Evidence-Based Medicine: Clopidogrel Plus Aspirin in Acute Ischemic Stroke

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Our patient . . .

A 63-year-old woman is brought to the ER after her husband found her this morning with new onset R- sided weakness and inability to speak. She was last seen feeling well and functioning normally at 10 pm the night before.

According to her family, she has had no recent illnesses. Her appetite has been good. Her weight has been stable. She has not complained of fevers, chills, chest discomfort, difficulty breathing, changes in bowel movements or urination. She has not complained of recent changes in vision, slurred speech, focal weakness, balance problems or headache. She has not fallen recently and has had no other trauma.

Medications:

- ASA 81 mg po daily
- Lisinopril 20 mg po daily
- HCTZ 25 mg po daily
- Metformin 1000 mg po daily
- Liraglutide 1.2 mg SQ daily
- Alendronate 70 mg po weekly

PMH:

- HTN
- Type 2 diabetes mellitus
- Osteoporosis
- Osteoarthritis of the knees

Social history: She lives with her husband. She works at a local store. She smoked 1ppd x 20 years but quit 10 years ago. There is no hx of alcohol or drug use. She walks for exercise for 20 minutes three times weekly.

Fam hx:

- Mother d. 89 stroke; hx HTN
- Father d. 90, COPD; hx type 2 diabetes
- 1 brother age 60, HTN
- 1 sister age 56, HTN
- Three children, ages 38, 35, and 30, all healthy

On exam, the patient is a mildly overweight woman who is sleepy and aphasic. She opens her eyes briefly with verbal and tactile stimuli and follows some commands.

Vitals: bp 170/100 p 84 RR 20 temp afebrile O2 sat 93% on RA

HEENT:	PERRL; eyes conjugate oropharynx: moist mucous membranes; no exudate
Neck:	supple; no anterior or posterior cervical adenopathy; trachea midline; no thyromegaly
Car:	r/r/r without r/m/g; no JVD; there is a soft left carotid bruit
Lungs:	CTA without w/r/r
Abd:	nondistended; soft, nontender; no organomegaly
Extr:	no edema; dp pulses 1+ symmetric
Skin:	no rashes or other skin lesions

Neuro:

Cranial nerves:

II,III:	PERRL; eyes conjugate; she has a right visual field cut to confrontational testing
III, IV, VI:	EOMI
V:	facial sensation to light touch symmetric
VII:	there is a R lower facial drop; strength is 5/5 over both sides of the forehead
VIII:	hearing adequate to finger rub
IX, X:	soft palate elevates symmetrically with gag
XI:	shoulder shrug 5/5 bilaterally
XII:	tongue deviates to the L

Motor:

- Bulk: normal in all four extremities
- Tone: R arm flaccid; R leg tone normal
- Strength: R arm 0/5
  R leg: hip flexion 4/5; leg extension 4/5; plantar flexion 4/5
  L arm: 5/5 throughout
  L leg: 5/5 throughout

Sensation: Withdraws to painful stimuli to L arm and L leg only

Cerebellar: L finger to nose and heel to shin testing intact; unable to complete R finger to nose or heel to shin testing.

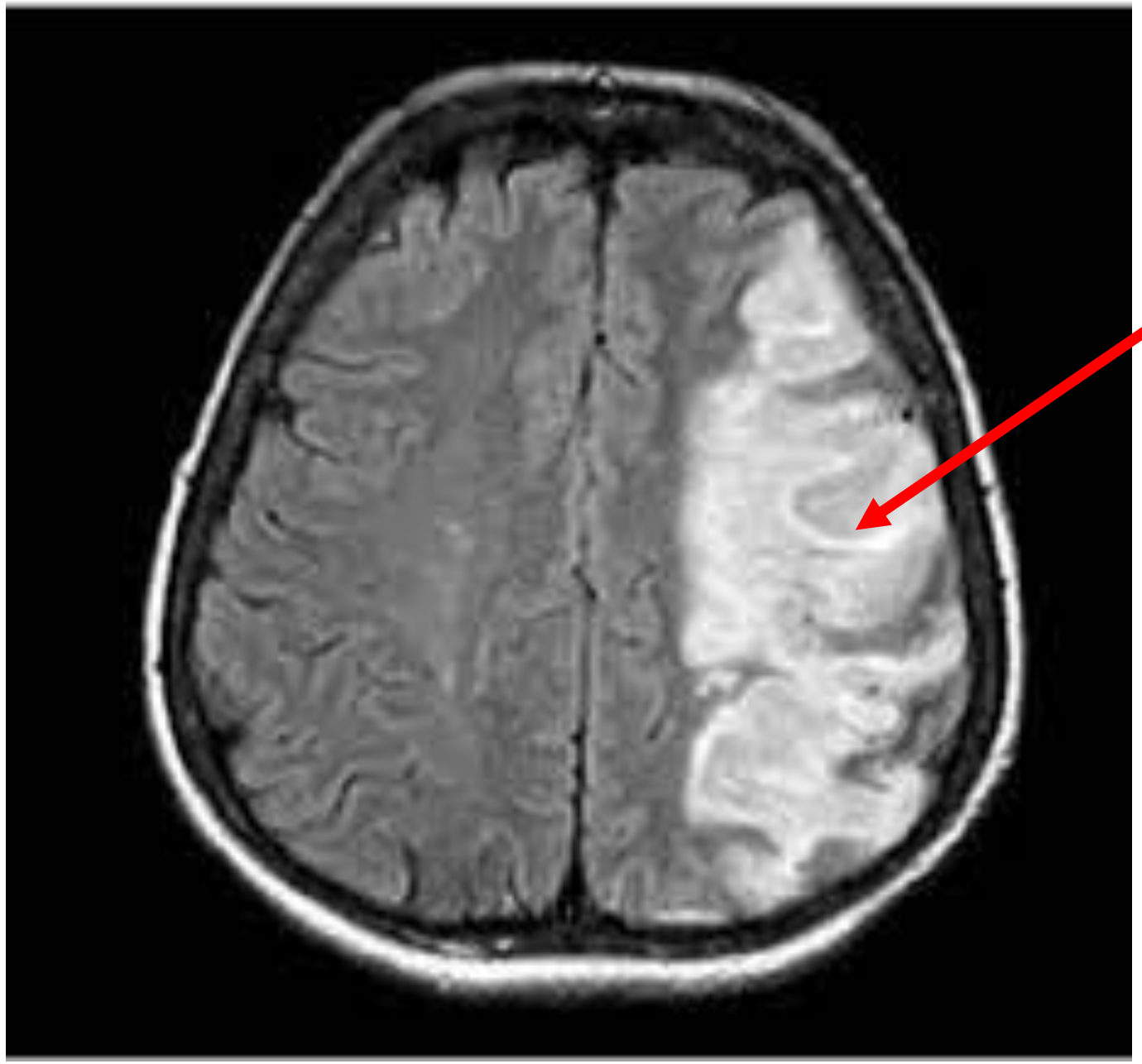
Reflexes:

	Right	Left
biceps	2+	2+
triceps	2+	2+
brachioradialis	2+	2+
patellar	1+	1+
ankle jerks	3+	1+
Babinski	present	absent

EKG: shows a normal sinus rhythm, rate 80, normal axis, PR interval 156 msec, QRS duration: 110 msec, QTc interval 450 msec. There are nonspecific ST and T wave changes

A Head CT is negative for hemorrhage or other acute changes . . .

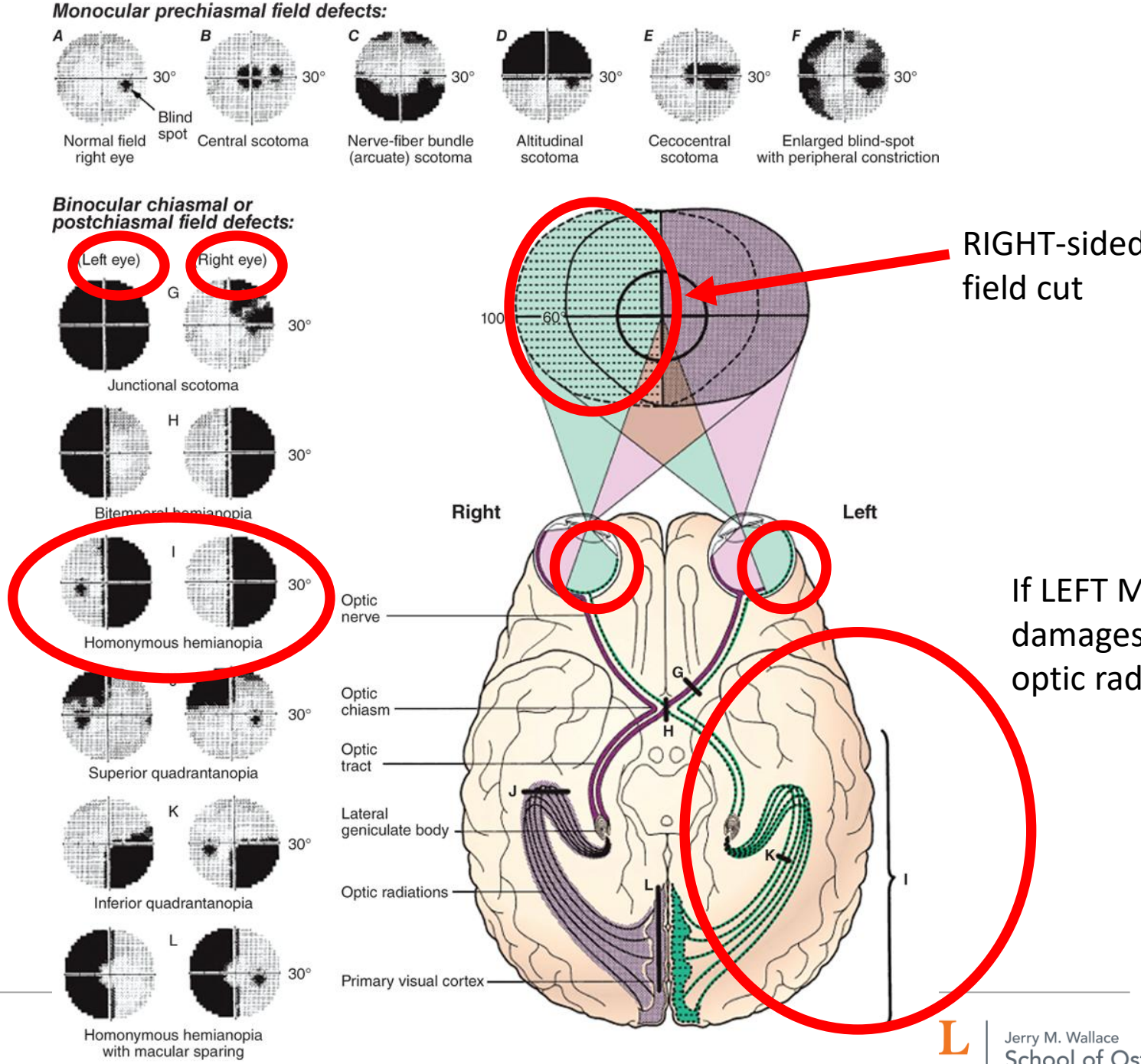
A brain MRI is performed . . .



L MCA distribution ischemic infarction

researchgate.net

Results in a RIGHT-sided visual field cut (ie. RIGHT homonymous hemianopia)



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Citation: Chapter 28 Disorders of the Eye, Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. *Harrison's Principles of Internal Medicine, 20e;* 2018. Available at: https://accessmedicine.mhmedical.com/content.aspx?sectionid=192011900&bookid=2129 Accessed: May 18, 2021

Jerry M. Wallace School of Osteopathic Medicine

The patient is diagnosed with an acute left middle cerebral artery distribution ischemic stroke.

Per the report of the patient's family, the patient has been compliant with her daily ASA.

You ask your team if the patient should stop ASA and take clopidogrel daily OR continue ASA and add clopidogrel to decrease her risk of another ischemic CVA. However, you and the patient's family a concerned about the risk of bleeding . . .

Clinical Question:
What are the efficacy and safety of clopidogrel plus aspirin compared to aspirin alone in ischemic stroke and high-risk TIA?

Source:
Johnston SC et al, Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med* 2018; 379:215-25.

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

1. Was the assignment of patients to treatment randomized? And was the randomization list concealed?

2. Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

1. Were the patients and clinicians kept “blind” to which treatment was being received?

2. Aside from the experimental treatment, were the groups treated equally?

3. Were the groups similar at the start of the trial?

If the study satisfies these criteria, then it has *internal validity.*

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

Do these results apply to your patient?

(ie. Do the results have *external validity*?)

- Is the patient so different from those in the trial that its results cannot help you?
- How great would the potential benefit of therapy actually be for your individual patient?

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

- Are your patient's values and preferences satisfied by the regimen and its consequences?
  - Do your patient and you have a clear assessment of their values and preferences?
  - Are they met by this regimen and its consequences?

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke

Design: Randomized, double-blind, placebo-controlled trial

Setting: Clinical centers in the US 10 other countries in North America, Europe, Australia and New Zealand

Was the assignment of patients treatment randomized?
And was the randomization list concealed?

Were the patients and clinicians kept “blind” to which treatment was being received?

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke: Patients included

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke: Patients included

- 18 years or older
- Randomized within 12 hours after an acute ischemic stroke
- NIHSS score of 3 or less OR

ABCD2 score of 4 or more

- Head CT or Brain MRI negative for intracranial hemorrhage or other condition explaining neurologic symptoms
- Written consent obtained

National Institutes of Health Stroke Scale (NIHSS)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (ie, repeated requests to patient to make a special effort).

Instructions	Scale definition
1a. Level of consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert;** but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert;** requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. Level of consciousness questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.

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1c. Level of consciousness commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (ie, follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.
2. Best gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (cranial nerves III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.

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3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).
4. Facial palsy: Ask - or use pantomime to encourage - the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).

National Institutes of Health Stroke Scale (NIHSS)

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5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____ **5a. Left arm** **5b. Right arm**
6. Motor leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____ **6a. Left leg** **6b. Right leg**

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7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain:_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.

National Institutes of Health Stroke Scale (NIHSS)

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9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____

National Institutes of Health Stroke Scale (NIHSS)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (ie, repeated requests to patient to make a special effort).

11. Extinction and inattention (formerly neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.

Adapted from: Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. Stroke 1997; 28:307.

Patients included in the trial had a NIHSS score of 3 or less (ie. not a severe stroke)

ABCD^2 score

The ABCD^2 score can be used to estimate the risk of ischemic stroke in the first two days after TIA. The score is tallied as follows:	
Age:	
≥60 years	1 point
<60 years	0 points
Blood pressure elevation when first assessed after TIA:	
Systolic ≥140 mmHg **or** diastolic ≥90 mmHg	1 point
Systolic <140 mmHg **and** diastolic <90 mmHg	0 points
Clinical features:	
Unilateral weakness	2 points
Isolated speech disturbance	1 point
Other	0 points
Duration of TIA symptoms:	
≥60 minutes	2 points
10 to 59 minutes	1 point
<10 minutes	0 points
Diabetes:	
Present	1 point
Absent	0 points

Data from: Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007; 369:283.

Patients in the trial had a ABCD2 score of 4 or more (ie. high-risk TIA)

Clopidogrel plus ASA vs ASA alone in ischemic stroke: Patients excluded

Clopidogrel plus ASA vs ASA alone in Ischemic Stroke: Patients excluded

- *Isolated* symptoms of TIA including one of the following
  - Numbness
  - Visual changes
  - Dizziness
  - Vertigo
- Received thrombolytic therapy within one week before the TIA
- At time of screening, candidate for:
  - Thrombolysis
  - Endovascular therapy
  - Endarterectomy

Clopidogrel plus ASA vs ASA alone in Ischemic Stroke: Patients excluded

- Planned therapy with
  - Antiplatelet medication
  - Anticoagulant medication

  (ie. patients with documented or suspection atrial fib or CAD)

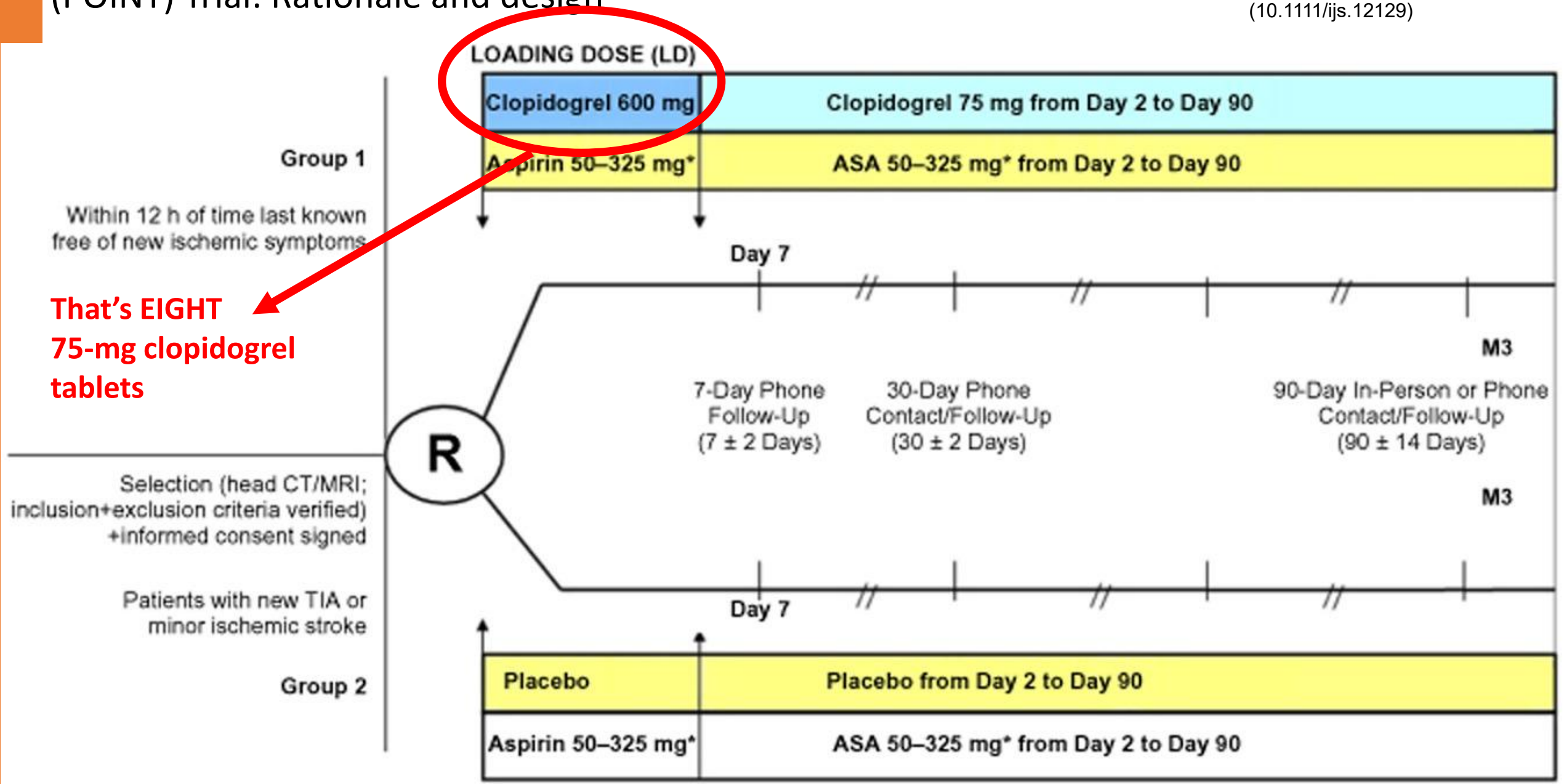
- Other contraindication to clopidogrel or ASA

- Anticipated use of NSAIDS for more than 7 days during trial period.

Clopidogrel plus ASA vs ASA alone in Ischemic Stroke: Interventions

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial: Rationale and design

International Journal of Stroke,
Volume: 8, Issue: 6,
Pages: 479-483, First published:
23 July 2013, DOI:
(10.1111/ijs.12129)



Clopidogrel Plus ASA vs ASA Alone in Ischemic or High-Risk TIA: Interventions

- Intention-to-treat analysis: every subject included in data analysis once randomization has occurred.

Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Clopidogrel plus ASA vs ASA alone in Ischemic Stroke: Outcomes

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke: Primary Outcomes

- Primary efficacy outcome: composite of
  - Ischemic stroke
  - Myocardial infarction
  - Death from ischemic vascular disease

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke: Primary Outcomes

- Primary safety outcome: major hemorrhage
  - Symptomatic intracranial hemorrhage
  - Intraocular bleeding causing vision loss
  - Transfusion of two of more units or prbcs or whole blood
  - Hospitalization due to bleeding
  - Prolonging existing hospitalization due to bleeding

Clopidogrel plus ASA vs ASA alone in Ischemic Stroke: Secondary Outcomes

- Secondary efficacy outcomes:
  - Individual events
    - Ischemic stroke
    - Myocardial infarction
    - Death from ischemic vascular disease
  - Total number of ischemic and hemorrhagic strokes

Clopidogrel plus ASA vs ASA alone in Ischemic Stroke: Secondary Outcomes

- Secondary safety outcomes:
  - Hemorrhagic stroke
  - Symptomatic intracerebral hemorrhage
  - Other symptomatic intracranial hemorrhage
  - Major hemorrhage other than intracranial hemorrhage
  - Minor hemorrhage (including asymptomatic intracranial hemorrhage)
  - Death from any cause

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke: Study Power

Prespecified Interim Data Analyses

Interim Analysis	Date	HR for primary efficacy endpoint	P value
First	March 2013	0.77	0.22
Second	April 2016	0.70	0.012
Third	November 2017	0.75	0.015

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Study Power

- Assuming a primary outcome event rate in the ASA alone group of 15%

- A sample of 4,150 patients would ensure:
  - A Hazard ratio of 0.75 in the primary efficacy endpoint between the clopidogrel plus ASA vs ASA alone. (ie. A 25% difference in the primary outcome between the two groups.)

  WITH

  - 90% Power (ie. 90% probability of detecting an outcome difference)

  AND WITH

  - Alpha level (ie. p value of 0.05) (ie. a 5% probability that the outcome difference detected is not a true difference *but occurred by chance alone*)

First interim data analysis . . .

- A *significantly lower rate of the primary endpoint was observed* in the ASA only group at first interim analysis (ie. only about 6.5% instead of 15%)

First interim data analysis . . .

SO

- The target sample size was increased from 4,150 to 5,840 patients which was calculated to ensure
  - A Hazard ratio of 0.75 in the primary efficacy endpoint between the clopidogrel plus ASA vs ASA alone. (ie. A 25% difference in the primary outcome between the two groups.)

  WITH

  - *80% Power* (ie. 80% probability of detecting an outcome difference)

  AND WITH

  - Alpha level (ie. p value of 0.05) (ie. a 5% probability that the outcome difference detected is not a true difference *but occurred by chance alone*)

Trial discontinuation . . .

- In August 2017, the prespecified minimum number of major hemorrhages was **exceeded** in trial. The trial patients were followed closely until . . .

- Data and safety monitoring board met in December 2017
  - Findings:
    - Significant excess of patients with major hemorrhage in the combined clopidogrel plus ASA-treated patients AND
    - Significant difference in the *primary efficacy point* between groups (ie. ischemic stroke, myocardial infarction, death from ischemic vascular disease)

Trial discontinuation . . .

- Data and safety monitoring board met in December 2017
  - Recommended stopping enrollment in the trial . . .

Trial discontinuation . . .

- At time of trial discontinuation:
  - 4,881 patients enrolled (83.6% of target number of 5,840)
  - 93.4% of enrolled patients had been followed through the 90-day trial or had died

Trial discontinuation . . .

Study Group	Discontinuation of study medication (%)	Withdrawal from trial OR lost to follow up (%)
Clopidogrel plus ASA	29.6	6.4
ASA Alone	27.5	6.8

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke: Main Results

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics:

Characteristic	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
Median age (years)	65	65
Female sex (%)	45.1	44.8

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics

Race (%)	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
White	75.2	74.9
Black	20.0	20.7
Hispanic	6.2	6.3
Asian	3.3	2.8
Other	1.5	1.6

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics:

Region (%)	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
United States	82.8	82.9
Other countries	17.2	17.1

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics:

Medical history (%)	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
Ischemic heart disease	10.6	9.8
HTN	69.9	68.9
Diabetes mellitus	28.0	27.1

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics:

Medication use at presentation (%)	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
ASA	58.3	57.0
Clopidogrel	2.0	1.7

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics:

Time from presentation to randomization (hours)	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
Mean	7.4	7.3

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics:

Qualifying Event (%)	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
TIA	43.4	43.0
Ischemic stroke	56.6	57.0

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Baseline Patient Characteristics:

Mean qualifying neurologic score	Clopidogrel plus ASA (N= 2432)	ASA Alone (N=2449)
ABCD2 for TIA	5.0	5.0
NIHSS for Ischemic Stroke	2.0	2.0

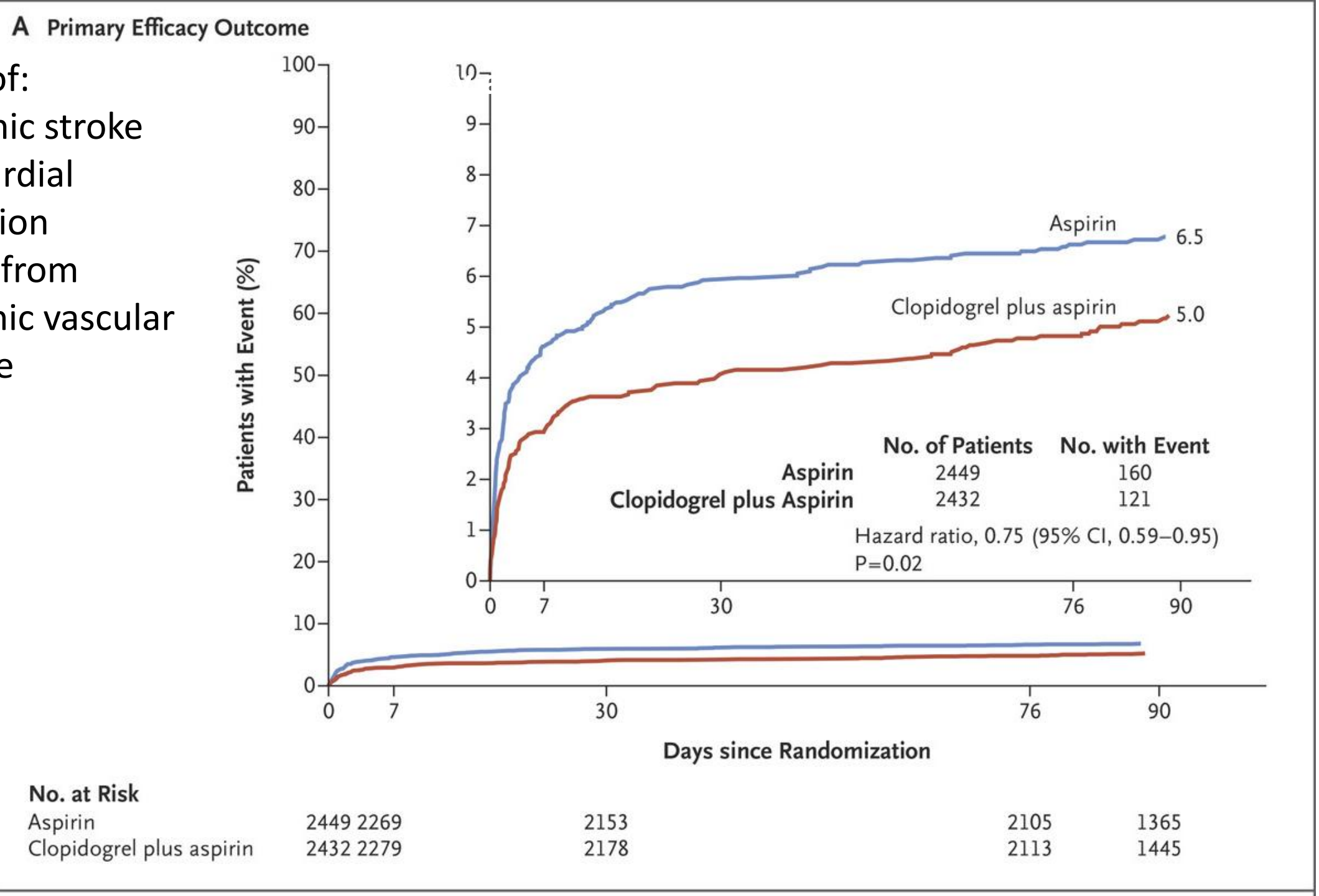
- Aside from the experimental treatment, were the groups treated equally?
- Were the groups similar at the start of the trial?

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Primary Outcomes

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Primary Efficacy Outcome

Composite of:

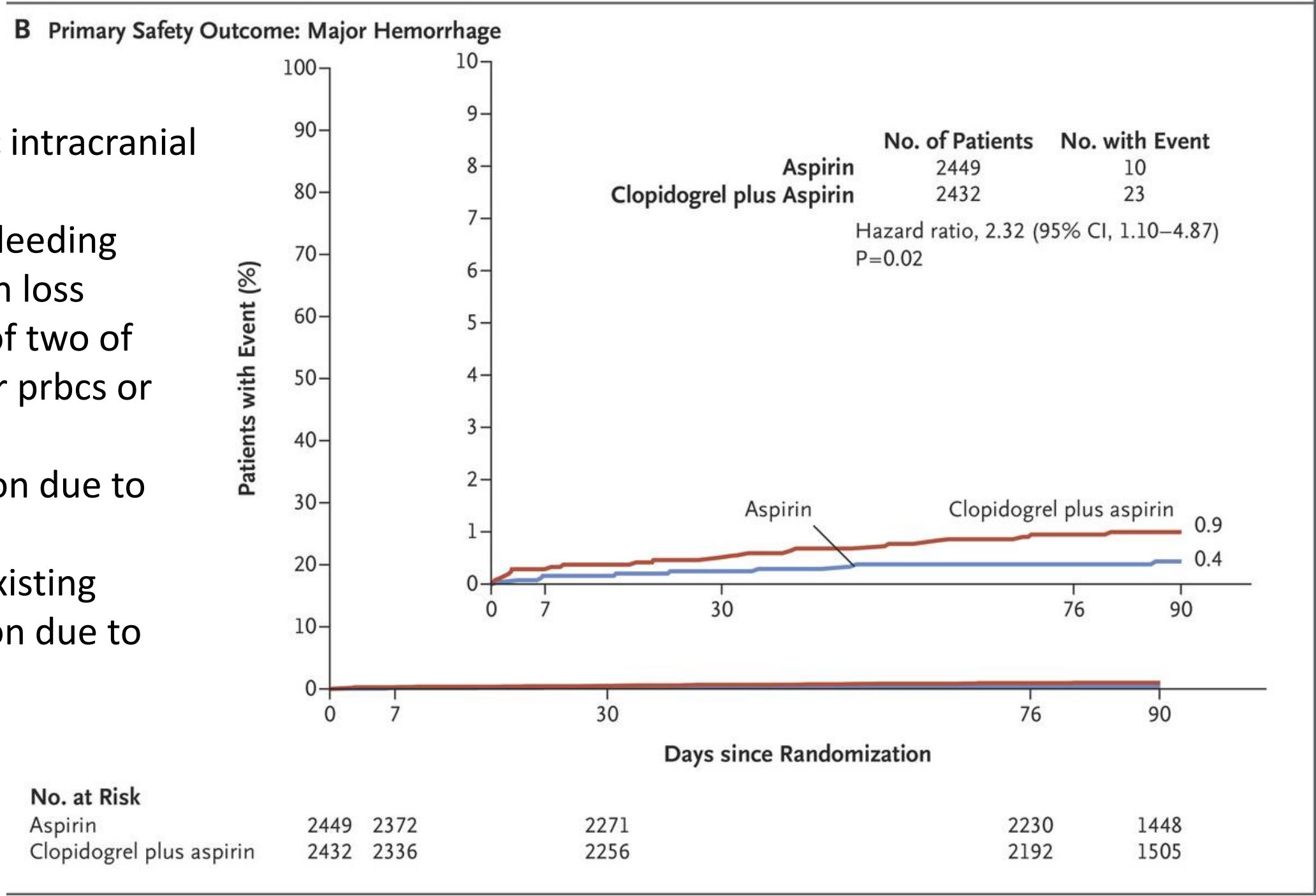
- Ischemic stroke
- Myocardial infarction
- Death from ischemic vascular disease



Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Primary Safety Outcome

Composite of:

- Symptomatic intracranial hemorrhage
- Intraocular bleeding causing vision loss
- Transfusion of two of more units or prbcs or whole blood
- Hospitalization due to bleeding
- Prolonging existing hospitalization due to bleeding



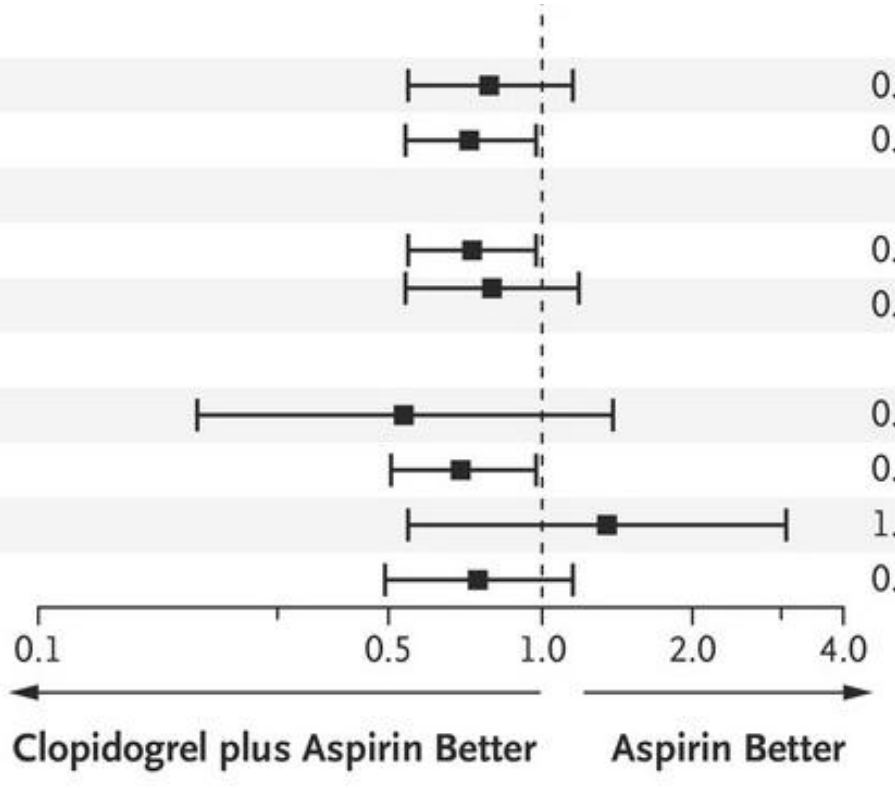
Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Subgroup Analysis of Primary Safety Outcome

Hazard Ratio of Primary Efficacy Outcome--Composite of:

- Ischemic stroke
- Myocardial infarction
- Death from ischemic vascular disease

Subgroup analyses: Prior ASA. Prior statin, ASA dose during trial

Subgroup	No. of Patients	Clopidogrel plus Aspirin	Aspirin	Hazard Ratio (95% CI)	P Value for Interaction
		no. of patients with event (%)			
Previous aspirin therapy					0.71
No	2067	48 (4.7)	62 (5.9)	0.79 (0.55–1.16)	
Yes	2814	73 (5.2)	98 (7.0)	0.73 (0.54–0.98)	
Previous statin therapy					0.72
No	2991	77 (5.2)	107 (7.1)	0.73 (0.55–0.98)	
Yes	1890	44 (4.6)	53 (5.7)	0.80 (0.54–1.20)	
Aspirin dose during trial					0.54
0 mg	193	7 (7.0)	11 (11.8)	0.54 (0.21–1.39)	
1–81 mg	3012	61 (4.1)	86 (5.7)	0.70 (0.51–0.97)	
82–100 mg	423	12 (5.6)	9 (4.3)	1.30 (0.55–3.08)	
>100 mg	1131	37 (6.6)	50 (8.7)	0.76 (0.49–1.16)	



Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Secondary Outcomes

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Secondary Efficacy Outcomes

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Secondary Efficacy Outcomes:

Secondary Efficacy Outcome	Clopidogrel plus ASA (N= 2432) (%)	ASA Alone (N=2449) (%)	Hazard Ratio (95% CI)	P value
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

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Secondary Efficacy Outcomes:

Secondary Efficacy Outcome	Clopidogrel plus ASA (N= 2432) (%)	ASA Alone (N=2449) (%)	Hazard Ratio (95% CI)	P value
Death from ischemic vascular disease	0.2	0.2	1.51(0.43-5.35)	0.52
Ischemic or hemorrhagic stroke	4.8	6.4	0.74(0.58-0.94)	0.01

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Secondary Safety Outcomes

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Secondary Safety Outcomes:

Secondary Efficacy Outcome	Clopidogrel plus ASA (N= 2432) (%)	ASA Alone (N=2449) (%)	Hazard Ratio (95% CI)	P value
Hemorrhagic stroke	0.2	0.1	1.68(0.40-7.03)	0.47
Symptomatic intracerebral hemorrhage	0.1	0.1	1.01(0.14-7.14)	0.99

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Secondary Efficacy Outcomes:

Secondary Efficacy Outcome	Clopidogrel plus ASA (N= 2432) (%)	ASA Alone (N=2449) (%)	Hazard Ratio (95% CI)	P value
Other symptomatic intracranial hemorrhage	0.1	0	N/A	0.16
Major hemorrhage other than intracranial hemorrhage	0.7	0.3	2.45(1.01-5.90)	0.04

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke: Secondary Efficacy Outcomes:

Secondary Efficacy Outcome	Clopidogrel plus ASA (N= 2432) (%)	ASA Alone (N=2449) (%)	Hazard Ratio (95% CI)	P value
Minor hemorrhage	1.6	0.5	3.12(1.67-5.83)	< 0.001
Death from any cause	0.7	0.5	1.51(0.73-3.13)	0.27

The bottom line . . . Benefits vs harms of clopidogrel plus ASA vs ASA alone in ischemic stroke or high-risk TIA . . .

Clopidogrel Plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Benefits vs Harms

Outcome	Clopidogrel plus ASA (N= 2432) (%)	ASA Alone (N=2449) (%)	ARR or AHI (%)	Number needed to treat or harm
Ischemic stroke	4.6	6.3	ARR 1.7	1/0.017= NNT of 59
Major hemorrhage	0.9	0.4	AHI 0.5	1/0.005= NNH of 200
ANY intracranial bleeding	0.37	0.20	AHI 0.17	1/0.0017= NNH 589

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Main Conclusions

Clopidogrel plus ASA vs ASA Alone in Ischemic Stroke or High-Risk TIA: Favorable features of the trial

- Large, multinational

- Diverse ethnic backgrounds represented in the sample size, though most patients were white and most patients lived in the United States

Patients given clopidogrel plus ASA compared to ASA alone for 90days after an ischemic stroke or high-risk TIA . . . .

- Had a lower risk of new ischemic stroke
- Had a lower risk of a composite outcome of ischemic stroke, MI or death from ischemic vascular disease

BUT

- Had NO significant difference in the individual outcomes
  - MI
  - Death from ischemic vascular disease
  - Hemorrhagic stroke (5 patients vs 3 patients, respectively)
  - Death from any cause
- Had a higher risk of **major** hemorrhage

Problems with this trial and these results

- The event rates in the trial sample size were unexpectedly low. For the primary efficacy outcome (composite of ischemic stroke, MI or death from ischemic vascular causes): 5.0% and 6.5 % in the two treatment groups when an *event rate of 15% was anticipated* in the ASA-only group. Smaller numbers of events make it harder to draw definitive conclusions.

Problems with this trial and these results

- The patients included had very minor strokes. Patients we see in the community setting often present with strokes involving larger anatomic regions and more deficits on exam. If patients like those we see in practice were included in this trial, I suspect the risk of hemorrhagic stroke and major hemorrhage would have been much higher.

- The restrictive inclusion criteria *call into question the trial's external validity* when using its results to care for patients presenting with stroke or TIA in the community.

Problems with this trial and these results

- Even with the restrictive inclusion criteria for minor strokes only, *the trial was stopped early anyway due to an excess number of major hemorrhages.*

- The 600-mg loading dose of clopidogrel is the dose used when PCI is used for an acute coronary syndrome. The brain DOES NOT EQUAL the heart. *I definitely have reservations about giving EIGHT 75-mg clopidogrel tablets to a patient who presents with acute ischemic stroke.*

Back to our patient. . .

Is the patient so different from those in the trial that its results cannot help you?

A 63-year-old woman is brought to the ER after her husband found her this morning with new onset R- sided weakness and inability to speak. She was last seen feeling well and functioning normally at 10 pm the night before.

According to her family, she has had no recent illnesses. Her appetite has been good. Her weight has been stable. She has not complained of fevers, chills, chest discomfort, difficulty breathing, changes in bowel movements or urination. She has not complained of recent changes in vision, slurred speech, focal weakness, balance problems or headache. She has not fallen recently and has had no other trauma.

Medications:

- ASA 81 mg po daily
- Lisinopril 20 mg po daily
- HCTZ 25 mg po daily
- Metformin 1000 mg po daily
- Liraglutide 1.2 mg SQ daily
- Alendronate 70 mg po weekly

PMH:

- HTN
- Type 2 diabetes mellitus
- Osteoporosis
- Osteoarthritis of the knees

Social history: Lives with husband. She works at a local store. She smoked 1ppd x 20 years but quit 10 years ago. There is no hx of alcohol or drug use. She walks for exercise for 20 minutes three times weekly.

Fam hx:

- Mother d. 89 Stroke; hx HTN
- Father d. 90, COPD; hx type 2 diabetes
- 1 brother age 60, HTN
- 1 sister age 56, HTN
- Three children, ages 38, 35, and 30, all healthy

On exam, the patient is a mildly overweight woman who is sleepy and aphasic. She opens her eyes briefly with verbal and tactile stimuli and follows some commands.

Vitals: bp 170/100 p 84 RR 20 temp afebrile O2 sat 93% on RA

HEENT:	PERRL; eyes conjugate oropharynx: moist mucous membranes; no exudate
Neck:	supple; no anterior or posterior cervical adenopathy; trachea midline; no thyromegaly
Car:	r/r/r without r/m/g; no JVD; there is a soft left carotid bruit
Lungs:	CTA without w/r/r
Abd:	nondistended; soft, nontender; no organomegaly
Extr:	no edema; dp pulses 1+ symmetric
Skin:	no rashes or other skin lesions

Neuro:

Cranial nerves:

II,III:	PERRL; eyes conjugate; she has a right visual field cut to confrontational testing
III, IV, VI:	EOMI
V:	facial sensation to light touch symmetric
VII:	there is a R lower facial drop; strength is 5/5 over both sides of the forehead
VIII:	hearing adequate to finger rub
IX, X:	soft palate elevates symmetrically with gag
XI:	shoulder shrug 5/5 bilaterally
XII:	tongue deviates to the L

Motor:

- Bulk: normal in all four extremities
- Tone: R arm flaccid; R leg normal
- Strength: R arm 0/5
  R leg: hip flexion 4/5; leg extension 4/5; plantar flexion 4/5
  L arm: 5/5 throughout
  L leg: 5/5 throughout

Sensation: Withdraws to painful stimuli to L arm and L leg only

Cerebellar: L finger to nose and heel to shin testing intact; unable to complete R finger to nose or heel to shin testing.

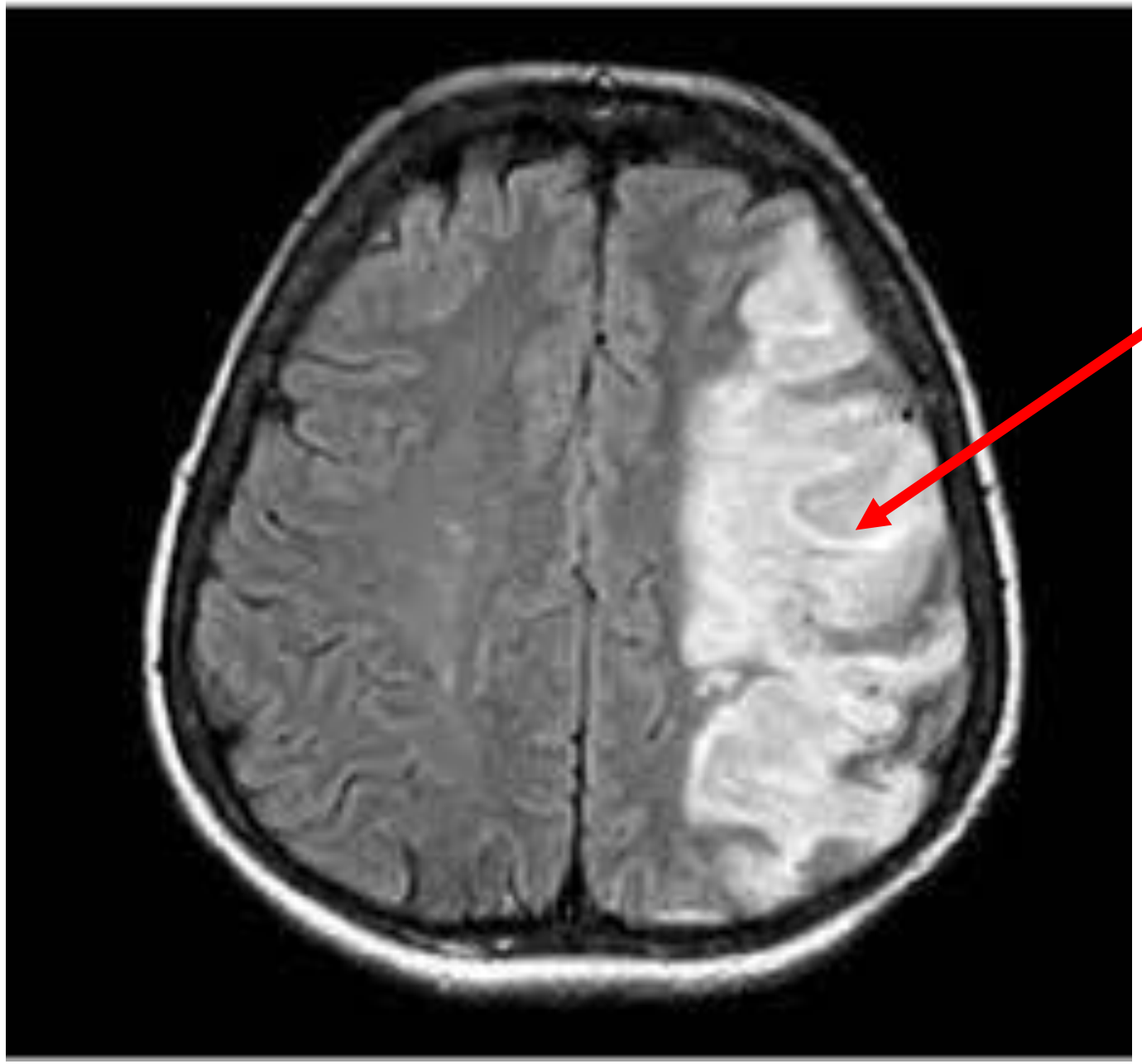
Reflexes:

	Right	Left
biceps	2+	2+
triceps	2+	2+
brachioradialis	2+	2+
patellar	1+	1+
ankle jerks	3+	1+
Babinski	present	absent

EKG: shows a normal sinus rhythm, rate 80, normal axis, PR interval 156 msec, QRS duration: 110 msec, QTc interval 450 msec. There are nonspecific ST and T wave changes

A Head CT is negative for hemorrhage or other acute changes . . .

A brain MRI is performed . . .



L MCA distribution ischemic infarction

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You discuss with your team that the available evidence of benefit for clopidogrel plus ASA in ischemic stroke is limited to patients with much milder stroke findings.

Our patient's NIHSS score is a about 22 and the trial studied patients with a mean NIHSS score of 2.

The trial lacks external validity and its results cannot be used to guide the care of your patient. In addition, there was a significant increase in the risk of major hemorrhage in the trial. Lastly, you suspect that your patient's risk of hemorrhagic transformation is *much higher* than that in the trial due to the large anatomic distribution of your patient's stroke.

Instead, you order to stop ASA and start clopidogrel 75-mg per NG tube daily *instead of, rather than in addition to ASA*. You also prescribe statin therapy and continue the patient's evaluation and management.

Questions?

Thank you!

CAMPBELL UNIVERSITY | Jerry M. Wallace School of Osteopathic Medicine