DUAL ANTI-PLATELET THERAPY (DAPT) IN ACUTE ISCHEMIC STROKE

A PRESENTATION FOR HEALTHTRUST MEMBERS

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PARTH PARIKH, PHARMD, PGY-2
EMERGENCY MEDICINE PHARMACY RESIDENT, RUTGERS UNIVERSITY/ROBERT WOOD JOHNSON UNIVERSITY HOSPITAL

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PHARMACIST OBJECTIVES

- Define the role of anti-platelet therapy in patients with acute ischemic attack (AIS)
- Recall the current literature for the use of dual anti-platelet therapy (DAPT) in AIS
- Differentiate amongst patients who would benefit most from DAPT
- Outline a treatment regimen using DAPT in a patient-specific case

PHARMACY TECHNICIAN OBJECTIVES

- Identify anti-platelet agents used in secondary prevention of ischemic stroke
- Specify one patient type that would benefit from antiplatelet agents after an initial stroke

MEET PATIENT YJ

YJ is a 57 y/o Caucasian male with a past medical history (PMH) significant for HTN and HLD. While watching TV at home, he started feeling weakness in his left arm and leg. His wife also noticed he had a slight left sided facial droop. Concerned for stroke, his wife called EMS and he was brought in to the emergency department.

EPIDEMIOLOGY

Stroke is the 5th leading cause of death in the United States

Globally, stroke is the 2nd leading cause of death

Stroke is the leading cause of disability in the United States

Source: Vital Signs: Recent trends in stroke death rates – United States, 2000-2015. MMWR 2017;66.

HEALTHCARE IMPACT

$40.1 Billion estimated indirect and direct costs

Costs estimated to increase to $94.3 billion by 2025

Aging population

Sources: Vital Signs: Recent trends in stroke death rates – United States, 2000-2015. MMWR 2017;66.
Benjamin EJ, Blaha MJ, Chiuve SE, et al. on behalf of the. Circulation. 2017;135:e229-e445.

ISCHEMIC STROKE

Small vessel occlusion (Lacunar stroke)

- Small noncortical infarcts due to occlusion of a single branch of a larger cerebral artery
- Syndromes may include pure motor hemiparesis, ataxic hemiparesis, and dysarthria-clumsy hand syndrome

Thrombotic (Atherosclerotic stroke)

- Narrowing of the vasculature secondary to atherosclerosis thrombus formation
- Symptoms often have gradual onset and may wax and wane

Cryptogenic stroke

- No identifiable cause for stroke

Cardioembolic stroke

- Obstruction of vasculature caused by a dislodged emboli (blood clot)
- Sudden onset of symptoms

Source: Go S, Worman DJ. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8e* New York, NY: McGraw-Hill; 2016.

TRANSIENT ISCHEMIC ATTACK (TIA)

- Transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction
  - Historically defined by duration of symptoms
  - Current "tissue-based" definition relies on imaging for diagnosis
- Symptoms similar to that with stroke
  - Unilateral paresis
  - Diplopia
- Warning sign for future stroke

Source: Stroke. 2009;40:2276-2293.

RISK OF STROKE RECURRENCE AFTER MINOR STROKE OR TIA

- 20% risk of stroke within 90 days of initial incident of stroke or TIA
- Highest risk within the first 7 days but especially within 48 hours
- Patients who recover from initial deficit at greatest risk of deterioration

Sources: Hill MD et al, Neurology. 2004;62(11):2015-20.
Kennedy J et al. Lancet Neurol. 2007;6(11):961-9.

SECONDARY PREVENTION OF STROKE

A
- Anti-thrombotics

B
- Blood pressure control

C
- Cholesterol lowering

D
- Diabetes control

Source: Kernan WN et al. Stroke. 2014;45(7):2160-236.

SECONDARY PREVENTION OF STROKE

- Guideline recommended anti-thrombotic agents
- Initiate within 24–48 hours of index event

★ Aspirin	Aspirin/dipyridamole	★ Clopidogrel	Ticlopidine
• 75–325 mg daily	• 25 mg/200 mg daily	• 75 mg daily	• 250 mg twice daily

Source: Kernan WN et al. Stroke. 2014;45(7):2160-236.

ANTI-PLATELETS FOR SECONDARY PREVENTION OF STROKE

- Studies suggest a relative risk reduction of stroke, MI or death by ~22% with the use of antiplatelet agents

Study	Drug	Population	Pertinent results
Johnson et al (1999)	Aspirin	N = 9629 Stroke or TIA	↓ risk of recurrent stroke with aspirin
Rothwell et al (2016)	Aspirin	N =15778 Minor stroke or TIA	↓ 6 week risk of recurrent stroke with aspirin
CAPRIE (1996)	Clopidogrel	N = 9185 Stroke, MI, or PVD	↓ risk of ischemic stroke, MI, or vascular death No significant risk reduction in stroke subgroup
ESPS-2 (1996)	Aspirin/dipyridamole	N = 6602 Stroke or TIA	↓ risk of recurrent stroke or death with aspirin/dipyridamole

PHARMACIST ASSESSMENT QUESTION 1

- What of the following statements is true regarding the role of anti-platelet agents in the secondary prevention of acute ischemic stroke?
  a. Antiplatelet agents provide a relative risk reduction of recurrent stroke
  b. Antiplatelet agents provide a relative risk reduction of recurrent stroke, MI or death
  c. Antiplatelet agents provide only a placebo effect when utilized for secondary prevention of ischemic stroke
  d. Antiplatelet agents provide no benefit for secondary prevention of ischemic stroke

PHARMACIST RESPONSE QUESTION 1

- What of the following statements is true regarding the role of anti-platelet agents in the secondary prevention of acute ischemic stroke?
  a. Antiplatelet agents provide a relative risk reduction of recurrent stroke
  b. Antiplatelet agents provide a relative risk reduction of recurrent stroke, MI or death
  c. Antiplatelet agents provide only a placebo effect when utilized for secondary prevention of ischemic stroke
  d. Antiplatelet agents provide no benefit for secondary prevention of ischemic stroke

DAPT TRIALS

MATCH TRIAL (2004)

Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or TIA in high risk patients – MC, R, DB, PC	
Objective	To assess whether aspirin plus clopidogrel would further reduce the risk of recurrent ischemic events in high-risk patients after ischemic stroke or TIA
Primary Outcome	Efficacy: Composite of ischemic stroke, MI, vascular death, or rehospitalization for an acute ischemic event Safety: Incidence of life threatening bleed
Methods	Inclusion*: Ischemic stroke or TIA in previous 3 months with an additional risk factor – previous ischemic stroke, MI, angina pectoris, diabetes mellitus, or symptomatic PAD within previous 3 years Exclusion*: Age < 40 years; severe comorbid conditions; increased risk of bleeding Intervention: Treatment arm: clopidogrel 75 mg + aspirin 75 mg daily for 18 months Control arm :clopidogrel 75 mg daily for 18 months

MC = multi-center; R= randomized; DB = double-blind; PC = placebo-controlled

*Select criteria

Source: Diener HC, et al. The Lancet. 2004. 364(9431):331-337.

MATCH TRIAL RESULTS

- ~82% of patients started on therapy after ≥ 7 days
- No major variability in baseline characteristics between groups

Efficacy Outcome	Aspirin + Clopidogrel N = 3793	Clopidogrel only N = 3802	Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)	P-value
Primary efficacy	16%	17%	1% (95% CI -0.06-2.7)	6.4% (-4.6-16.3)	0.244

Bleeding events	Aspirin + clopidogrel	Clopidogrel only	% Difference (95% CI)	P-value
Life threatening	3%	1%	1.26 (0.64–1.88)	<0.0001
Major bleed	2%	1%	1.36 (0.86–1.86)	<0.0001

Source: Diener HC, et al. The Lancet. 2004. 364(9431):331-337.

CHARISMA TRIAL (2006)

Clopidogrel and aspirin vs. aspirin alone for the prevention of atherothrombotic events – MC, R, DB, PC	
Objective	To assess if long term treatment with clopidogrel plus aspirin provides more cardiovascular event protection than aspirin alone
Primary Outcome	Efficacy: Composite of MI, any stroke or death from cardiovascular causes Safety: Incidence of severe bleeding
Methods	Inclusion*: Age ≥ 45 years with multiple atherothrombotic risk factors and/or established cardiovascular disease including TIA/Stroke in past 5 years Exclusion*: Long term NSAID or anti-thrombotic therapy; established indication for clopidogrel therapy Intervention: Treatment arm: clopidogrel 75 mg + aspirin 75–162 mg daily Control arm: aspirin 75–162 mg daily

MC = multi-center; R= randomized; DB = double-blind; PC = placebo-controlled
*Select criteria

Source: Bhatt DL, et al. N Engl J Med. 2006. 354(16):1706-1717.

CHARISMA TRIAL RESULTS

- ~36% of patients with history of TIA or stroke
- No major variability in baseline characteristics between groups

Outcome	Aspirin + Clopidogrel N = 7802	Aspirin only N = 7801	Relative risk reduction (95% CI)	P-value
Primary efficacy	6.8%	7.3%	0.93 (0.83–1.05)	0.22
Ischemic stroke (nonfatal)	1.7%	2.1%	0.81 ((0.64–1.02)	0.07
Stroke (nonfatal)	1.9%	2.4%	0.79 (0.86–0.995)	0.03
Severe bleeding	1.7%	1.3%	1.25 (0.97–1.61)	0.09
Moderate bleeding	2.1%	1.3%	1.62 (1.27–2.08)	<0.001

Source: Bhatt DL, et al. N Engl J Med. 2006. 354(16):1706-1717.

FASTER TRIAL (2007)

Fast assessment of stroke and TIA to prevent early recurrence – MC, R, B, PC	
Objective	Assess if early initiation of clopidogrel plus aspirin and simvastatin would reduce risk of stroke after TIA or minor stroke
Outcome	Primary: 90 day risk of stroke Secondary: 90 day risk of stroke, MI, and vascular death Tertiary: 90 day risk of stroke, TIA, acute coronary syndrome, and all-cause death
Methods	Inclusion*: Age ≥ 40; Weakness or speech disturbance for > 5 min Exclusion*: Indication for tPA; current anticoagulation or statin use; pure sensory, vertigo, or dizziness, ataxia or visual disturbance symptoms without speech disturbance or weakness Intervention: Study arm 1: aspirin 81 mg + clopidogrel 75 mg (300 mg load) Study arm 2: aspirin 81 mg + clopidogrel 75 mg (300 mg load) + simvastatin 40 mg Study arm 3: aspirin 81 mg + simvastatin 40 mg Study arm 4: aspirin 81 mg

MC = multi-center; R= randomized; B = blinded; PC = placebo-controlled

*Select criteria

Source: Kennedy J et al. Lancet Neurol. 2007;6(11):961-9.

FASTER TRIAL RESULTS

- Median NIHSS of 1
- Median time to randomization ~8.5 hours
- 23.5% with previous history of TIA or stroke
- Clopidogrel effect
  - 4% absolute risk reduction compared to placebo; however not statistically significant
- Bleeding effect
  - 3% symptomatic bleeding with clopidogrel use; RR 3%; 95% CI (0.6–5.4); P = 0.03

Source: Kennedy J et al. Lancet Neurol. 2007;6(11):961-9.

SPS3 TRIAL (2012)

Effects of clopidogrel added to aspirin in patients with recent lacunar stroke – MC, R, DB, PC	
Objective	Assess if clopidogrel plus aspirin along with blood pressure control, reduces risk of stroke in patients with lacunar stroke compared to only aspirin and blood pressure control
Primary Outcome	Efficacy: All strokes, including ischemic and hemorrhagic Safety: All major hemorrhages
Methods	Inclusion*: ≥ 30 years of age; symptomatic lacunar stroke in past 180 days Exclusion*: History of intracerebral or intracranial hemorrhage; disabling stroke; cortical ischemic stroke Intervention: Treatment arm: clopidogrel 75 mg + aspirin 325 mg Control arm: aspirin 325 mg daily

MC = multi-center; R= randomized; DB = double-blind; PC = placebo-controlled
*Select criteria

Source: Benavente OR et al. N Engl J Med. 2012;367(9):817-25.

SPS3 TRIAL RESULTS

- ~15% of patients with history of TIA or stroke
- 28% of patients on aspirin at time of qualifying event
- No major variability in baseline characteristics between groups
- Trial stopped early due to safety concerns

Outcome	Aspirin only N = 1503	Clopidogrel + aspirin N = 1517	Hazard ratio (95% CI)	P-value
All strokes (%/yr)	2.7%	2.5%	0.92 (0.72–1.16)	0.48
Ischemic stroke (%/yr)	2.4%	2.0%	0.82 (0.63–1.09)	0.13
All deaths (%/yr)	1.4%	2.1%	1.52 (1.14–2.04)	0.004
All major hemorrhages (%/yr)	1.1%	2.1%	1.97 (1.41–2.71)	<0.001

Source: Benavente OR et al. N Engl J Med. 2012;367(9):817-25.

CHANCE TRIAL (2013)

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack – MC, R, DB, PC	
Objective	To assess if treatment with dual therapy of clopidogrel and aspirin would reduce the risk of recurrent stroke compared to monotherapy with aspirin alone
Primary Outcome	Efficacy: New stroke at 90 days Safety: Moderate to severe bleeding
Methods	Inclusion*: Age >40; diagnosis of acute minor ischemic stroke or TIA Exclusion*: Hemorrhage; tumor; other major nonischemic brain disease; need for anticoagulation therapy Intervention: Treatment arm: Day 1: aspirin 75–300 mg + clopidogrel 300 mg; Days 2–21: aspirin 75 mg + clopidogrel 75 mg; Days 22–90: clopidogrel 75 mg Control arm: Day 1: aspirin 75–300 mg; Days 2–90: Aspirin 75 mg

MC = multi-center; R= randomized; DB = double-blind; PC = placebo-controlled

*Select criteria

Source: Wang Y et al. N Engl J Med. 2013;369(1):11-9.

DEMOGRAPHICS

Characteristics	Aspirin (N = 2586)	Clopidogrel and Aspirin (N = 2584)
Age, median	62	63
Female sex, %	34.7	33
Qualifying event, %		
TIA	28.2	27.7
Minor stroke	71.8	72.3
$ABCD^2$ score, median	4	4
Medical history, %		
Ischemic stroke	20	20
TIA	3.1	3.6
Myocardial infarction	2.0	1.7

Source: Wang Y et al. N Engl J Med. 2013;369(1):11-9.

RESULTS

Efficacy Outcomes	Aspirin	Clopidogrel and Aspirin	Hazard Ratio (95% CI)	P value
Primary				
Stroke	11.7	8.2	0.68 (0.57–0.84)	<0.001
Secondary				
Stroke, MI, or death from cardiovascular causes	11.9	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	11.4	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	0.3	0.3	1.01 (0.38–2.70)	0.98
MI	0.1	0.1	1.44 (0.24–8.63)	0.69
TIA	1.8	1.5	0.82 (0.53–1.26)	0.36

Source: Wang Y et al. N Engl J Med. 2013;369(1):11-9.

RESULTS

Safety Outcomes	Aspirin	Clopidogrel and Aspirin	Hazard Ratio (95% CI)	P value
Bleeding, %				
Severe	0.2	0.2	0.94 (0.24–3.79)	0.94
Moderate	0.2	0.1	0.73 (0.16–3.26)	0.68
Mild	0.7	1.2	1.57 (0.88–2.79)	0.12
Any bleeding	1.6	2.3	1.41 (0.95–2.10)	0.09

Source: Wang Y et al. N Engl J Med. 2013;369(1):11-9.

POINT TRIAL (2018)

Clopidogrel and Aspirin in AIS and High-Risk TIA – MC, R, DB, PC	
Objective	Evaluate dual clopidogrel and aspirin therapy compared to aspirin alone in patients with minor ischemic stroke or TIA
Primary Outcome	Efficacy: Composite of ischemic stroke, MI, or death from ischemic vascular causes Safety: Risk of major hemorrhage
Methods	Inclusion*: AIS with NIHSS ≤ 3; high-risk TIA: Exclusion*: Symptoms limited to isolated numbness, visual changes, or dizziness; planned anticoagulant therapy Intervention: Treatment arm: Day 1: aspirin 50–325mg + clopidogrel 600 mg; Day 2–90: aspirin 50–325mg + clopidogrel 75 mg Control arm: Day 1–90: aspirin 50–325mg

Source: Johnston SC et al. N Engl J Med. 2018;379(3):215-225.

DEMOGRAPHICS

Characteristics	Clopidogrel and Aspirin (N = 2432)	Aspirin (N = 2449)
Age, median	65	65
Female sex, %	45.1	44.8
Qualifying event, %		
TIA	43.4	43.0
Ischemic stroke	56.6	57.0
$ABCD^2$ score, median	5.0	5.0
NIHSS for ischemic stroke	2.0	2.0
Medical history, %		
Ischemic heart disease	10.6	9.8
Hypertension	69.9	68.9
Diabetes mellitus	28.0	27.1

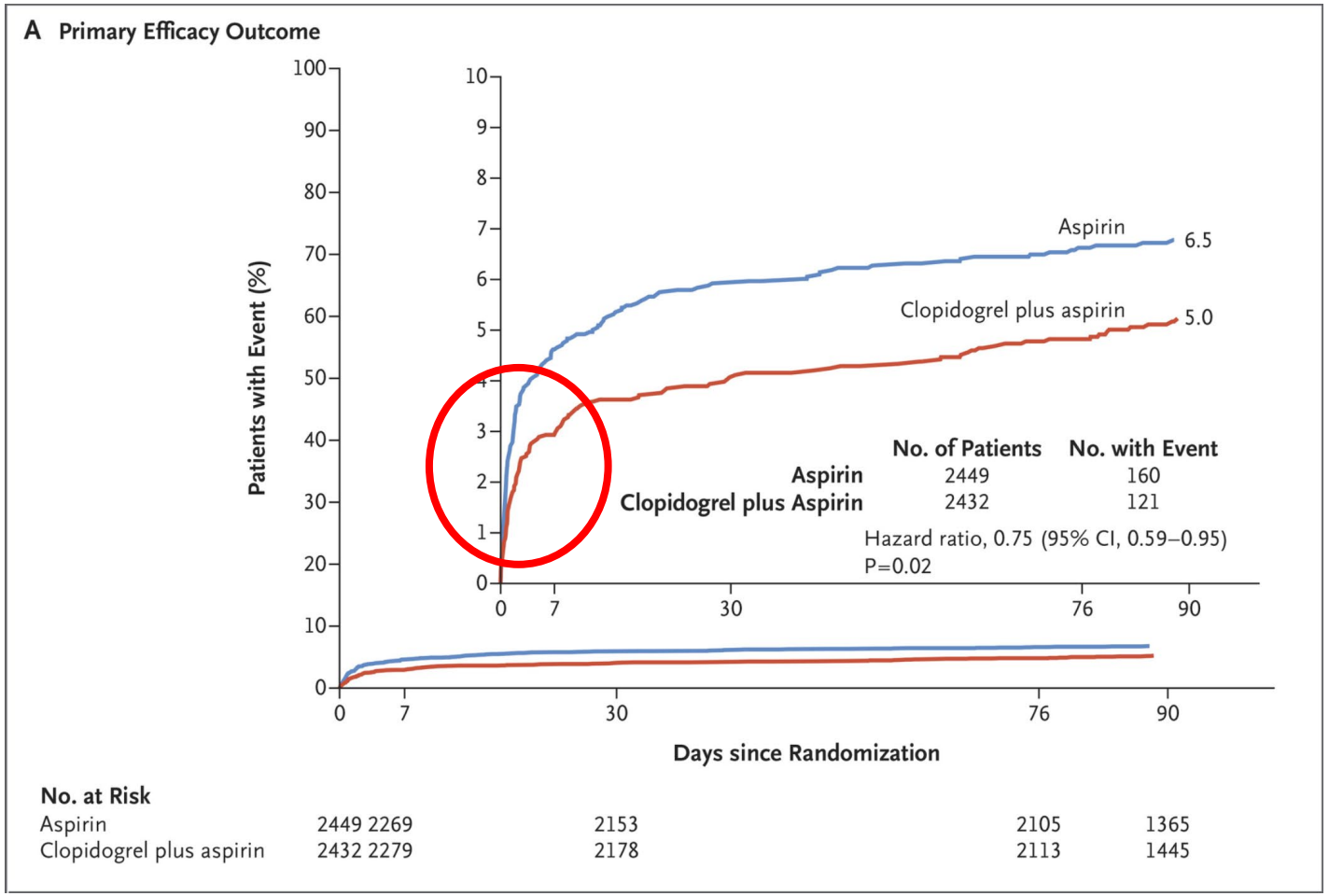
Source: Johnston SC et al. N Engl J Med. 2018;379(3):215-225.

RESULTS

Efficacy Outcomes	Clopidogrel and Aspirin	Aspirin	Hazard Ratio (95% CI)	P value
Primary				
Composite ischemic stroke, MI, or death from ischemic vascular causes	5.0	6.5	0.75 (0.59–0.95)	0.02
Secondary				
Ischemic stroke	4.6	6.3	0.72 (0.56–0.92)	0.01
MI	0.4	0.3	1.44 (0.55–3.78)	0.46
Death from ischemic vascular causes	0.2	0.2	1.51 (0.43–5.35)	0.52
Composite ischemic stroke, MI, death from ischemic vascular causes, or major hemorrhage	5.8	6.8	0.84 (0.67–1.05)	0.13

Source: Johnston SC et al. N Engl J Med. 2018;379(3):215-225.

RESULTS



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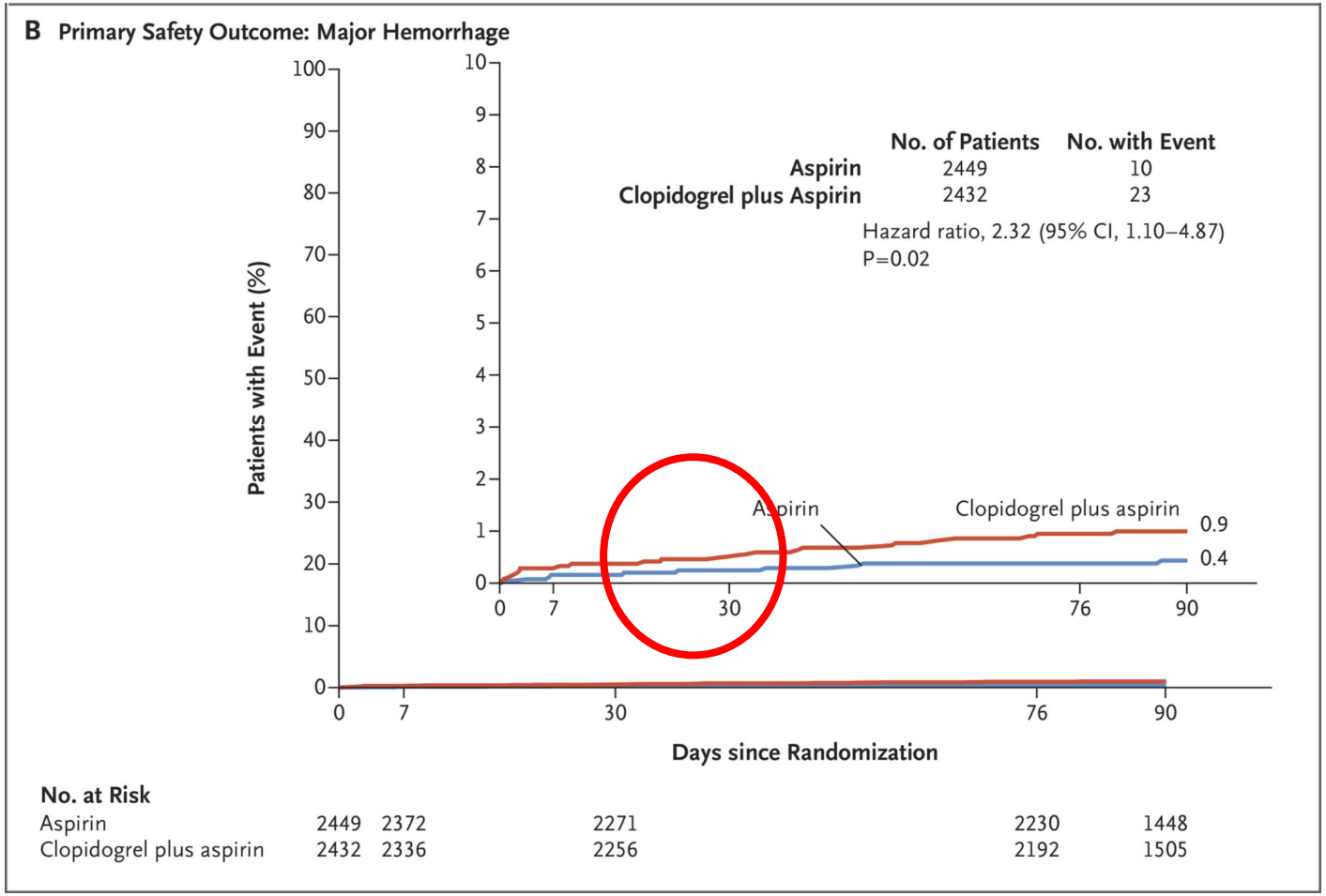
RESULTS



Source: Johnston SC et al. N Engl J Med. 2018;379(3):215-225.

TRIAL SUMMARIES

Trial	Bottom Line
Match Trial	No significant difference with DAPT in reduction of major vascular events but associated with significant risk of bleeding
CHARISMA	No significant reduction with DAPT in major cardiovascular events. Potential benefit of DAPT in risk reduction of any non-fatal stroke benefit probably outweighed by risk of bleeding
FASTER	No significant difference with DAPT in reduction of stroke at 90 days but associated with significant risk of symptomatic bleeding
SPS3	No significant difference with DAPT in reduction of all strokes but associated with significant risk of all major hemorrhages
CHANCE	Significant reduction in risk of stroke with DAPT at 90 days without a significant risk of hemorrhage
POINT	Significant reduction in risk of major ischemic events with DAPT at 90 days along with a significant risk of major hemorrhage

PHARMACY TECHNICIAN/PHARMACIST ASSESSMENT QUESTION 2

- Which combination of antiplatelet agents were utilized in the CHANCE and POINT trials?
  a. aspirin plus ticagrelor
  b. aspirin plus dipyridamole
  c. aspirin plus clopidogrel
  d. aspirin plus prasugrel

PHARMACY TECHNICIAN/PHARMACIST ASSESSMENT RESPONSE 2

- Which combination of antiplatelet agents were utilized in the CHANCE and POINT trials?
  a. aspirin plus ticagrelor
  b. aspirin plus dipyridamole
  c. **aspirin plus clopidogrel**
  d. aspirin plus prasugrel

PHARMACIST ASSESSMENT QUESTION 3

- Which of the following DAPT trials showed risk reduction of stroke with dual antiplatelet therapy?
  a. CHANCE Trial
  b. FASTER Trial
  c. MATCH Trial
  d. POINT Trial
  e. Both a and d

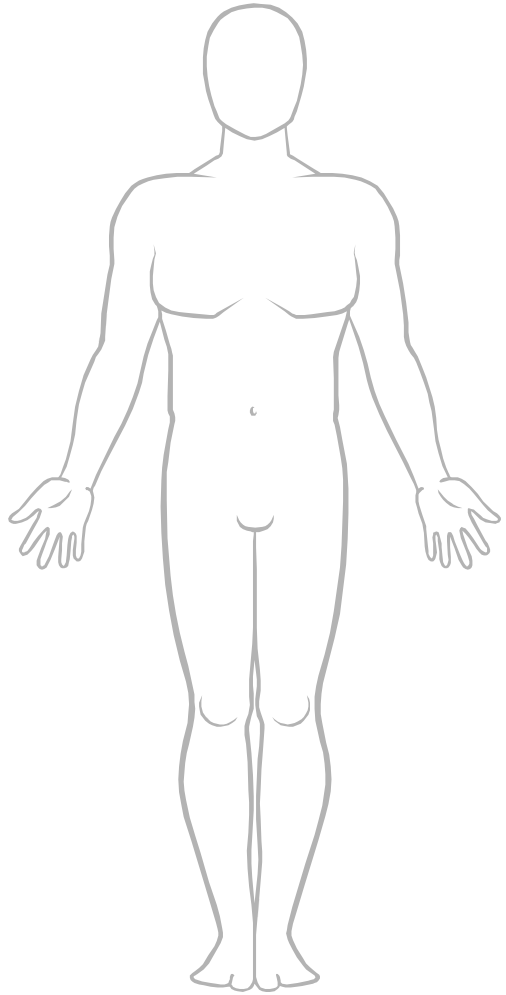
PHARMACIST ASSESSMENT RESPONSE 3

- Which of the following DAPT trials showed risk reduction of stroke with dual antiplatelet therapy?
  a. CHANCE Trial
  b. FASTER Trial
  c. MATCH Trial
  d. POINT Trial
  e. **Both a and d**

DETERMINING THE IDEAL DAPT CANDIDATE

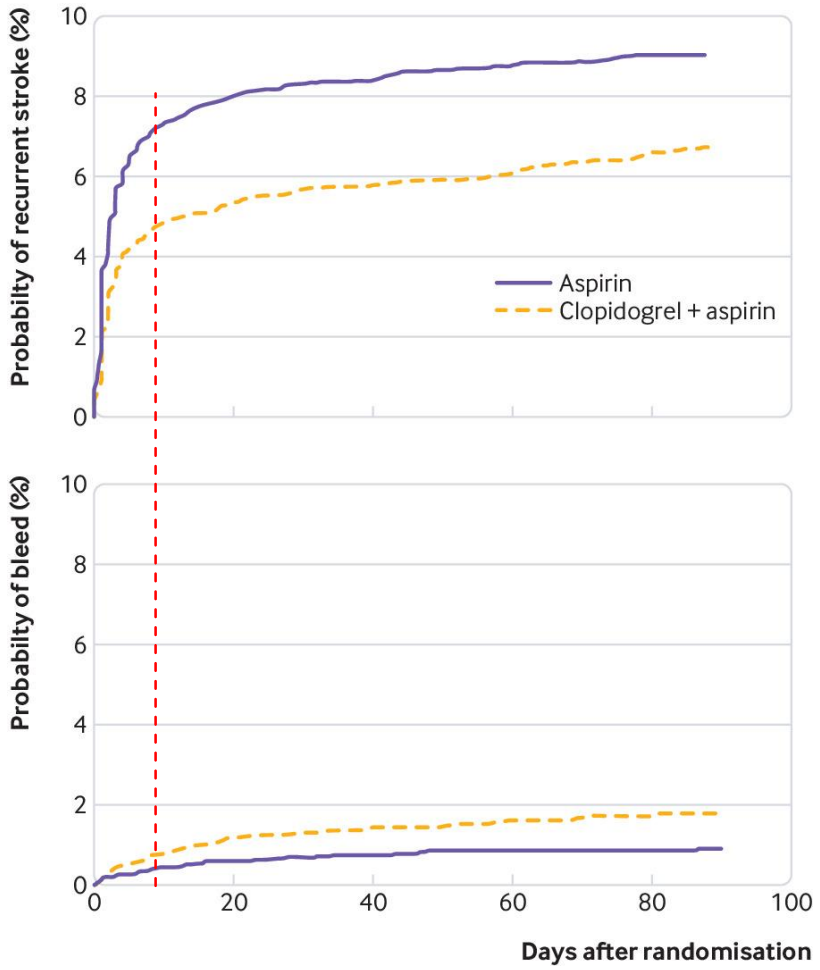
IDEAL PATIENT CHARACTERISTICS FOR DAPT

- Acute onset of minor ischemic stroke or TIA
  - NIHSS ≤ 3
  - $ABCD^2$ score > 4
  - Able to start DAPT within 24 hours of symptom onset
- No contraindications to receiving anti-platelet therapy
- No significant co-morbidities
- Low risk of bleeding
- Good outpatient follow-up



DURATION OF DAPT

- 2018 ACC/AHA Stroke guidelines
  - "**treatment for 21 days** with dual antiplatelet therapy (aspirin and clopidogrel) begun **within 24 hours** can be beneficial for early secondary stroke prevention"
- Meta analysis of the CHANCE, POINT, and FASTER trial showed risk of recurrent stroke in first 10 days
- Increased risk of bleeding with DAPT throughout course of treatment, but especially with prolonged treatment > 22 days



Source: Qiukui Hao et al. BMJ. 2018;363:k5108.

PHARMACY TECHNICIAN/PHARMACIST ASSESSMENT QUESTION 4

- Which of the following patient populations would benefit most from early initiation of antiplatelet therapy for secondary prevention?
  a. Ischemic stroke
  b. Hemorrhagic stroke
  c. Transient ischemic attack
  d. Both A and C
  e. None of the above

PHARMACY TECHNICIAN/PHARMACIST ASSESSMENT RESPONSE 4

- Which of the following patient populations would benefit most from early initiation of antiplatelet therapy for secondary prevention?
  a. Ischemic stroke
  b. Hemorrhagic stroke
  c. Transient ischemic attack
  d. **Both A and C**
  e. None of the above

BACK TO PATIENT YJ

YJ is a 57 y/o Caucasian male with a PMH significant for HTN and HLD. While watching tv at home, he started feeling weakness in his left arm and leg. His wife also noticed he had a slight left sided facial droop. Concerned for stroke, his wife called EMS and he was brought in to the emergency department.

On arrival:

Patient's symptoms appear to be resolved per neurology exam

NIHSS = 0

Admitted to observation unit for 24 hours

Neurology resident asks you if this patient would benefit from dual antiplatelet therapy. What would be your response?

PHARMACIST ASSESSMENT QUESTION 5

- What would be the most appropriate response to the neurology resident's question regarding patient YJ?
  a. Given the high severity of his stroke, he would not be an ideal candidate for DAPT
  b. Given his minor stroke, he would be an ideal candidate for DAPT if started within 24 hours
  c. The patient may be a candidate for DAPT, but should wait at least 72 hours before starting DAPT

PHARMACIST ASSESSMENT RESPONSE 5

- What would be the most appropriate response to the neurology resident's question regarding patient YJ?
  a. Given the high severity of his stroke, he would not be an ideal candidate for DAPT
  b. **Given his minor stroke, he would be an ideal candidate for DAPT if started within 24 hours**
  c. The patient may be a candidate for DAPT, but should wait at least 72 hours before starting DAPT

PHARMACIST ASSESSMENT QUESTION 6

- Based on literature reviewed and guideline recommendations, what would be the ideal duration of treatment with DAPT?
  a. 9 Days
  b. 21 Days
  c. 90 Days
  d. Indefinitely

PHARMACIST ASSESSMENT RESPONSE 6

- Based on literature reviewed and guideline recommendations, what would be the ideal duration of treatment with DAPT?
  a. 9 Days
  b. **21 Days**
  c. 90 Days
  d. Indefinitely

THANK YOU!

PARTH PARIKH

PARTHP90@PHARMACY.RUTGERS.EDU