Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017

Ischemic Stroke Risk Factors

Lifestyle factors
Unhealthy diet
Physical inactivity
Psychosocial stress
Excessive alcohol intake
Obesity / low waist-to-hip ratio
Cigarette smoking

Medical conditions
Hypertension
Diabetes mellitus
Dyslipidemia
Atrial Fibrillation

Non-modifiable risk factors
Sex (male)
Family history
↑ Age
Race/Ethnicity (Indigenous, South Asian, African)
Personal circumstances (access to healthy food, health and social services)

1. https://www.heartandstroke.ca/stroke/risk-and-prevention
2. O'Donnell MJ, Chin SL, Rangarajan S et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016; 388: 761-765.

Secondary Stroke Prevention

Antithrombotic therapy

- Antiplatelet therapy
- Anticoagulant therapy

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Hypertension management

- Acute phase
- Long-term

Diabetes management

"All patients with ischemic stroke or transient ischemic attack **should be prescribed antiplatelet therapy** for secondary prevention of recurrent stroke unless there is an indication for anticoagulation"[1]

Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017

Antiplatelet therapy in secondary stroke prevention

- Acetylsalicylic acid (ASA) 80-325 mg
- Clopidogrel 75 mg
- Acetylsalicylic acid (ASA) 25 mg – extended-release dipyridamole 200 mg

Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017

DAPT in secondary stroke prevention

ASA and clopidogrel inhibit platelet aggregation synergistically

In some trials of stroke patients, the combination of ASA and clopidogrel has not been successful and increases the risk of bleeding and mortality (MATCH, SPS3)

But, these trials delayed administering secondary prevention until 1-2 months after stroke

More recently, trials have suggested that certain patients may benefit from dual antiplatelet therapy (DAPT), started **right after the event** and continued for a **short period of time**, when the risk of re-stroke is highest

1. Diener HC et al. ASA and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. Jul 24-30 2004;364(9431):331-337
2. Benavente OR et al. Effects of clopidogrel added to ASA in patients with recent lacunar stroke. N Engl J Med. Aug 30 2012;367(9):817-825.

CHANCE (2013)

Population	Patients (in China) 40 years or older, randomized **within 24 hours** after having an acute ischemic stroke (NIHSS 3 or less) or a high-risk TIA ($ABCD^2$ score of 4 or more) of non-cardioembolic origin
Intervention	**DAPT:** Clopidogrel 300 mg load then 75 mg daily x 90 days + ASA 75-300 mg x 1 day then ASA 75 mg daily x first 21 days
Comparison	Placebo + ASA 75-300 mg x 1 day then ASA 75 mg daily x 90 days
Outcome	Stroke (ischemic or hemorrhagic)

The CHANCE investigators. Clopidogrel with ASA in Acute Minor Stroke or Transient Ischemic Attack. *N Engl J Med* 2013;369:11-19.

Table 2. Efficacy and Safety Outcomes.

Outcome	Aspirin (N=2586)		Clopidogrel and Aspirin (N=2584)		Hazard Ratio (95% CI)	P Value
	Patients with Event *no.*	Event Rate %	Patients with Event *no.*	Event Rate %		
Primary outcome						
Stroke	303	11.7	212	8.2	0.68 (0.57–0.81)	<0.001
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	307	11.9	216	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	295	11.4	204	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98
Myocardial infarction	2	0.1	3	0.1	1.44 (0.24–8.63)	0.69
Death from cardiovascular causes	5	0.2	6	0.2	1.16 (0.35–3.79)	0.81
Death from any cause	10	0.4	10	0.4	0.97 (0.40–2.33)	0.94
Transient ischemic attack	47	1.8	39	1.5	0.82 (0.53–1.26)	0.36
Safety outcomes						
Bleeding*						
Severe	4	0.2	4	0.2	0.94 (0.24–3.79)	0.94
Moderate	4	0.2	3	0.1	0.73 (0.16–3.26)	0.68
Mild	19	0.7	30	1.2	1.57 (0.88–2.79)	0.12
Any bleeding	41	1.6	60	2.3	1.41 (0.95–2.10)	0.09

* Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria as follows: severe bleeding was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention; moderate bleeding as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention; and mild bleeding as bleeding not requiring transfusion and not causing hemodynamic compromise (e.g., subcutaneous bleeding, mild hematomas, and oozing from puncture sites).[22]

The CHANCE investigators. Clopidogrel with ASA in Acute Minor Stroke or Transient Ischemic Attack. *N Engl J Med* 2013;369:11-19.

POINT (2018)

Population	Patients (mostly North American) 18 years or older, randomized **within 12 hours** after having an acute ischemic stroke (NIHSS 3 or less) or a high-risk TIA ($ABCD^2$ score of 4 or more) of non-cardioembolic origin
Intervention	**DAPT:** Clopidogrel 600mg load then 75mg daily + ASA 50-325mg daily x 90 days
Comparison	Placebo + ASA 50-325mg daily x 90 days
Outcome	Composite of ischemic stroke, MI, or death from ischemic vascular causes Primary safety outcome – major hemorrhage

The POINT investigators. Clopidogrel and ASA in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med.* 2018

Table 2. Efficacy and Safety Outcomes.

Outcome	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary efficacy outcome				
Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes	121 (5.0)	160 (6.5)	0.75 (0.59–0.95)	0.02
Secondary efficacy outcomes				
Ischemic stroke	112 (4.6)	155 (6.3)	0.72 (0.56–0.92)	0.01*
Myocardial infarction	10 (0.4)	7 (0.3)	1.44 (0.55–3.78)	0.46*
Death from ischemic vascular causes	6 (0.2)	4 (0.2)	1.51 (0.43–5.35)	0.52*
Ischemic or hemorrhagic stroke	116 (4.8)	156 (6.4)	0.74 (0.58–0.94)	0.01*
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	141 (5.8)	167 (6.8)	0.84 (0.67–1.05)	0.13*
Primary safety outcome				
Major hemorrhage	23 (0.9)	10 (0.4)	2.32 (1.10–4.87)	0.02
Other safety outcomes				
Hemorrhagic stroke	5 (0.2)	3 (0.1)	1.68 (0.40–7.03)	0.47
Symptomatic intracerebral hemorrhage	2 (0.1)	2 (0.1)	1.01 (0.14–7.14)	0.99
Other symptomatic intracranial hemorrhage	2 (0.1)	0		0.16
Major hemorrhage other than intracranial hemorrhage	17 (0.7)	7 (0.3)	2.45 (1.01–5.90)	0.04
Minor hemorrhage	40 (1.6)	13 (0.5)	3.12 (1.67–5.83)	<0.001
Death from any cause	18 (0.7)	12 (0.5)	1.51 (0.73–3.13)	0.27

* Post hoc correction for multiple testing of five secondary end points by the Bonferroni method resulted in a P value of 0.01 to indicate a significant difference between groups.

The POINT investigators. Clopidogrel and ASA in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med.* 2018

Table S4. Efficacy and Safety Stratified by Time Period

Time Period	Outcome	Clopidogrel-Aspirin (N=2432)		Aspirin (N=2449)		Hazard Ratio (95% CI)	P Value
		Patients with Event *no.*	Event Rate *%*	Patients with Event *no.*	Event Rate *%*		
0-7 days	Ischemic stroke, MI, or ischemic vascular death	70	2.9%	111	4.5%	0.74 (0.55 - 0.99)	0.04
	Major hemorrhage	7	0.3%	4	0.2%	1.82 (0.53 – 6.22)	0.34
8-90 days	Ischemic stroke, MI, or ischemic vascular death	51	2.1%	49	2.0%	1.03 (0.70-1.53)	0.88
	Major hemorrhage	16	0.7%	6	0.2%	2.69 (1.05 - 6.86)	0.04
0-30 days	Ischemic stroke, MI, or ischemic vascular death	96	3.9%	141	5.8%	0.73 (0.56 - 0.95)	0.02
	Major hemorrhage	12	0.5%	6	0.2%	2.05 (0.76 - 5.56)	0.16
31-90 days	Ischemic stroke, MI, or ischemic vascular death	25	1.0%	19	0.8%	1.30 (0.72 - 2.36)	0.39
	Major hemorrhage	11	0.5%	4	0.2%	2.77 (0.88 - 8.70)	0.08

The POINT investigators. Clopidogrel and ASA in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med.* 2018

From the guidelines…

"In very high risk TIA patients […] or minor stroke of non-cardioembolic origin (NIHSS 0-3), a combination of clopidogrel and ASA **should be given for a duration of 21 to 30 days** followed by antiplatelet monotherapy (such as ASA or clopidogrel alone) [Evidence Level A].

A minimal loading dose of 300 mg Clopidogrel (based on dose in CHANCE) up to 600mg (based on dose used in POINT) and 160 mg of ASA should be given at the start of treatment [Evidence Level A].

Dual antiplatelet therapy should be started **as soon as possible after brain imaging**, within 24 hours of symptom onset, and ideally within 12 hours."

Boulanger JM et al. Canadian Stroke Best Practices Guidelines: Acute Stroke Management. Int J Stroke, 2018.

Case 1:

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Current Medications:
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Relevant Findings & Laboratory Results:
- BP 187/95, HR 77
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- LDL 3.2 mmol/L
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- ECG: Normal Sinus Rhythm
- 48-hour Holter pending, no AF on tele
- TTE: Normal LV/RV size and function, no obvious thrombus, no significant valvular pathology
- CTA head/neck: Diffuse atherosclerosis without significant stenosis

NIHSS = 3

What medications should be started for appropriate secondary stroke prevention?

Polling question: most appropriate antithrombotic therapy for Harry right now?

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Lipid management

Hypertension management

- Acute phase
- Long-term

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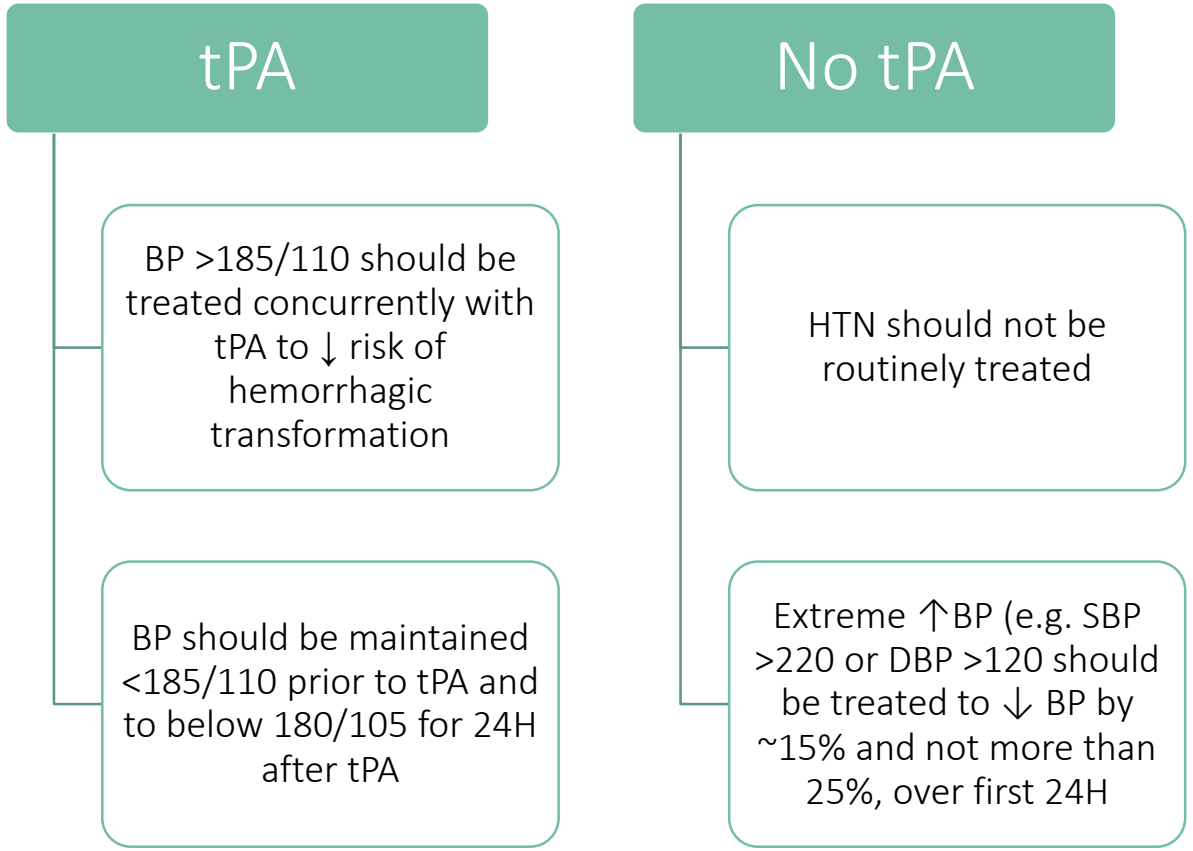
Hypertension: acute phase



Boulanger JM et al. Canadian Stroke Best Practices Guidelines: Acute Stroke Management. Int J Stroke, 2018.

Hypertension: long-term

Hypertension is the single most important modifiable risk factor for stroke prevention

"Randomized controlled trials have not defined the optimal time to initiate blood pressure lowering therapy after stroke or transient ischemic attack. Blood pressure lowering treatment should be **initiated or modified before discharge from hospital** [Evidence Level B]"[1]

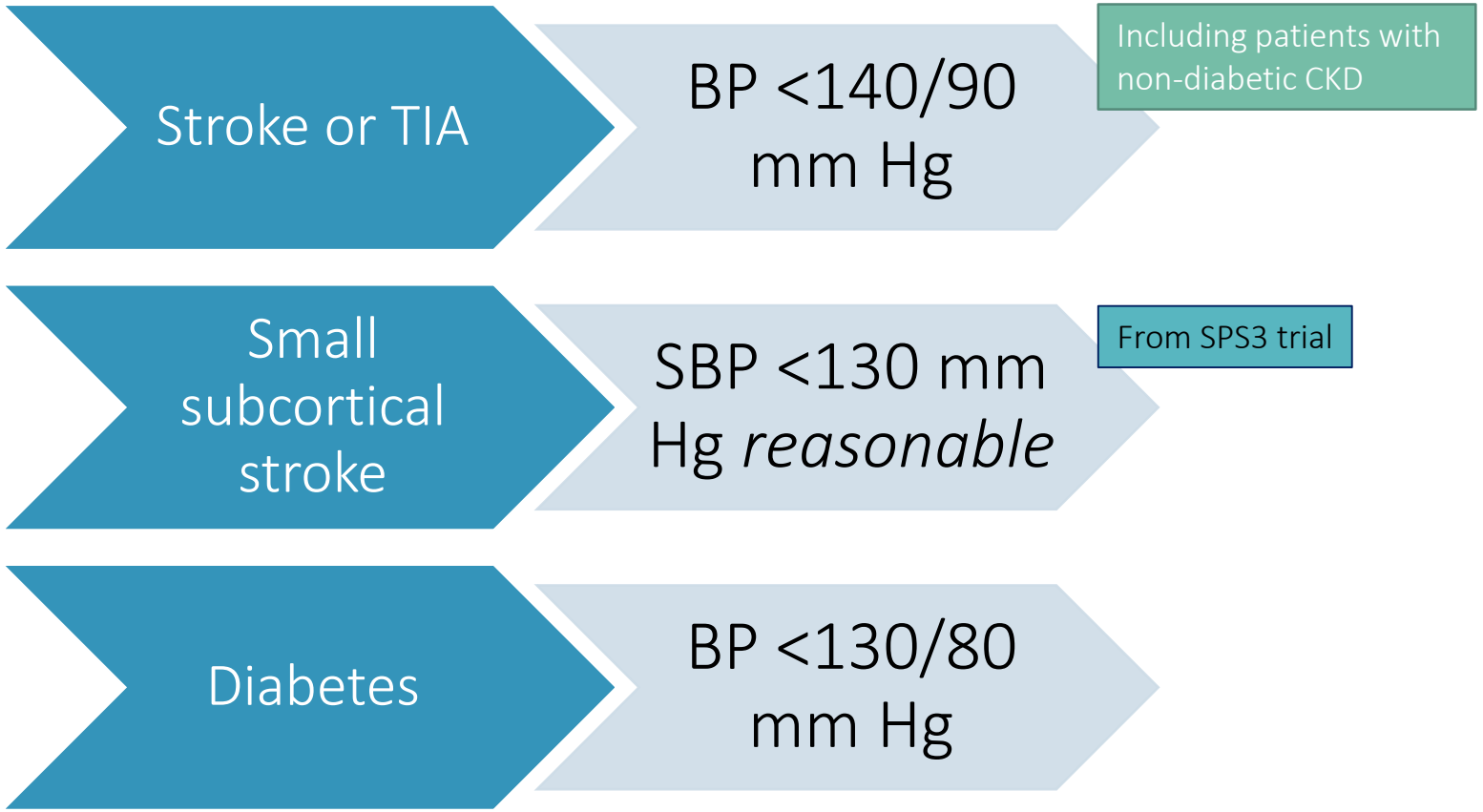
"Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack (Grade A).

Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred (Grade B)"[2]

Based on PROGRESS trial results (2001)

1. Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017
2. Nerenberg, Kara A. et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. *Can J Cardiol*.

Hypertension: long-term targets



Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017

What if…?

The patient was taking ASA 81mg daily prior to the stroke?

Case 2

George is a 64 year old patient admitted to hospital with a new R MCA territory stroke 3 days ago

Past Medical History:
- Hypertension
- BPH

Home Medications:
- Candesartan 32mg PO daily
- Hydrochlorothiazide 25mg PO daily
- Tamsulosin SR 0.4mg PO daily

Relevant Findings & Laboratory Results:
- BP 135/85, HR 68
- Weight 80kg
- HbA1C 5.8%
- LDL 4.5 mmol/L
- Hgb 154 g/dL
- SCr 88 umol/L
- ECG: Normal Sinus Rhythm
- 48-hour Holter : Normal Sinus Rhythm
- TTE: Normal LV/RV size and function, no obvious thrombus, no significant valvular pathology
- CTA head/neck: Extensive intracranial atherosclerosis, including ~80% stenosis of middle cerebral artery

NIHSS 8

What medications should be started for appropriate secondary stroke prevention?

Polling question: most appropriate antithrombotic therapy for George?

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ICAS: Intracranial Atherosclerotic Stenosis

Atherosclerotic lesions affecting intracranial large arteries: **internal carotid, middle cerebral, vertebral,** and **basilar arteries**

Carries a large risk of stroke and is associated with a high risk of recurrent stroke

- Approximately 23% at 1 year despite treatment with ASA and standard management of vascular risk factors

The SAMMPRIS investigators. Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis. *N Engl J Med* 2011;365:993-1003.

What is the most appropriate antithrombotic therapy for patients with ICAS?

Management of ICAS

Medical Management

- Anticoagulation
  - Warfarin
  - DOAC
- Antiplatelet therapy
  - SAPT
  - DAPT

Invasive therapy

- Intracranial stenting

Antithrombotic therapy for ICAS

Antiplatelet vs Anticoagulant: Warfarin-ASA in Intracranial Disease (WASID) trial (2005)

Population: Patients with recent TIA or stroke and intracranial artery stenosis of 50 to 99%

Intervention: Dose-adjusted warfarin (INR 2-3)

Comparator: ASA 1300 mg daily

Outcome: Ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke

Results: Enrollment ended early (after 569 patients) because of safety concerns in warfarin group

Endpoint	ASA vs. Warfarin
Death	4.3% vs 9.7% [HR 0.46 (0.23-0.90)]
Major hemorrhage	3.2% vs 8.3% [HR 0.39 (0.18-0.84)]
MI or sudden death	2.9% vs 7.3% [HR 0.40 (0.18-0.91)]
Death from vascular causes	3.2% vs 5.9%
Primary end point	22.1% vs 21.8% [HR 1.04 (0.73-1.48)]

Chimowitz MI, et al. "Comparison of warfarin and ASA for symptomatic intracranial arterial stenosis." *N Engl J Med*. 2005. 352(13):1305-1306.

WASID (2005)

Failure of warfarin therapy mainly driven by high bleed incidence

Table 4. Post Hoc Analysis of On-Treatment, INR-Specific Rates of Major Hemorrhage, Ischemic Stroke, and Major Cardiac Events among Patients Randomly Assigned to Receive Warfarin.*

INR Category†	No. of Patient-yr‡	Major Hemorrhage		Ischemic Stroke		Major Cardiac Event§	
		No. of Events	No. of Events per 100 Patient-yr (95% CI)	No. of Events	No. of Events per 100 Patient-yr (95% CI)	No. of Events	No. of Events per 100 Patient-yr (95% CI)
<2.0	92.5	1	1.1 (0.03–6.0)	23	24.9 (15.8–37.3)	10	10.8 (5.2–19.9)
2.0–3.0	256.9	9	3.5 (1.6–6.6)	13	5.1 (2.7–8.7)	1	0.4 (0.01–2.2)
3.1–4.4	52.6	8	15.2 (6.6–30.0)	3	5.7 (1.2–16.7)	3	5.7 (1.2–16.7)
≥4.5	4.9	6	123.3 (45.3–268.4)	1	20.6 (0.5–114.5)	0	0 (0–61.6)

* The analysis did not include follow-up time or events while patients were not receiving study medication. The events not included were 3 of 27 major hemorrhages, 9 of 49 ischemic strokes, and 7 of 21 major cardiac events. INR denotes international normalized ratio, and CI confidence interval.
† The categories coincide with the prespecified target INR range (2.0 to 3.0) and critically high INR range (≥4.5).[13]
‡ The method assumed a linear interpolation to estimate INRs between consecutive INR tests. For example, if two consecutive INRs obtained a month apart were in the therapeutic range, the method assumed that the INR was in the therapeutic range for the entire month.
§ A major cardiac event was defined as myocardial infarction or sudden death.

Chimowitz MI, et al. "Comparison of warfarin and ASA for symptomatic intracranial arterial stenosis." *N Engl J Med*. 2005. 352(13):1305-1306.

SAMMPRIS (2011)

Population	Patients with recent TIA or stroke with ICAS of 70-99% of the diameter of a major intracranial artery
Intervention	Aggressive medical management using ASA 325 mg + clopidogrel 75 mg x 90 days PLUS angioplasty + stenting
Comparison	Aggressive medical management using ASA 325 mg + clopidogrel 75 mg x 90 days
Outcome	Stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days

Results:

- Enrollment ended after 451 patients randomized because 30-day rate of stroke or death was 14.7% in the stent group and 5.8% in the medical management group
- 1- year rate of primary endpoint in stent group was 20.0% vs 12.2% in the medical management group

The SAMMPRIS investigators. Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis. *N Engl J Med* 2011;365:993-1003.

“Aggressive medical management”

Identical between the two groups:

- ASA 325 mg daily + Clopidogrel 75 mg daily for 90 days after enrolment
- Management of primary risk factors:
  - *Target SBP <140 mmHg (<130 mmHg for diabetic patients)*
  - *Target LDL <1.81 mmol/L*
- Management of secondary risk factors:
  - *Diabetes*
  - *Elevated non-HDL*
  - *Smoking*
  - *Excess weight*
  - *Insufficient exercise*

The SAMMPRIS investigators. Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis. *N Engl J Med* 2011;365:993-1003.

Table 3. Primary and Secondary End Points and Other Major Adverse Events.

End Point	Medical-Management Group (N=227)			PTAS Group (N=224)			P Value*
	Patients with Event	Probability at 30 Days	Probability at 1 Yr	Patients with Event	Probability at 30 Days	Probability at 1 Yr	
	no. (%)	*% (95% CI)*		*no. (%)*	*% (95% CI)*		
Primary end point†	26 (11.5)	5.8 (3.4–9.7)	12.2 (8.4–17.6)	46 (20.5)	14.7 (10.7–20.1)	20.0 (15.2–26.0)	0.009
Ischemic stroke in territory of qualifying artery within 30 days after enrollment	10 (4.4)			23 (10.3); 1 fatal (0.4)			
Ischemic stroke in other territory within 30 days after enrollment	2 (0.9)			0			
Symptomatic brain hemorrhage within 30 days after enrollment‡	0			10 (4.5); 4 fatal (1.8)			
Non–stroke-related death within 30 days after enrollment	1 (0.4)§			0			
Ischemic stroke in territory of qualifying artery beyond 30 days after enrollment	13 (5.7)			13 (5.8)			
Secondary end points							
Any stroke or death	37 (16.3)	5.8 (3.4–9.7)	17.5 (12.8–23.6)	52 (23.2)	14.7 (10.7–20.1)	23.4 (18.1–29.8)	0.06
Death¶	7 (3.1)	0.4 (0.1–3.1)	4.1 (2.0–8.5)	7 (3.1)	2.2 (0.9–5.3)	3.4 (1.6–7.2)	0.95
Any stroke	32 (14.1)	5.3 (3.1–9.2)	14.9 (10.6–20.7)	50 (22.3)	14.7 (10.7–20.1)	22.3 (17.2–28.7)	0.03
Ischemic stroke in territory of qualifying artery	23 (10.1)			36 (16.1)			
Ischemic stroke in other territory	8 (3.5)			4 (1.8)			
Symptomatic brain hemorrhage‡	1 (0.4)			10 (4.5)‖			
Disabling or fatal stroke**	13 (5.7)	1.8 (0.7–4.8)	6.4 (3.7–11.1)	19 (8.5)	7.0 (4.3–11.4)	9.0 (5.7–13.9)	0.21
Ischemic stroke in territory of qualifying artery	7 (3.1)			8 (3.6)			
Ischemic stroke in other territory	5 (2.2)			3 (1.3)			
Symptomatic brain hemorrhage‡	1 (0.4)			8 (3.6)			
Myocardial infarction	7 (3.1)	1.3 (0.4–4.1)	4.0 (1.9–8.4)	5 (2.2)	0.5 (0.1–3.2)	2.2 (0.8–5.8)	0.60
Major non–stroke-related hemorrhage††	4 (1.8)	0.9 (0.2–3.5)	1.4 (0.4–4.2)	10 (4.5)	2.7 (1.2–5.9)	3.6 (1.8–7.1)	0.10
Subdural	1 (0.4)			0			
Gastrointestinal	3 (1.3)			4 (1.8)			
Ocular	0			1 (0.4)			
Lingual hematoma	0			1 (0.4)			
Angiogram access site	0			4 (1.8)			
Any major hemorrhage‡‡	5 (2.2)	0.9 (0.2–3.5)	1.8 (0.7–4.8)	22 (9.8)	8.0 (5.1–12.5)	9.0 (5.9–13.5)	<0.001
Symptomatic brain hemorrhage‡	1 (0.4)			10 (4.5)‖			
Asymptomatic brain hemorrhage§§	0			2 (0.9)			
Major non–stroke-related hemorrhage	4 (1.8)			10 (4.5)			

The SAMMPRIS investigators. Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis. *N Engl J Med* 2011;365:993-1003.

ICAS: Guidelines

Intracranial stenting NOT recommended for the treatment of intracranial 70-99% stenosis

DAPT with ASA 325 mg and Clopidogrel 75 mg started within 30 days of stroke or TIA and treated for up to 90 days **should be considered for each patient on an individual basis** along with aggressive management of all vascular risk factors (blood pressure, lipids, diabetes mellitus, and other at-risk lifestyle patterns)

Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017

Case 3

Catherine is a 72 year old female patient admitted to hospital with new bilateral, multi-territory strokes (infarcts in the right ACA, right MCA, & left PCA territories) today.

Past Medical History:

- Hypertension
- GERD
- Osteoarthritis

Home Medications:

- {Coversyl Plus} Perindopril 4mg – Indapamide 1.25mg PO daily
- Pantoprazole 40mg PO daily
- Acetaminophen 500mg po 3 to 4 times daily PRN
- Ibuprofen 400mg po PRN if acetaminophen not effective

Relevant Findings & Laboratory Results:

- BP 140/85, HR 77
- Weight 55kg
- HbA1C 5.6%
- LDL 3.6 mmol/L
- Hgb 122 g/dL
- SCr 68 umol/L
- ECG: Atrial Fibrillation
- TTE: Dilated left atrium, normal LV/RV size and function, no obvious thrombus, mild TR
- CTA: unremarkable

What medications should be started for appropriate secondary stroke prevention?

Polling question: most appropriate antithrombotic therapy for Catherine **right now**?

A. Acetylsalicylic acid (ASA)
B. Clopidogrel
C. ASA and Dipyridamole
D. A, B, or C
E. DAPT – ASA + Clopidogrel x 21-30 days, then SAPT with either agent
F. DAPT – ASA + Clopidogrel x 90 days, then SAPT with either agent
G. Oral anticoagulation

Polling question: most appropriate antithrombotic therapy for Catherine **long-term**?

A. Acetylsalicylic acid (ASA)
B. Clopidogrel
C. ASA and Dipyridamole
D. A, B, or C
E. DAPT – ASA + Clopidogrel x 21-30 days, then SAPT with either agent
F. DAPT – ASA + Clopidogrel x 90 days, then SAPT with either agent
G. Oral anticoagulation

Case 3

Catherine is a 72 year old female patient admitted to hospital with new bilateral, multi-territory strokes (infarcts in the right ACA, right MCA, & left PCA territories) today.

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- Hgb 122 g/dL
- SCr 68 umol/L
- **ECG: Atrial Fibrillation**
- TTE: Dilated left atrium, normal LV/RV size and function, no obvious thrombus, mild TR
- CTA: unremarkable

$CHADS_2 = 3$

$CHA_2DS_2\text{-}VASc = 5$

$HASBLED = 3$

What medications should be started for appropriate secondary stroke prevention?

Anticoagulation for SPAF

Patients with transient ischemic attack or ischemic stroke and non-valvular atrial fibrillation **should receive oral anticoagulation** [Evidence Level A]

In most patients requiring anticoagulants for atrial fibrillation, **direct non-vitamin K oral anticoagulants (DOAC)** such as apixaban, dabigatran, edoxaban, or rivaroxaban should be prescribed in preference over warfarin [Evidence Level A]

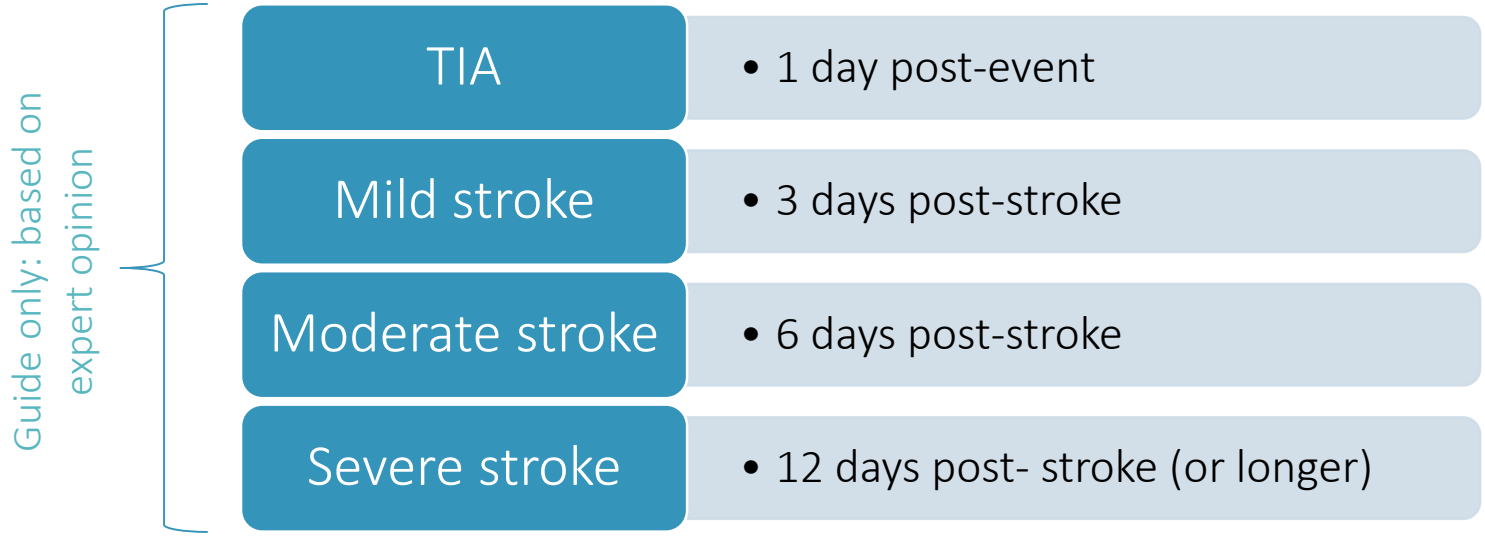
For patients **already receiving warfarin** with good International Normalized Ratio (INR) control (Range 2.0 – 3.0, with TTR >70%), **continuing warfarin** is a **reasonable** anticoagulation option [Evidence Level B]

Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017

Anticoagulation: when to start?

"The optimal timing to start anticoagulant therapy after stroke has not been defined by clinical trial evidence, and should be based on individual benefit/risk assessment taking into account the **clinical circumstances, infarct size, imaging appearances, age, comorbidities,** and **estimated stroke recurrence risk**."

Bridging with **antiplatelet therapy** is suggested until the patient is anticoagulated



1. Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017
2. Heidbuchel et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. European heart journal. 2013;34(27):2094-2106

Polling Question: most appropriate lipid-lowering therapy for Catherine?

A. Atorvastatin 80mg
B. Atorvastatin 10mg
C. Rosuvastatin 40mg
D. A or C
E. Ezetimibe 10mg
F. No therapy

SPARCL (2006)

Population	Adult patients who had ischemic or hemorrhagic stroke or TIA within one to six months before study entry • Had LDL cholesterol of 2.6 to 4.9 mmol/L • Had no known coronary heart disease • **Excluded:** atrial fibrillation, other cardiac sources of embolism, and subarachnoid hemorrhage
Intervention	Atorvastatin 80 mg daily
Comparison	Placebo
Outcome	First nonfatal or fatal stroke (followed for 4.9 years)

Amarenco P et al. High-Dose Aootrvastatin after Stroke of Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL). NEJM 2006;355(6);54955

Table 2. Estimates of the Hazard Ratio for the Primary and Secondary Efficacy Outcome Measures.

Outcome*	Atorvastatin (N=2365)	Placebo (N=2366)	Unadjusted P Value†	Prespecified Adjusted Model‡	
				HR (95% CI)	P Value
	no. (%)				
Primary outcome					
Nonfatal or fatal stroke§	265 (11.2)	311 (13.1)	0.05	0.84 (0.71–0.99)	0.03
Nonfatal stroke	247 (10.4)	280 (11.8)	0.14	0.87 (0.73–1.03)	0.11
Fatal stroke	24 (1.0)	41 (1.7)	0.04	0.57 (0.35–0.95)	0.03
Secondary outcomes					
Stroke or TIA	375 (15.9)	476 (20.1)	<0.001	0.77 (0.67–0.88)	<0.001
TIA	153 (6.5)	208 (8.8)	0.004	0.74 (0.60–0.91)	0.004
Major coronary event§	81 (3.4)	120 (5.1)	0.006	0.65 (0.49–0.87)	0.003
Death from cardiac causes	40 (1.7)	39 (1.6)	0.90	1.00 (0.64–1.56)	1.00
Nonfatal myocardial infarction	43 (1.8)	82 (3.5)	0.001	0.51 (0.35–0.74)	<0.001
Resuscitation after cardiac arrest	1 (<0.1)	1 (<0.1)	—	—	—
Major cardiovascular event	334 (14.1)	407 (17.2)	0.005	0.80 (0.69–0.92)	0.002
Acute coronary event	101 (4.3)	151 (6.4)	0.001	0.65 (0.50–0.84)	0.001
Any coronary event	123 (5.2)	204 (8.6)	<0.001	0.58 (0.46–0.73)	<0.001
Revascularization¶	94 (4.0)	163 (6.9)	<0.001	0.55 (0.43–0.72)	<0.001
Any cardiovascular event	530 (22.4)	687 (29.0)	<0.001	0.74 (0.66–0.83)	<0.001
Death	216 (9.1)	211 (8.9)	0.77	1.00 (0.82–1.21)	0.98
Death from cardiovascular disease	78 (3.3)	98 (4.1)	0.14	0.78 (0.58–1.06)	0.11
Death from cancer	57 (2.4)	53 (2.2)	0.67	1.05 (0.72–1.53)	0.80
Death from infection	26 (1.1)	20 (0.8)	—	—	—
Accidental or violent death	11 (0.5)	6 (0.3)	—	—	—
Death from other causes	23 (1.0)	15 (0.6)	—	—	—
Unclassified deaths	21 (0.9)	19 (0.8)	—	—	—

Amarenco P et al. High-Dose Aootrvastatin after Stroke of Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL). NEJM 2006;355(6);54955

SPARCL (2006): Results

5-year absolute reduction in risk of any stroke 2.2%; relative risk reduction of 16%, adjusted hazard ratio 0.84 (95% CI 0.71–0.99; p = 0.03)

46 patients would need to be treated for 5 years to prevent one stroke

Reduction in ischemic stroke (HR 0.78, 95% CI 0.66–0.94) BUT increased risk of hemorrhagic stroke (HR 1.66, 95% CI 1.08- 2.55) in atorvastatin group

- Atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes
- Placebo group had 274 ischemic strokes and 33 hemorrhagic strokes.

Overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group (P=0.98)

Amarenco P et al. High-Dose Aootrvastatin after Stroke of Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL). NEJM 2006;355(6);54955

From the guidelines…

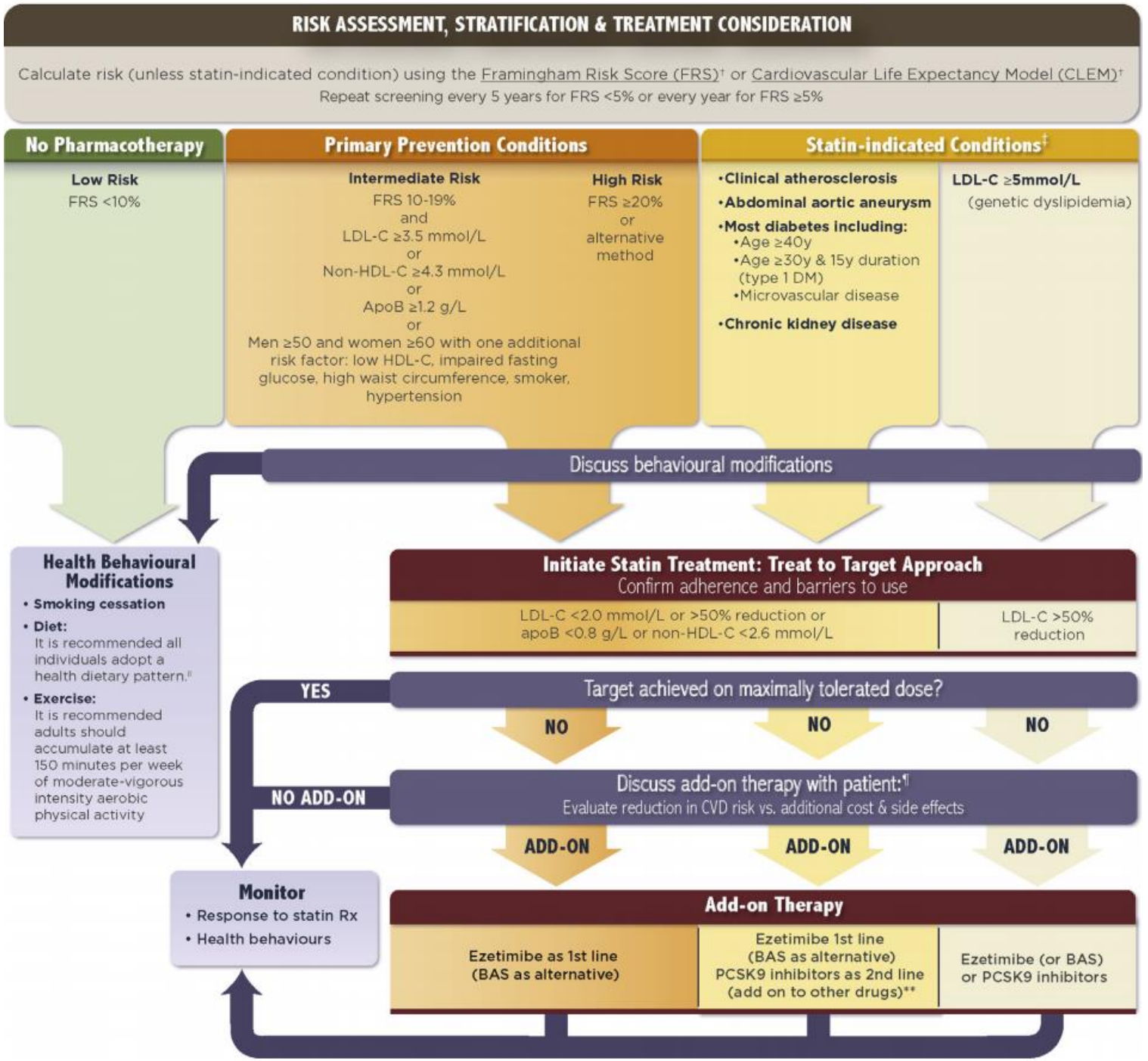
"A statin should be prescribed as secondary prevention to patients who have had an ischemic stroke or transient ischemic attack in order to achieve a **target LDL cholesterol** consistently less than 2.0 mmol/L or >50% reduction of LDL cholesterol, from baseline [Evidence Level B]

Statin therapy is **not indicated** for prevention of **intracerebral hemorrhage** [Evidence Level B]."

*"**Note:** The current clinical trial evidence does not include enough stroke patients with atrial fibrillation or other cardioembolic sources to make specific recommendations for this patient population. The decision to use statins in this setting should be based on the patient's global cardiovascular risk. It is unclear whether statins are of benefit in patients with a combination of atrial fibrillation and stroke."*

Wein et al. Canadian Stroke Best Practices Guidelines: Secondary Prevention of Stroke. Int J Stroke, 2017

CCS Dyslipidemia guidelines



Anderson TJ et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Journal of Cardiology. 32(11): 1263 - 1282

Statin-indicated conditions

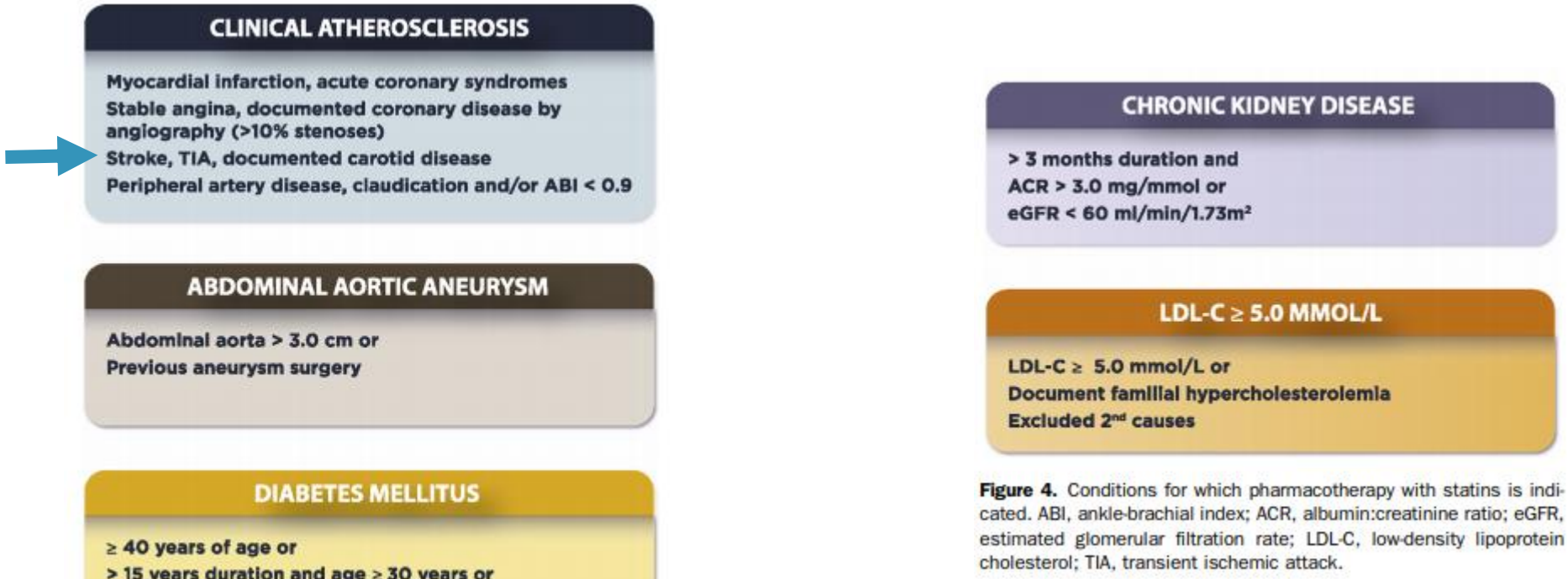


Figure 4. Conditions for which pharmacotherapy with statins is indicated. ABI, ankle-brachial index; ACR, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack.

Anderson TJ et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Journal of Cardiology. 32(11): 1263 - 1282

Case 3

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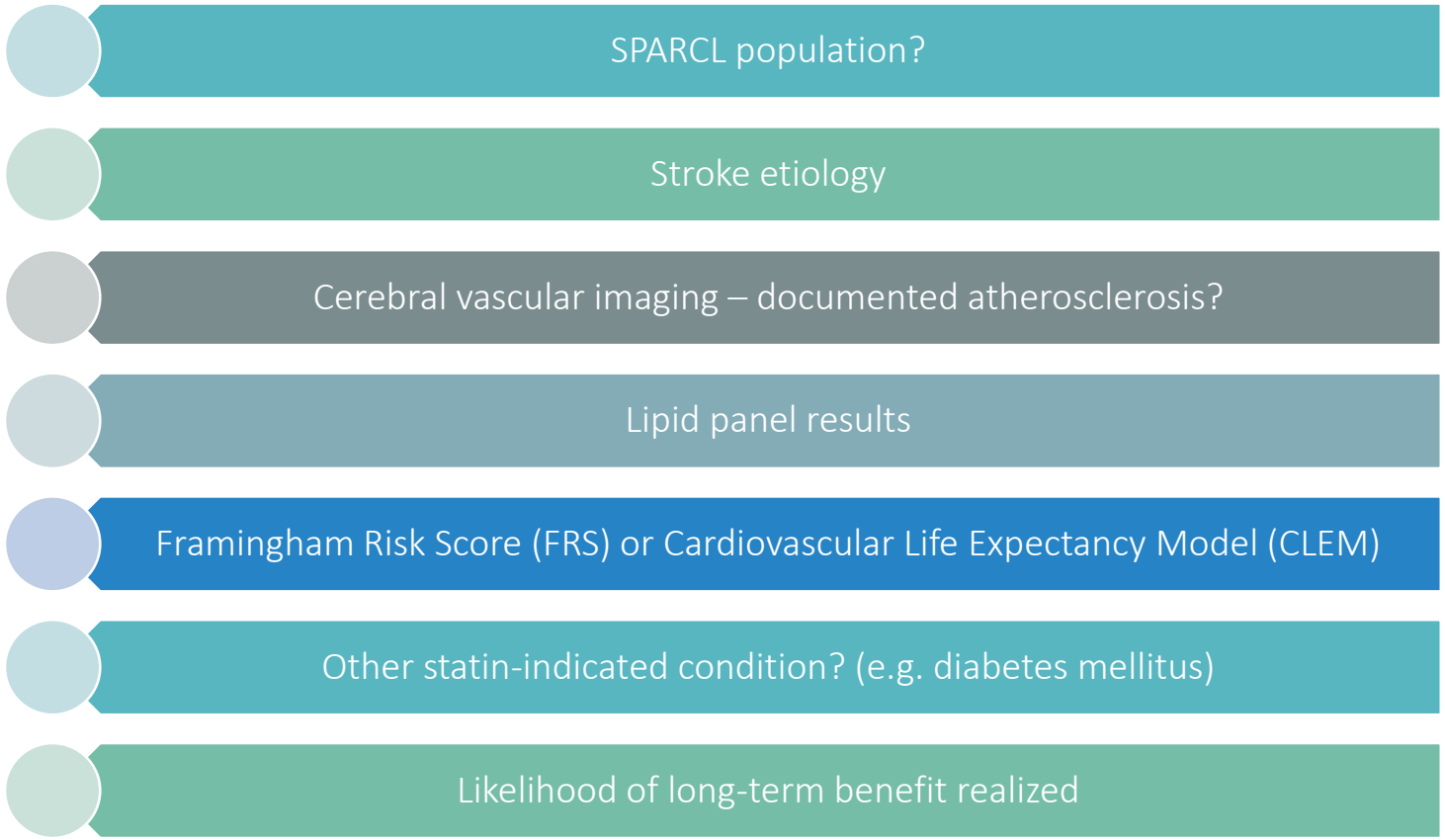
- Hgb 122 g/dL
- SCr 68 umol/L
- ECG: Atrial Fibrillation
- TTE: Dilated left atrium, normal LV/RV size and function, no obvious thrombus, mild TR
- CTA: unremarkable

Framingham Risk Score = 13.7%

What medications should be started for appropriate secondary stroke prevention?

Statin therapy: key considerations



What if…?

Catherine's ECG and 48H Holter did **NOT** show atrial fibrillation?

How does this affect the choice of antithrombotic therapy?

ESUS – "Embolic Stroke of Undetermined Source"

All 4 must be present:

1. Non-lacunar ischemic stroke on CT or MRI
2. Absence of atherosclerosis (extra- or intracranial) causing ≥50% luminal stenosis in arteries supplying the ischemic area
3. No major risk cardioembolic source

   Major risk source = atrial fibrillation (permanent or paroxysmal), sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, cardiac tumors (e.g. atrial myxoma), mitral stenosis, recent (<4 weeks) MI, left ventricular EF <30%, valvular vegetations, or infective endocarditis
4. No other specific cause of stroke identified

   E.g. arteritis, dissection, migraine/vasospasm, drug abuse

Hart, R et al. Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update. Stroke 2017;48:867-872.

Does Catherine meet the criteria for ESUS stroke?

ESUS: Potential Causes

Structural heart disease
- e.g. mitral annular calcification, calcific aortic valve, atrial septal aneurysm

Cancer-associated strokes

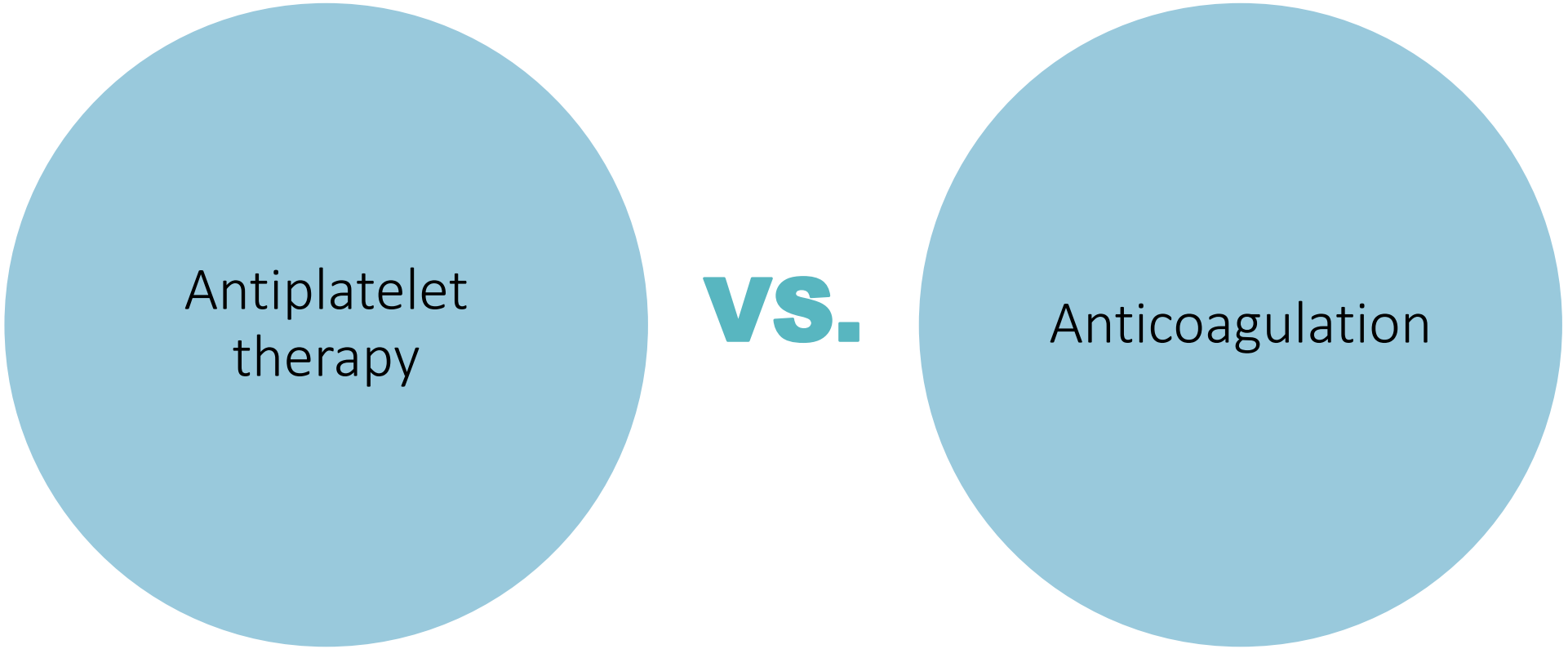
Arteriogenic emboli
- e.g. aortic arch atherosclerotic plaques

Paradoxical embolism from venous circulation
- e.g. involving patent foramen ovale or pulmonary arteriovenous fistula

Undetected paroxysmal atrial fibrillation

1. Nouh, A et al. Embolic Strokes of Unknown Source and Cryptogenic Stroke: Implications in Clinical Practice. Front Neurol. 2016; 7:37.
2. Martinez-Majander, N. Medical Management of ESUS - what have we learnt so far? European Stroke Organization. 2018.

ESUS Management



Summary: DOAC trials for ESUS patients

	NAVIGATE-ESUS[1]	RE-SPECT ESUS[2]	ATTICUS[3]
DOAC	Rivaroxaban 15mg daily	Dabigatran 150mg BID • 110mg BID if ≥75 years old and if est. CrCl 30-50mL/min	Apixaban 5mg BID
Comparator	ASA 100mg daily	ASA 100mg daily	ASA 100mg daily
Population	7213 patients with ESUS	5390 patients with ESUS	ESUS patients, still recruiting
Primary Efficacy Outcome	1st recurrence of stroke or systemic embolism • 172 patients in the rivaroxaban group (annualized rate, 5.1%) • 160 in the ASA group (annualized rate, 4.8%) • HR, 1.07; 95% CI, 0.87 to 1.33; P=0.52	Recurrent stroke • 177 patients (6.6%) in the dabigatran group (4.1% per year) • 207 patients (7.7%) in the ASA group (4.8% per year) • HR 0.85; 95% CI, 0.69 to 1.03; P=0.10	TBD
Primary Safety Outcome	Rate of major bleeding • 62 patients in the rivaroxaban group (annualized rate, 1.8%) • 23 in the ASA group (annualized rate, 0.7%) • HR 2.72; 95% CI, 1.68 to 4.39; P<0.001	Major bleeding • 77 patients (1.7% per year) in the dabigatran group • 64 patients (1.4% per year) in the ASA group • HR, 1.19; 95% CI, 0.85 to 1.66	
Conclusion	Rivaroxaban not superior to ASA to prevent recurrent stroke Rivaroxaban associated with a higher risk of bleeding vs ASA	Dabigatran was not superior to ASA in preventing recurrent stroke Incidence of major bleeding was not greater in the dabigatran group than in the ASA group	

1.Hart RG, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med 2018;378:2191-2201.
2.Diener HC, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med 2019;380:1906-17
3.https://clinicaltrials.gov/ct2/show/NCT02427126

ESUS: Antithrombotic Management

Available evidence does not support anticoagulation

Antiplatelet therapy mainstay of therapy **until** an indication for anticoagulation is present

Further diagnostic workup may be warranted

- Including prolonged Holter monitoring to capture paroxysmal AF if present (EMBRACE trial)

What if…?

Catherine had known atrial fibrillation at the time of her stroke and was already on anticoagulation with Apixaban 5mg q12h?

What if…?

Catherine was on ASA 81mg daily at the time of her stroke?

Case 4:

Jane is a 84 year old female patient admitted to hospital with a new L MCA stroke confirmed on CT today.

Past Medical History:

- Atrial Fibrillation
- Hypertension
- Dyslipidemia
- Type 2 Diabetes Mellitus
- Depression

Home Medications:

- Apixaban 5mg PO q12h
- Ramipril 5mg PO daily
- Bisoprolol 2.5mg PO daily
- Atorvastatin 10mg PO daily
- Metformin 500mg PO BID
- Sitagliptin 100mg PO daily
- Sertraline 50mg PO daily

Relevant Findings & Laboratory Results:

- BP 167/90, HR 84
- Weight 68kg
- HbA1C 7.6%
- LDL 2.3 mmol/L
- Hgb 123 g/L
- SCr 76 umol/L
- ECG: Atrial Fibrillation
- CTA: L carotid stenosis (90%); R carotid atherosclerosis without stenosis

What medications should be started for appropriate secondary stroke prevention?

Case 4:

Jane is a 84 year old female patient admitted to hospital with a new L MCA stroke confirmed on CT today.

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- Atrial Fibrillation
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- Metformin 500mg PO BID
- Sitagliptin 100mg PO daily
- Sertraline 50mg PO daily

Relevant Findings & Laboratory Results:

- **BP 167/90**, HR 84
- Weight 68kg
- **HbA1C 7.6%**
- **LDL 2.3 mmol/L**
- Hgb 123 g/L
- SCr 76 umol/L
- ECG: Atrial Fibrillation
- CTA: **L carotid stenosis (90%)**; R carotid atherosclerosis without stenosis

$CHADS_2 = 5$
$CHA_2DS_2VASc = 7$
HASBLED = 3

AF & cerebral atherosclerosis

Atrial fibrillation (AF) is a known major risk factor for ischemic stroke

- Oral anticoagulants significantly reduce the risk of stroke in patients with AF

Cerebral atherosclerosis is also a known major cause of ischemic stroke

- Management is variable but includes antiplatelet therapy

Ischemic stroke workup includes screening for both AF and cerebral atherosclerosis…
some patients have both

Wein et al. Canadian Stroke Best Practices Guidelines. Int J Stroke, 2017

Symptomatic Carotid Stenosis

Recent TIA or stroke AND ipsilateral **50 to 99 %** symptomatic carotid stenosis:

- Selected patients should be offered carotid endarterectomy (revascularization) **as soon as possible**

Recent TIA or stroke and ipsilateral **70-99 %** symptomatic carotid stenosis

- Carotid endarterectomy should be performed on an urgent basis

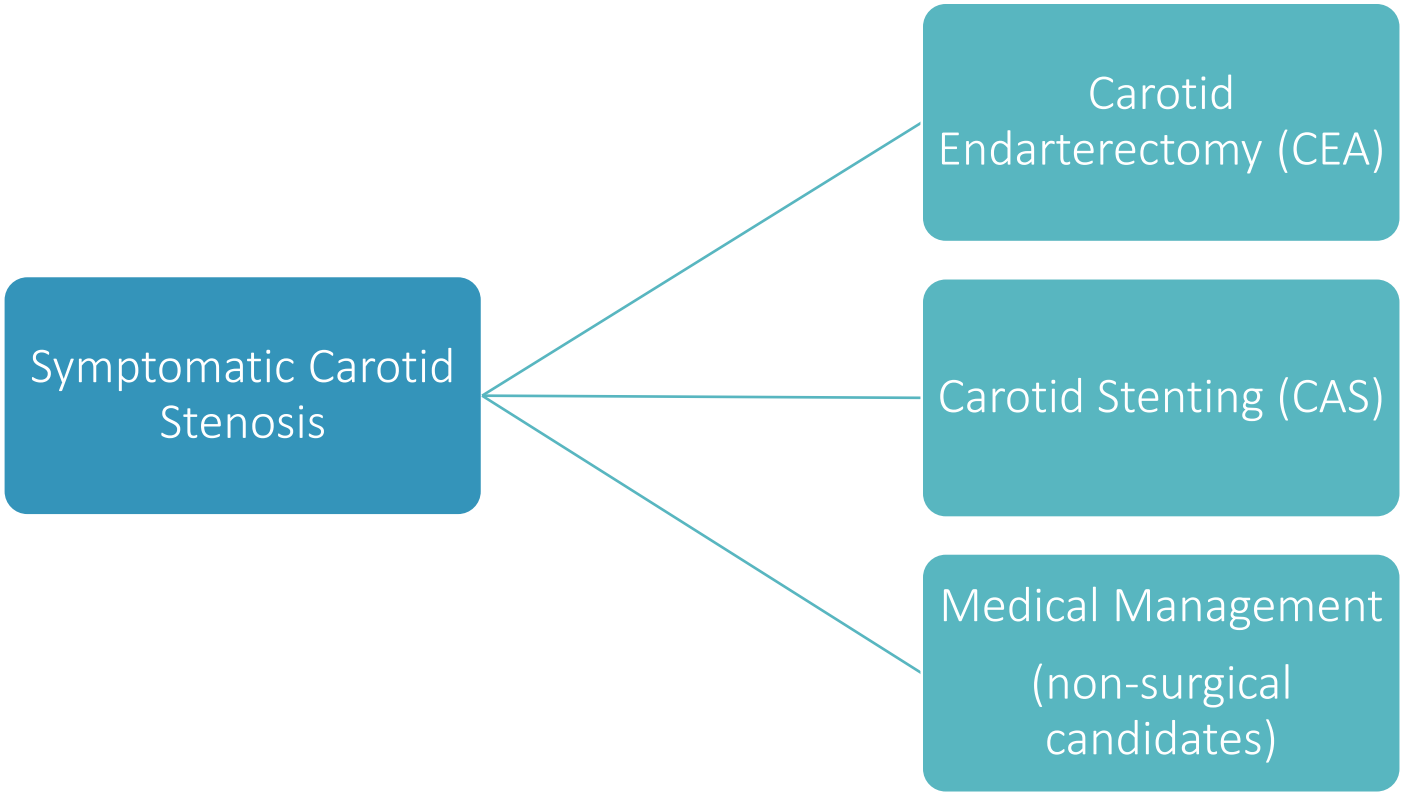
Carotid endarterectomy > carotid stenting: for patients over age 70 years who are otherwise fit for surgery.

Current evidence indicates stenting carries a higher peri-procedural risk of stroke and death in older patients.

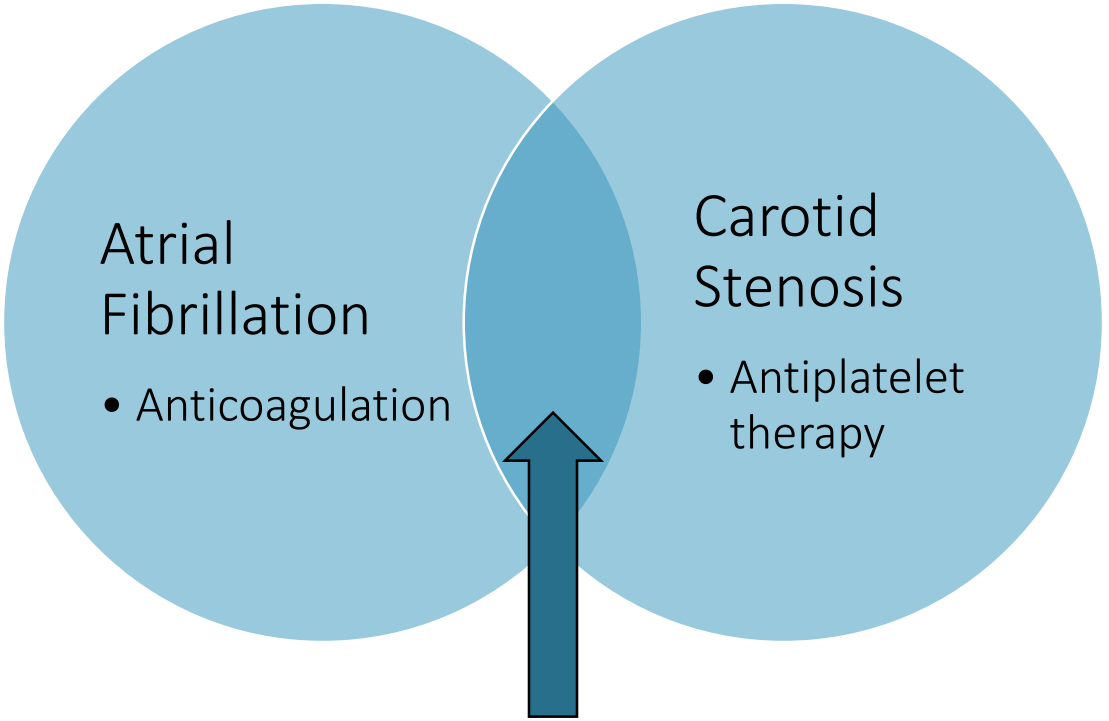
Carotid stenting may be considered for patients who are not operative candidates for technical, anatomic or medical reasons

Wein et al. Canadian Stroke Best Practices Guidelines. Int J Stroke, 2017

Potential Interventions

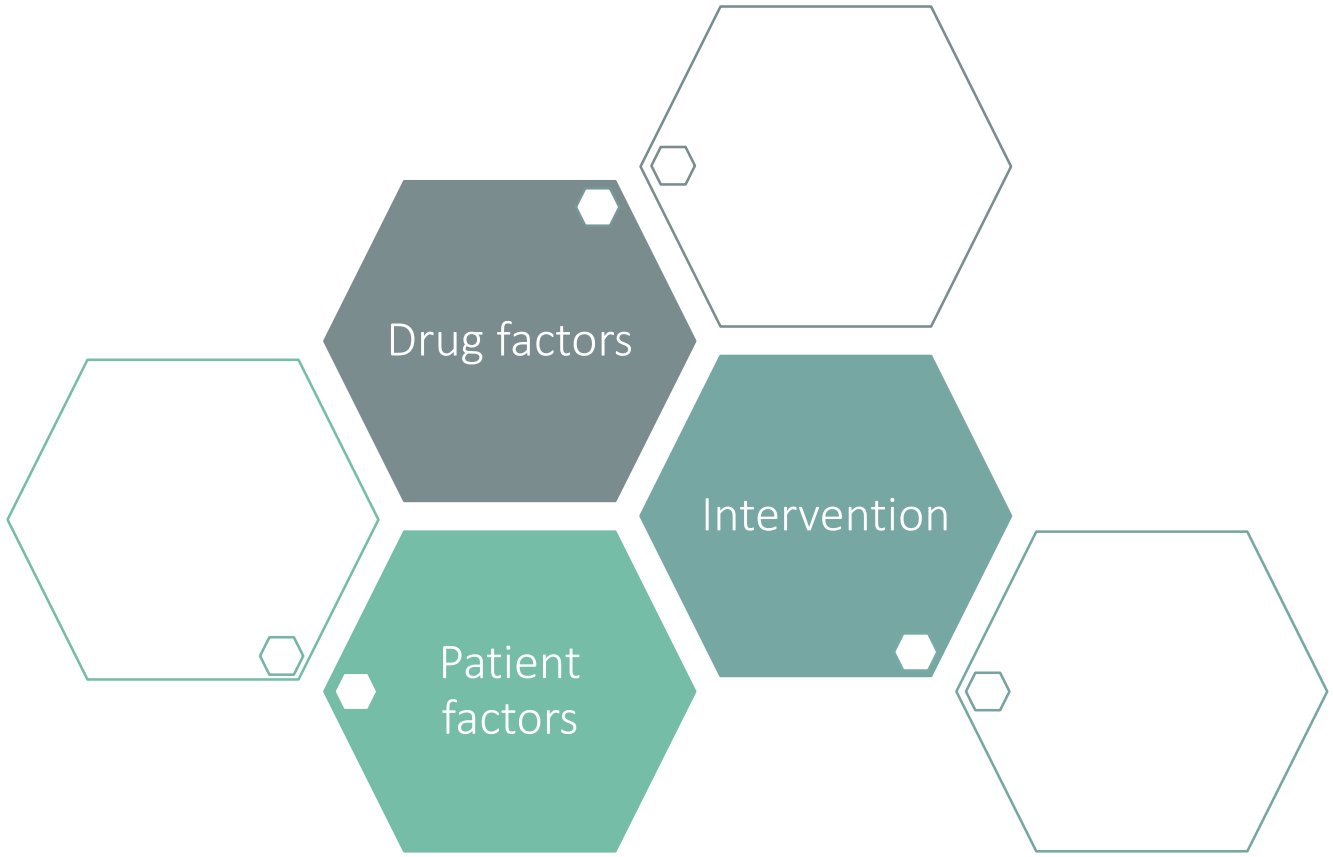


Clinical Question

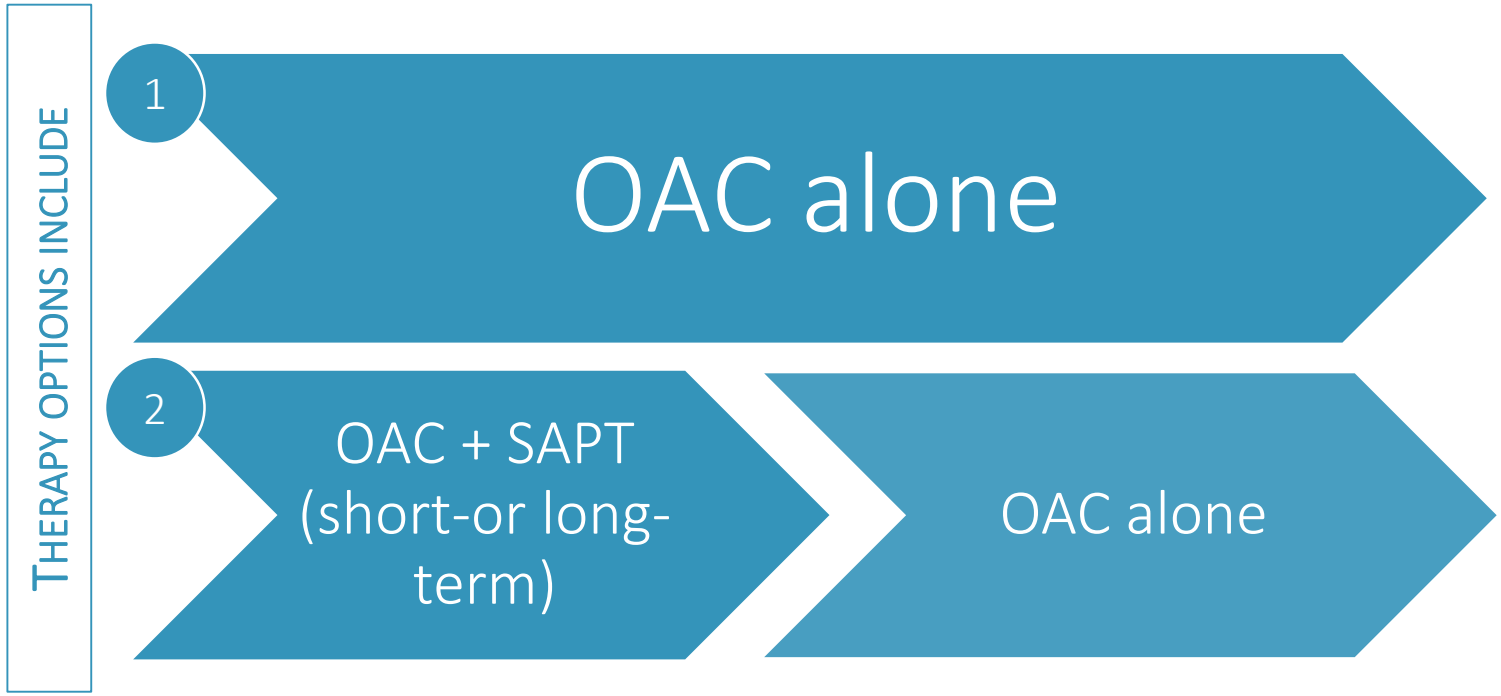


How do we make decisions surrounding antiplatelet + anticoagulant therapy in these cases?

Clinical decision depends on…

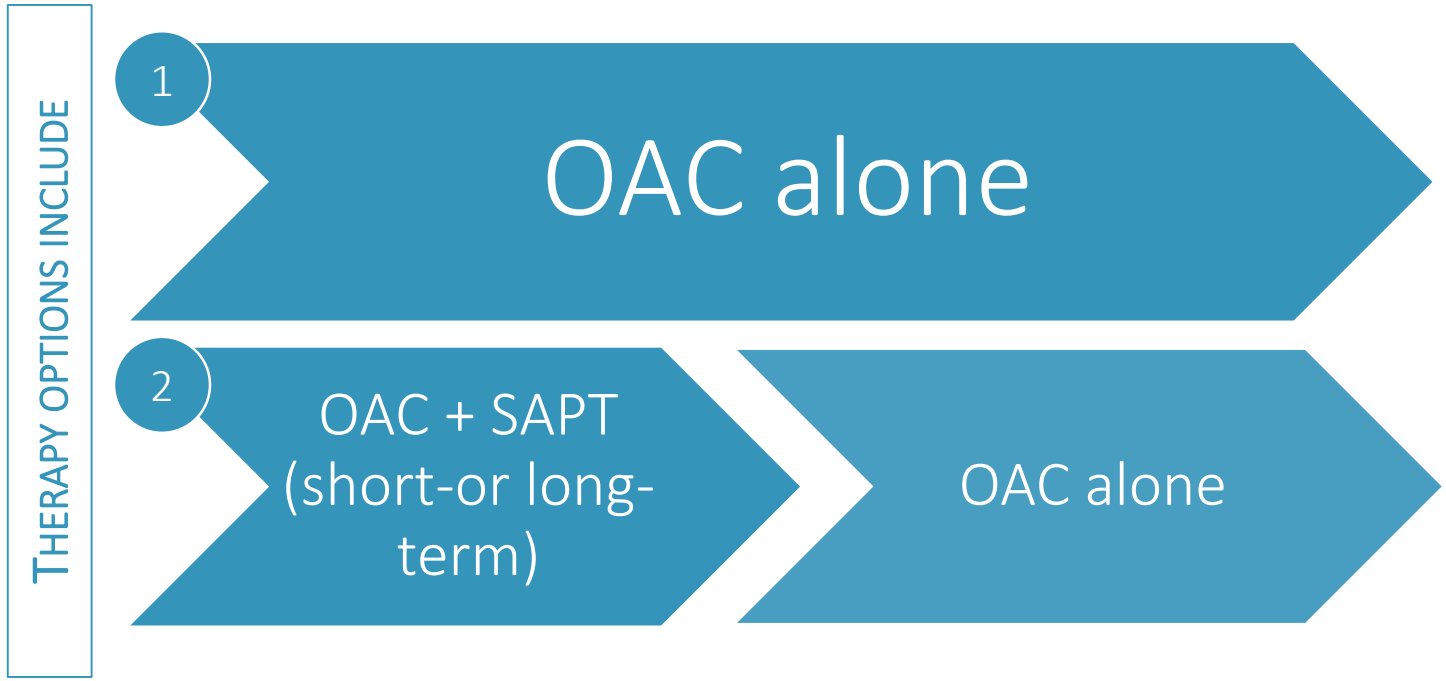


A. Carotid Endarterectomy (CEA) + AF



B. Carotid Stenting (CAS) + AF

C. Medical management + AF



Anticoagulant Selection

Guidelines recommend direct oral anticoagulant (DOAC) > warfarin for stroke prevention in nonvalvular AF[1]

Consider a DOAC with a favourable bleed risk profile especially for patients on dual or triple antithrombotic therapy

- May consider reversibility, e.g. idarucizumab with dabigatran
- Dabigatran cannot be crushed for patients with dysphagia

Some experts may elect to dose-reduce OAC while on triple antithrombotic therapy, depending on patient factors and preferences

- Uncommon given this population is at very high risk of stroke secondary to AF
- Extrapolated from coronary PCI trial data (covered in a separate module) and there are **no trials** to guide this in non-coronary PCI patients
- DAPT by itself confers some benefit for stroke risk reduction in AF

1. Verma et al; CCS Atrial Fibrillation Guidelines Committee. *Can J Cardiol*. 11 2014;30:1114-1130.

Antiplatelet Selection

If triple antithrombotic therapy, DAPT with clopidogrel and ASA

- Avoid ticagrelor with OAC given increased bleed risk versus clopidogrel
- Patients will generally step down to SAPT with ASA (due to lower cost) if they were not on ASA prior to their stroke
- Patients may step down to SAPT with clopidogrel instead if they were on ASA prior to their stroke

Use low-dose ASA, i.e. 80mg or 81mg PO daily

Managing modifiable risk factors for bleeding

For patients on combined anticoagulant & antiplatelet therapy:

- Control blood pressure to target
- Avoid co-prescription of NSAIDs
- Educate patients to limit alcohol intake to less than 8 standard drinks per week
- May consider co-prescription of proton-pump inhibitor (PPI) for gastroprotection in select patients with high risk of bleeding
  - PPI recommended for patients with prior history of gastrointestinal (GI) bleed[1]
  - PPI reasonable for patients of advanced age, on concomitant warfarin, DOACs, steroids, or NSAIDs[1]
- If warfarin is the anticoagulant:
  - Some experts may recommend an INR target of 2-2.5 (rather than 2-3) for stroke prevention in AF
  - Consider more frequent INR monitoring

1. JACC 2016 Vol 68 No. 10 - 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease

Clinical Tips

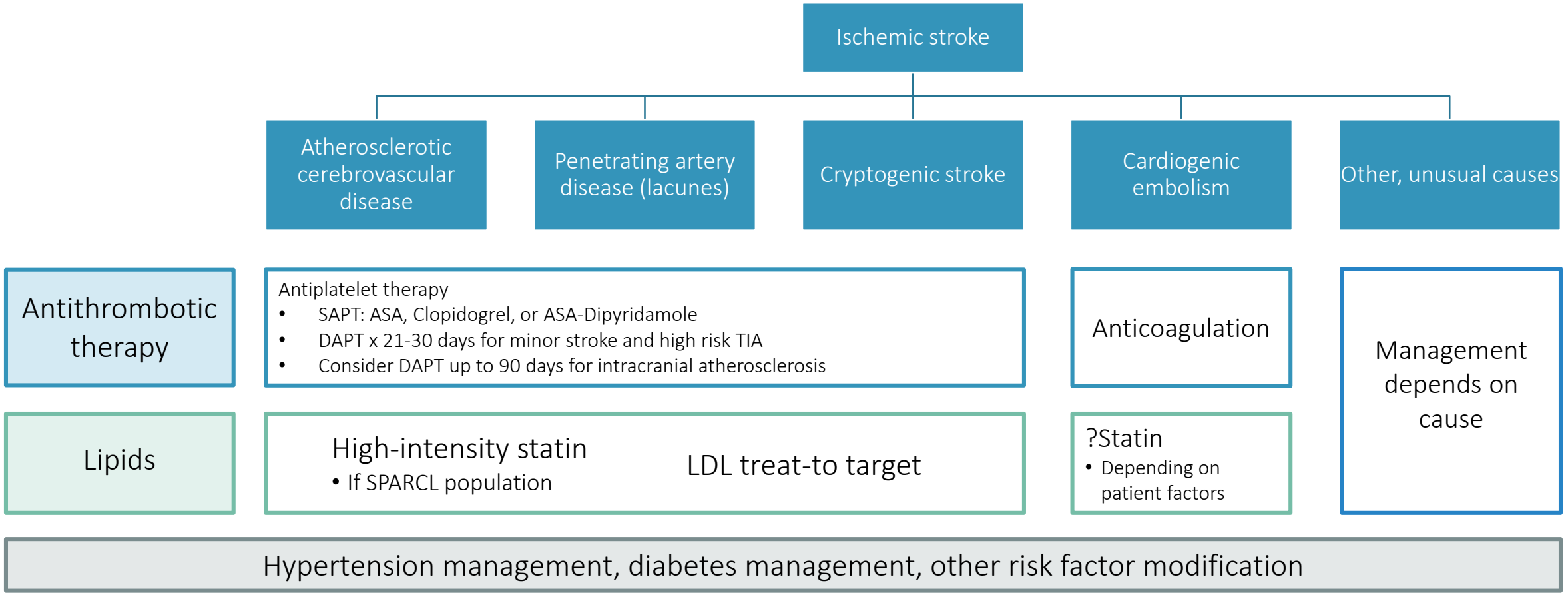
Review all patients on dual and triple antithrombotic therapy to ensure there is an appropriate indication for each agent

Educate and monitor patients on dual and triple antithrombotic therapy for signs and symptoms of bleeding

Ensure appropriate follow up and that dual and triple antithrombotic therapy is flagged for re-assessment

- There are very few cases for which a patient should be on dual or triple antithrombotic therapy indefinitely!

Summary


Ischemic stroke
Atherosclerotic cerebrovascular disease
Penetrating artery disease (lacunes)
Cryptogenic stroke
Cardiogenic embolism
Other, unusual causes
Antithrombotic therapy
Antiplatelet therapy
• SAPT: ASA, Clopidogrel, or ASA-Dipyridamole
• DAPT x 21-30 days for minor stroke and high risk TIA
• Consider DAPT up to 90 days for intracranial atherosclerosis
Anticoagulation
Management depends on cause
Lipids
High-intensity statin
• If SPARCL population
LDL treat-to target
?Statin
• Depending on patient factors
Hypertension management, diabetes management, other risk factor modification

Antithrombotic therapy summary