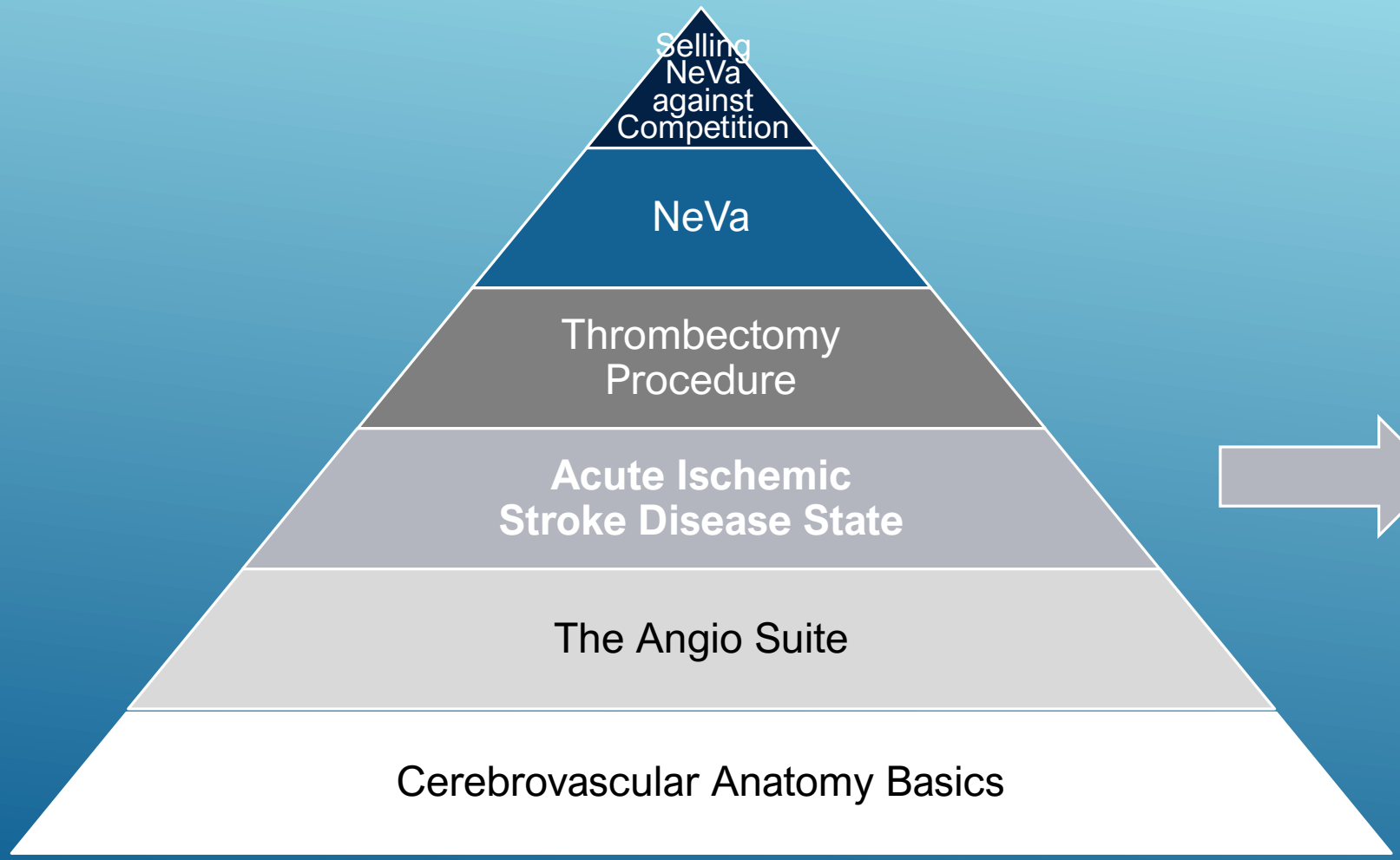
THE VESALIO DISTRIBUTOR TRAINING PROGRAM

Designed to give you confidence & credibility in front of physicians



TODAY

NeVa™

NEXT GENERATION STROKE TREATMENT

Designed for first pass success

MODULE 3: THE AIS DISEASE STATE

THE AIS DISEASE STATE

3.1. Introduction to AIS

- What is AIS
- AIS facts & figures in Europe
- Time is Brain
- Acting FAST

3.2. Treatment of AIS

- Penumbra & the goal of AIS treatment
- Overview of AIS treatment methods
- Evolution of AIS treatment: Technological and clinical milestones

3.3. Patient Selection & Guidelines

- Assessment scales used in AIS
- Patient selection for thrombectomy procedures
- AIS treatment guidelines and current debates

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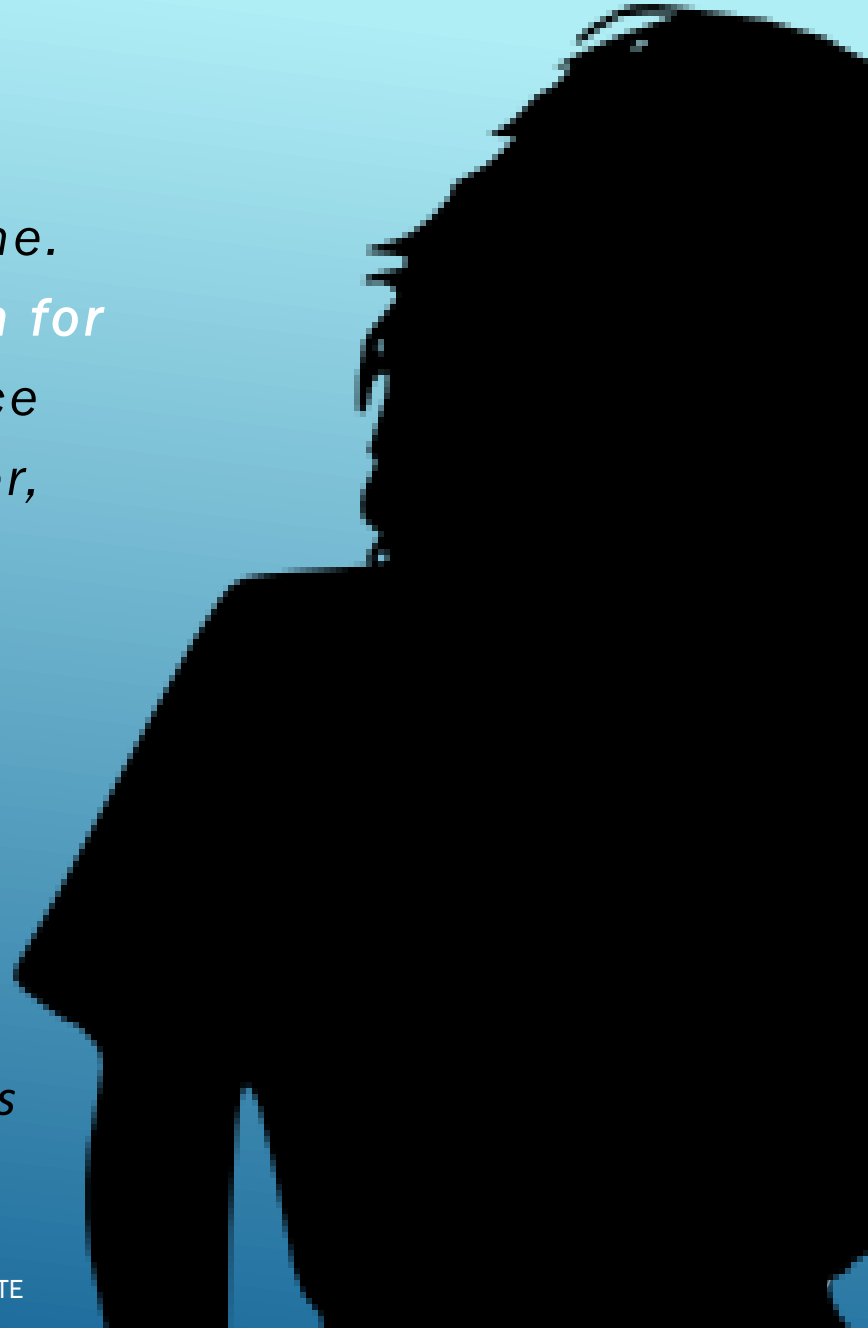
3.1. INTRODUCTION TO AIS

WHAT IS AIS



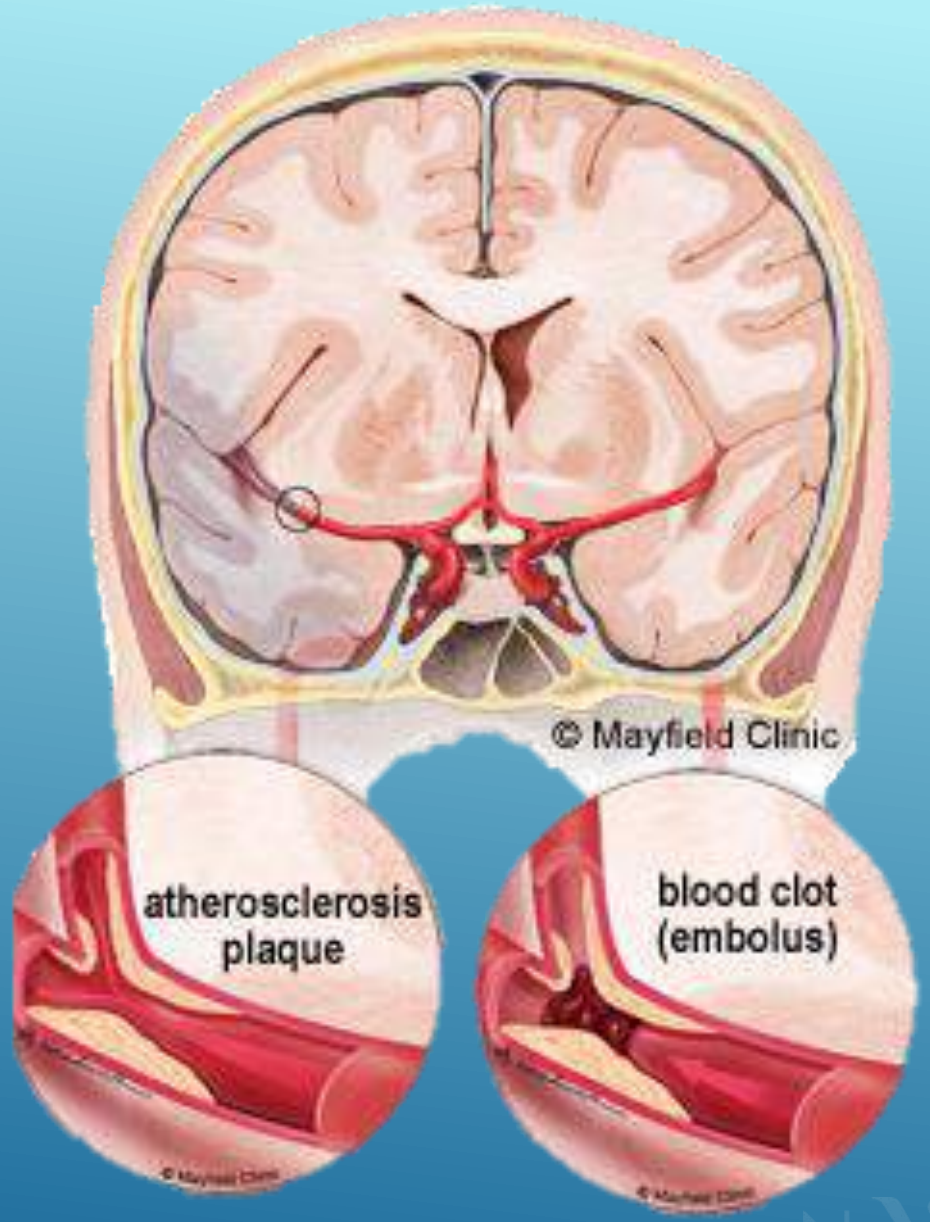
*"I had a heart attack and a stroke at the same time. The day before [the stroke], I **couldn't feel my arm for a couple of seconds**. At that moment I didn't notice the warning signs of stroke, and eleven hours later, while I was having a shower, I suddenly felt like something had exploded in my head. I was **not able to speak** any more and I **felt like the right side of my body had disappeared**. I **couldn't see with my right eye** like during a migraine, and I had **a sudden, terrible headache**."*

AIS survivor, 37, THE Netherlands

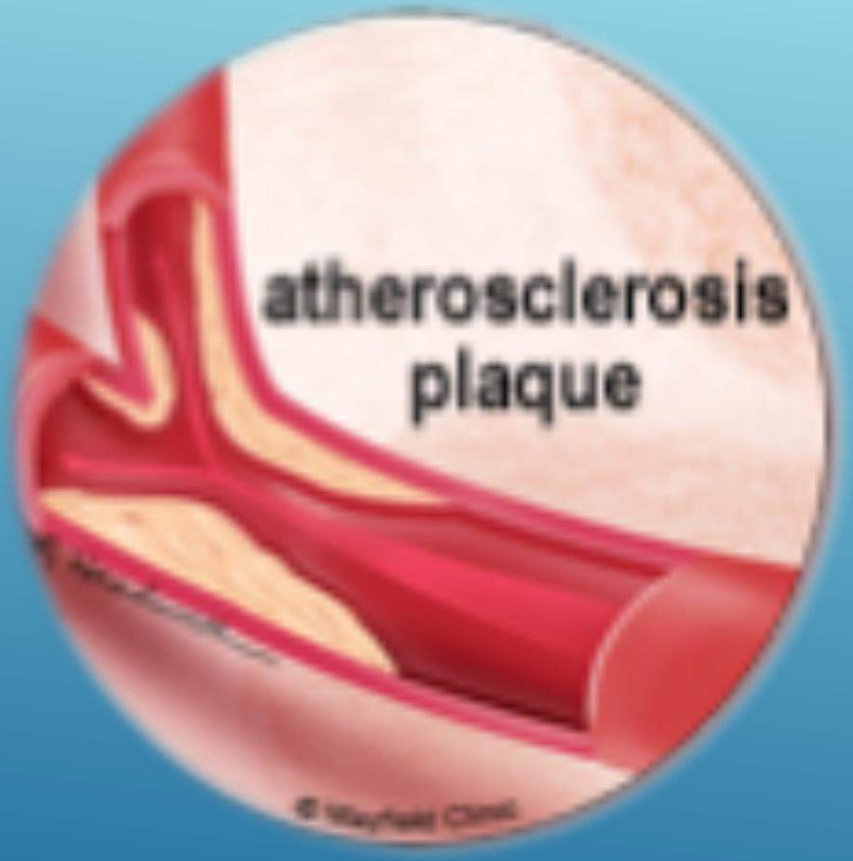
ISCHEMIC STROKE

Failure in the blood circulation in an area of the brain, usually from a clot blockage

Deprived of oxygen and other nutrients, the brain suffers damage, resulting in loss of neurological function

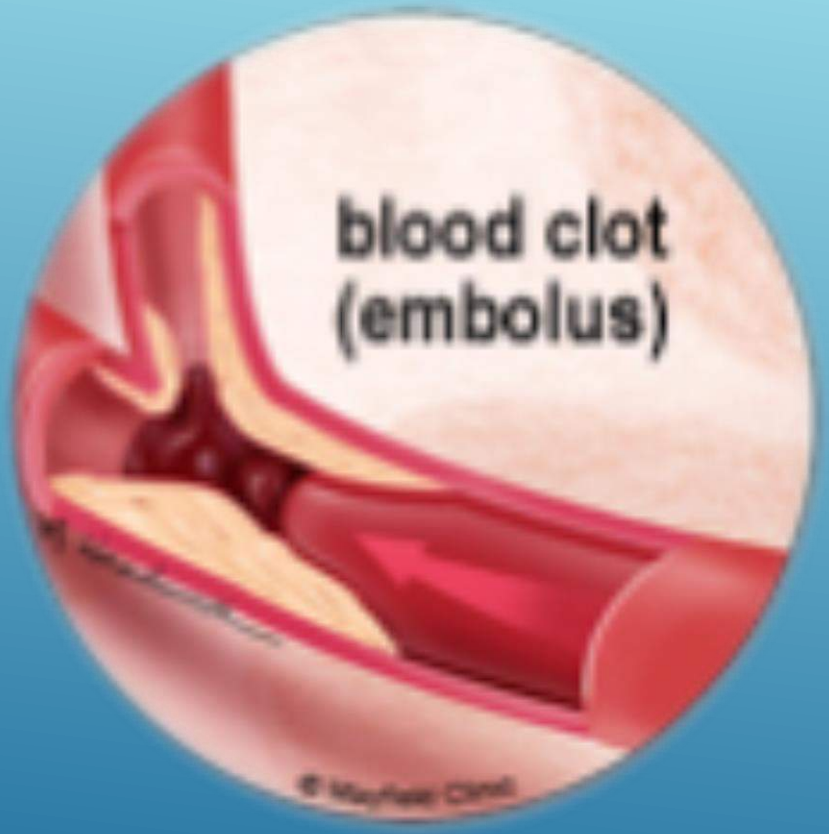


ATHEROSCLEROSIS



- Hardening of the arteries
- Cholesterol plaques are deposited within the walls of the arteries, narrowing the internal diameter of the artery
- Treatment focuses on opening up the clogged artery with angioplasty with balloon or stenting

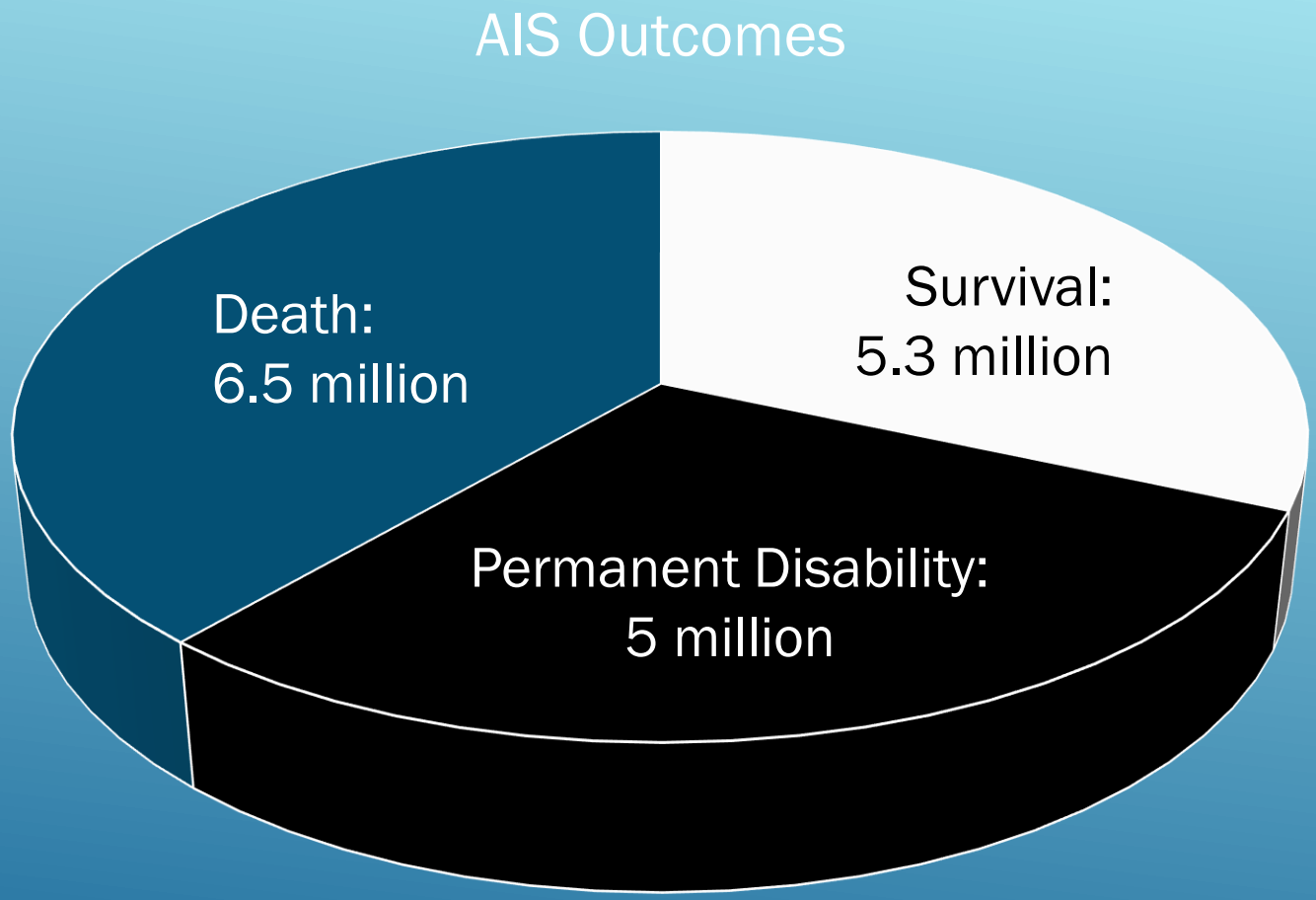
EMBOLIC STROKE



- Also called ACUTE ISCHEMIC STROKE
- A clot breaks off from the artery wall (becomes an embolus), and travels down the bloodstream to block a smaller artery
- Emboli usually come from the heart, where different diseases cause clot formation
- Treatment focuses on trying to lyse or eject the clot

3RD GLOBAL KILLER & LEADING CAUSE OF DISABILITY

- 87% of strokes are ischemic
- 15 million people suffer stroke worldwide each year
- Incidence is declining in developed countries but overall rate remains high due to the aging population



AIS FACTS & FIGURES IN EUROPE

IN EUROPE

More than 640 000 stroke events expected in 2018
with **28% increase** to ~820 000 in 2035

3 stroke events
&
1 stroke death

ECONOMIC BURDEN OF STROKE IN EUROPE

Direct healthcare costs estimated at

€20 BILLIONS

Informal care costs estimated at

€15,9 BILLIONS

Productivity loss due to death & morbidity estimated at

€9,4 BILLIONS

Total cost estimated at

€45 BILLIONS in 2015 & rising

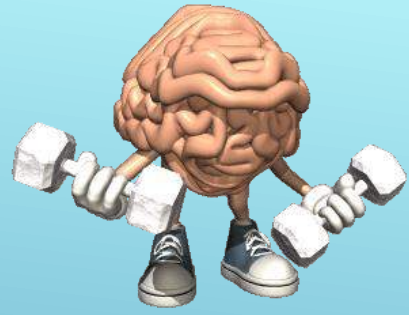
TIME IS BRAIN

What makes stroke so devastating?

What makes stroke so devastating?

#1. HUMAN PHYSIOLOGY

THE BRAIN IS DEMANDING & UNFORGIVING



Facts about the brain:

2%
of the body weight

Consumes
20%
of body's supply of
oxygen & glucose

Is fed by more than
160 000 km
of blood vessels

Cerebral metabolism requires
constant supply

When blood supply stops:

In 8-10 seconds → loss of consciousness

After 20 seconds → electrical activity stops

In 3–4 minutes → irreversible damage can occur

TIME IS BRAIN

In a typical large vessel AIS

1.9 million neurons

4 billion synapses

2 km of myelinated fibers

are lost every minute

Compared with the normal rate of neuron loss in brain aging,

the ischemic brain ages

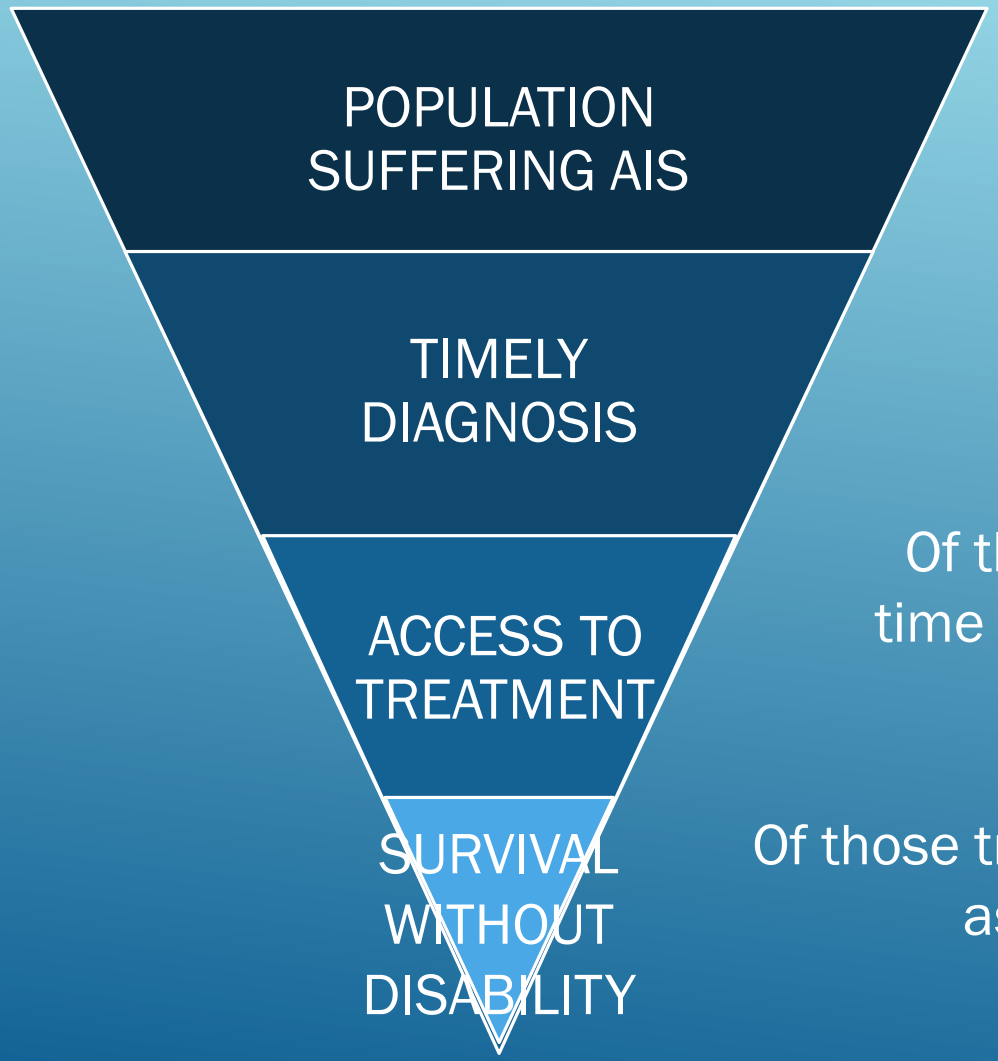
3.6 years each hour

without treatment

What makes stroke so devastating?

#2. LACK OF ORGANISATION

TREATMENT RATES ARE LOW DUE TO ISSUES OF TIMELY ACCESS



A population larger than half a million suffer AIS in Europe every year.

A limited number of AIS patients make it to a specialized service and get timely diagnosis.

Of those diagnosed, only some are eligible for treatment at the time of diagnosis. Several patients simply do not have access to some of the treatment options.

Of those treated, successful outcome depends on many factors such as achievement of recanalization, lack of complications, etc.

FACTORS LIMITING IDEAL STROKE TREATMENT

- Population awareness
- Geographic availability of comprehensive stroke centers with 24/7 interventional capabilities
- Number of trained INRs
- Government investment

STROKE CARE ORGANIZATION NEEDS IMPROVEMENT

In Europe, currently, only 30% of people who have a stroke get treated in a stroke unit.

(Even) Thrombolysis is still under-performed across all of Europe.

Medical and technological advances leading to new treatment options….must be made available to all patients across Europe…

GOAL: REDUCE DELAYS IN ACCESS TO EMERGENCY STROKE CARE

- Continuous education of public and of health professionals to recognize stroke and always treat it as an emergency;
- Improving emergency care pathways: There should be enough trained stroke specialists available and acute and emergency stroke services should be organized to maximize fast patient access to emergency care.

Source: Stroke Alliance For Europe Report - The_Burden_of_Stroke_in_Europe_Challenges_for_policy_makers

ACTING FAST CAN SAVE LIVES - WATCH

FAST → FASTER

F

FACE

- Drooping or numbness on one side of the face
- When asked, uneven smile

A

ARMS

- Weakness on one side of the body
- When asked to raise both arms, one of them drifts down

S

STABILITY

- Dizziness
- Difficulty keeping balance, trouble walking
- Loss of coordination

T

TALKING

- Slurring words, inability to speak
- Understanding issues
- Can’t repeat a simple sentence

E

EYES

- Difficulty seeing out of one or both eyes
- Double vision

R

REACT

- Call emergency line immediately
- Even if symptoms disappear
- Go to the hospital at once
- Note when symptoms began

RECAP: STROKE AND ITS BURDEN

AIS is failure in the blood circulation in an area of the brain, usually from a clot blockage. Deprived of oxygen and nutrients, the brain suffers damage, resulting in loss of neurological function.

Time is Brain:
Stroke is devastating because cerebral metabolism requires constant blood supply and irreversible damage starts 3-4 minutes after the onset of ischemia.

Recognizing AIS signs FAST matters:
Face, Arms, Speech: Time!

87% of strokes are ischemic and the burden of AIS to the society is heavy because of the number of deaths and disability it engenders:

In EUROPE:

- 3 strokes and 1 stroke death happens every 2 minutes
- The yearly economic burden of AIS was calculated at €45 billion in 2015

THE AIS DISEASE STATE

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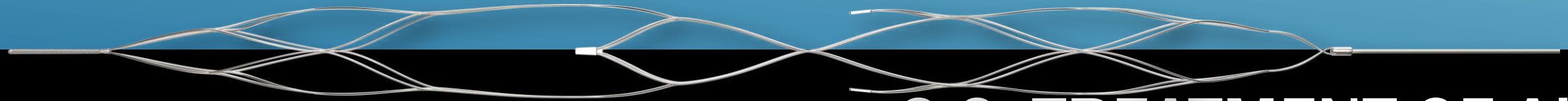
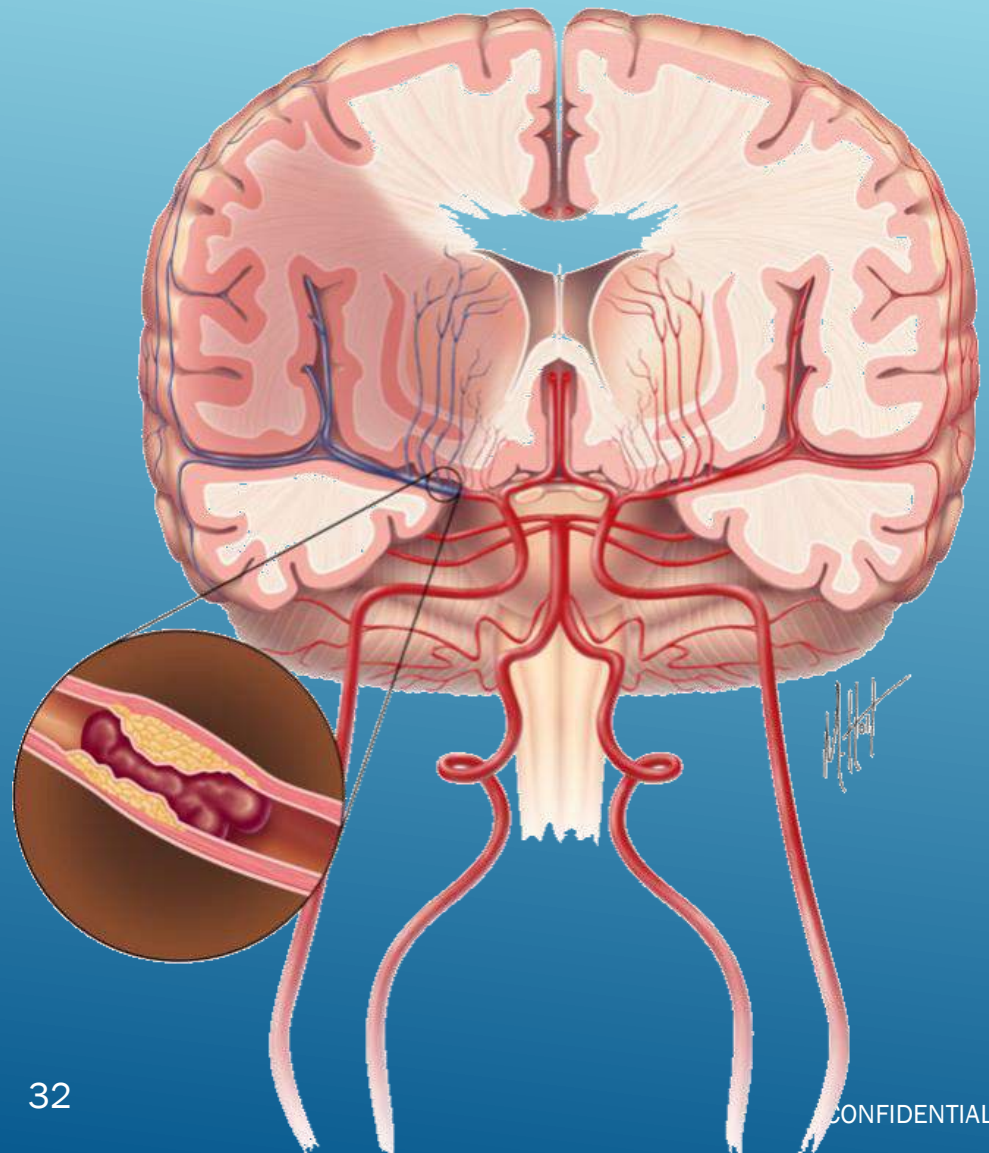
Designed for first pass success



3.2. TREATMENT OF AIS

GOAL OF AIS TREATMENT

SINCE INTERRUPTION OF BLOOD FLOW IS THE PROBLEM



SHOULD THE GOAL OF TREATMENT BE

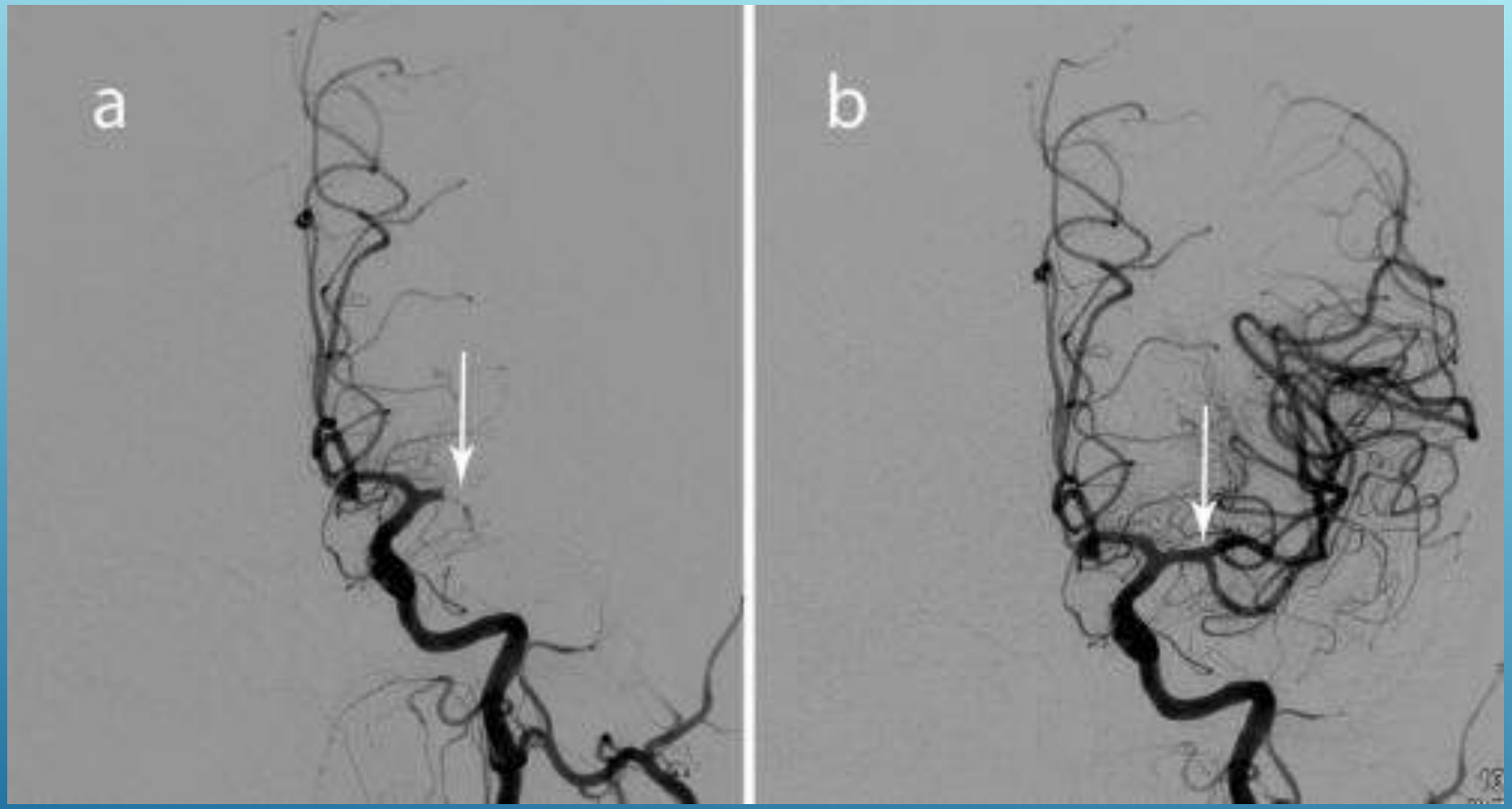
ACHIEVING RACANALIZATION?

AND

RESTORATION OF BLOOD FLOW?

RECANALIZATION = RESTORING FLOW

Angiogram images before (a) and after (b) mechanical embolectomy with restoration of flow through the left MCA M2.

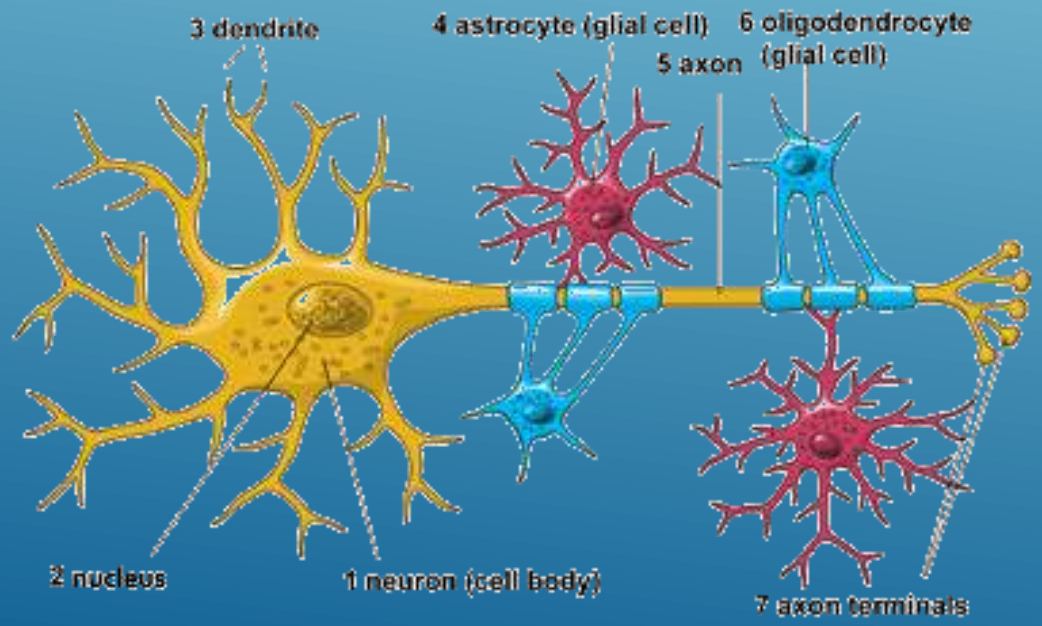


BUT, WHAT IS LOST CANNOT BE BROUGHT BACK!

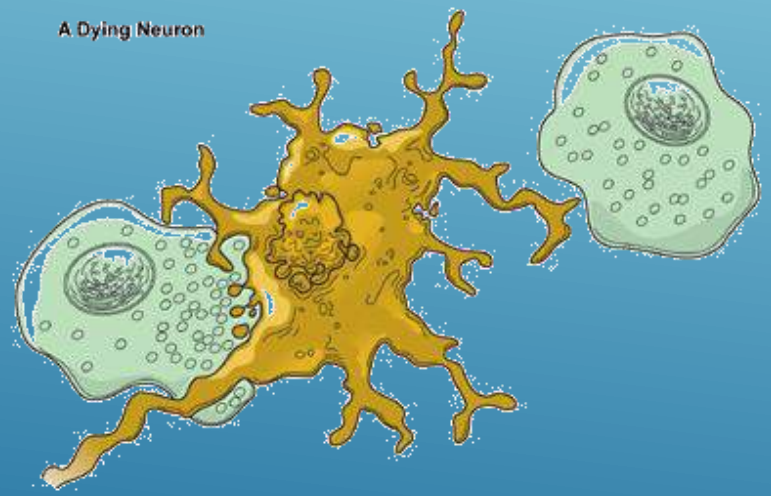
Brain cell death is irreversible.

Damage that occurs before treatment cannot be repaired.

Healthy Neuron



Dying Neuron

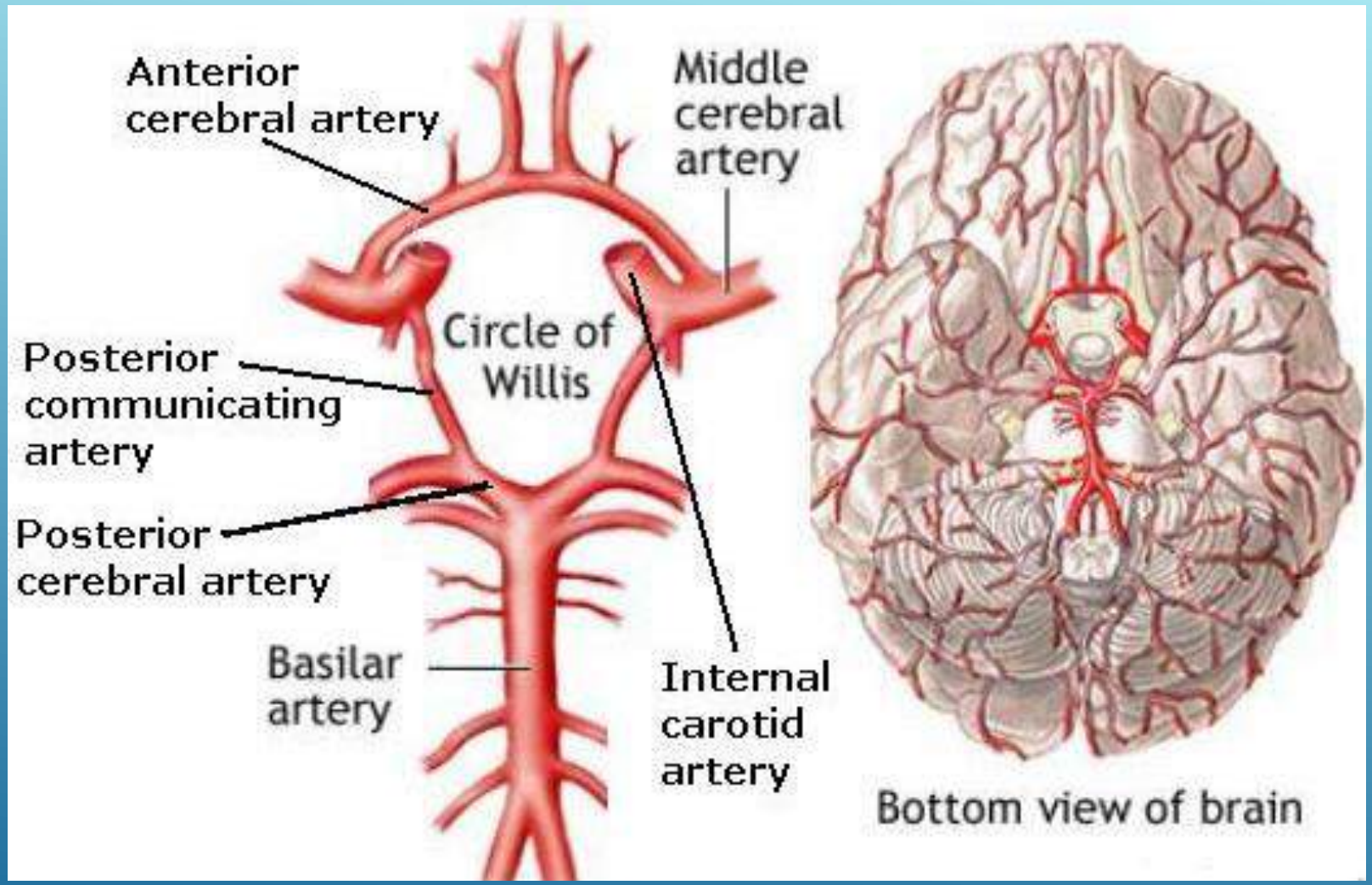


SO: THE GOAL OF AIS TREATMENT IS TO STOP SECONDARY INJURY PROCESSES & SAVE THE PENUMBRA

- Penumbra is ischemic tissue potentially destined for infarction but not yet irreversibly injured
- As time elapses, the ischemic core spreads through the penumbra

STRENGTH OF COLLATERAL FLOW DIRECTLY IMPACTS THE PENUMBRA

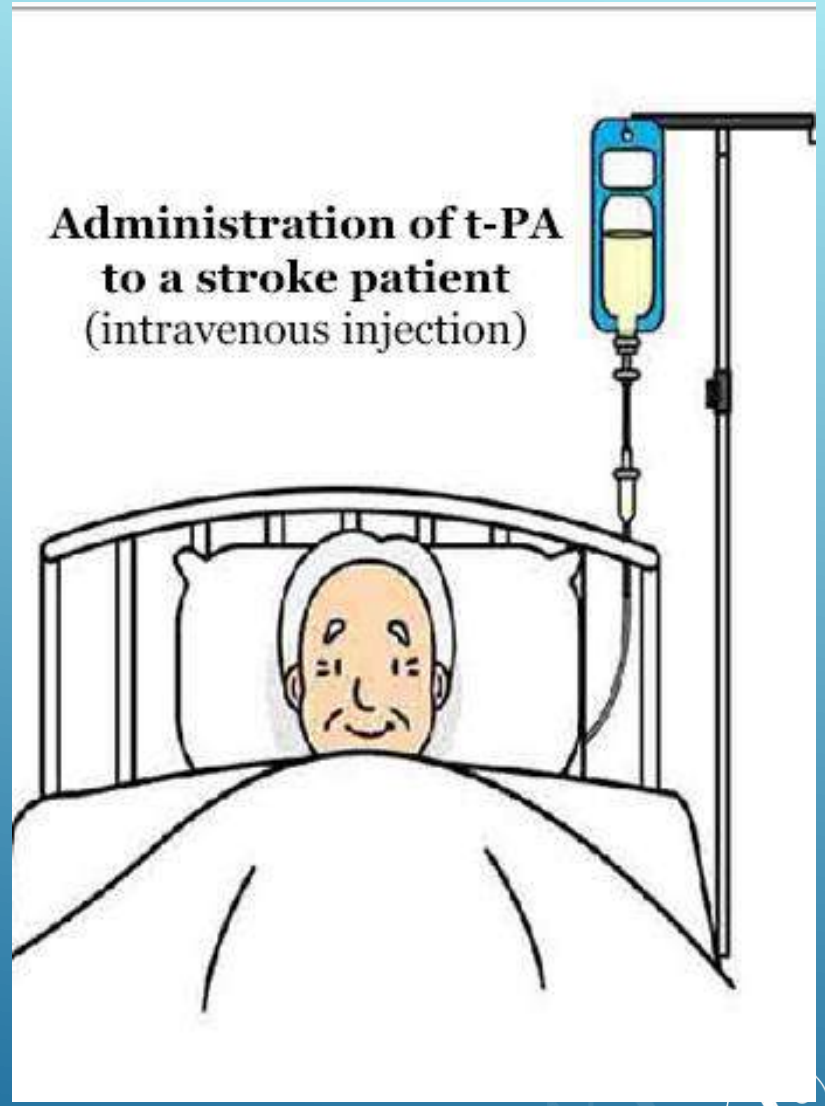
- The arrangement of the brain's arteries into the **Circle of Willis** creates redundancy and allows **collateral circulation**
- If circulation in one part of the brain becomes blocked (AIS) or narrowed (stenosed), blood flow from the other blood vessels can often preserve the cerebral perfusion well enough to avoid the symptoms of ischemia (for a while!)



OVERVIEW OF TREATMENT METHODS

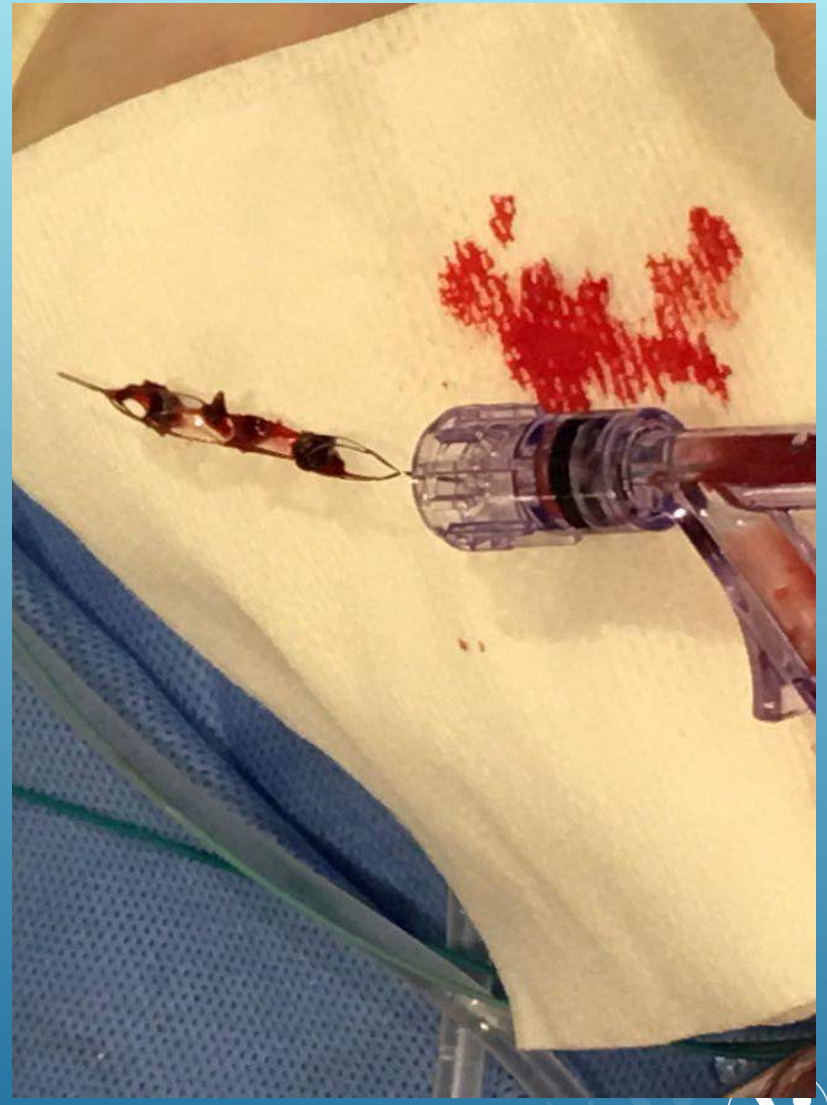
METHOD #1: LYSE WITH PHARMACOLOGICAL AGENTS

WHAT	THROMBOLYSIS (also called IV-tPA)
HOW	Works by stimulating clot breakdown by plasmin through infusion of analogs of tissue plasminogen activator
WHO	Neurologists, neuro-nurses administer
WHERE	Any hospital, can even be administered in an ambulance
WHEN	Used since 1990s
FACTS	Established protocols & guidelines exist
	Accepted threshold for treatment is max 4,5 hours from onset of symptoms
	Has some counter-indications (Most imp: hemorrhage)
	Limited recanalization success



METHOD #2: REMOVE CLOT MECHANICALLY

WHAT	THROMBECTOMY
HOW	Works by surgical removal of a blood clot from the vessel Endovascular procedure with incision at femoral artery, catheters guided to the site of clot & device deployed
WHO	INRs & stroke teams administer
WHERE	Cath Lab
WHEN	Emerged around 2004
FACTS	Guidelines emerged in 2015 (ESO Karolinska Update)
	Accepted threshold for treatment 6 hours from onset of symptoms → getting longer for large vessel occlusions
	Recanalization rates are as high as 90%
	Successful outcomes > 50%



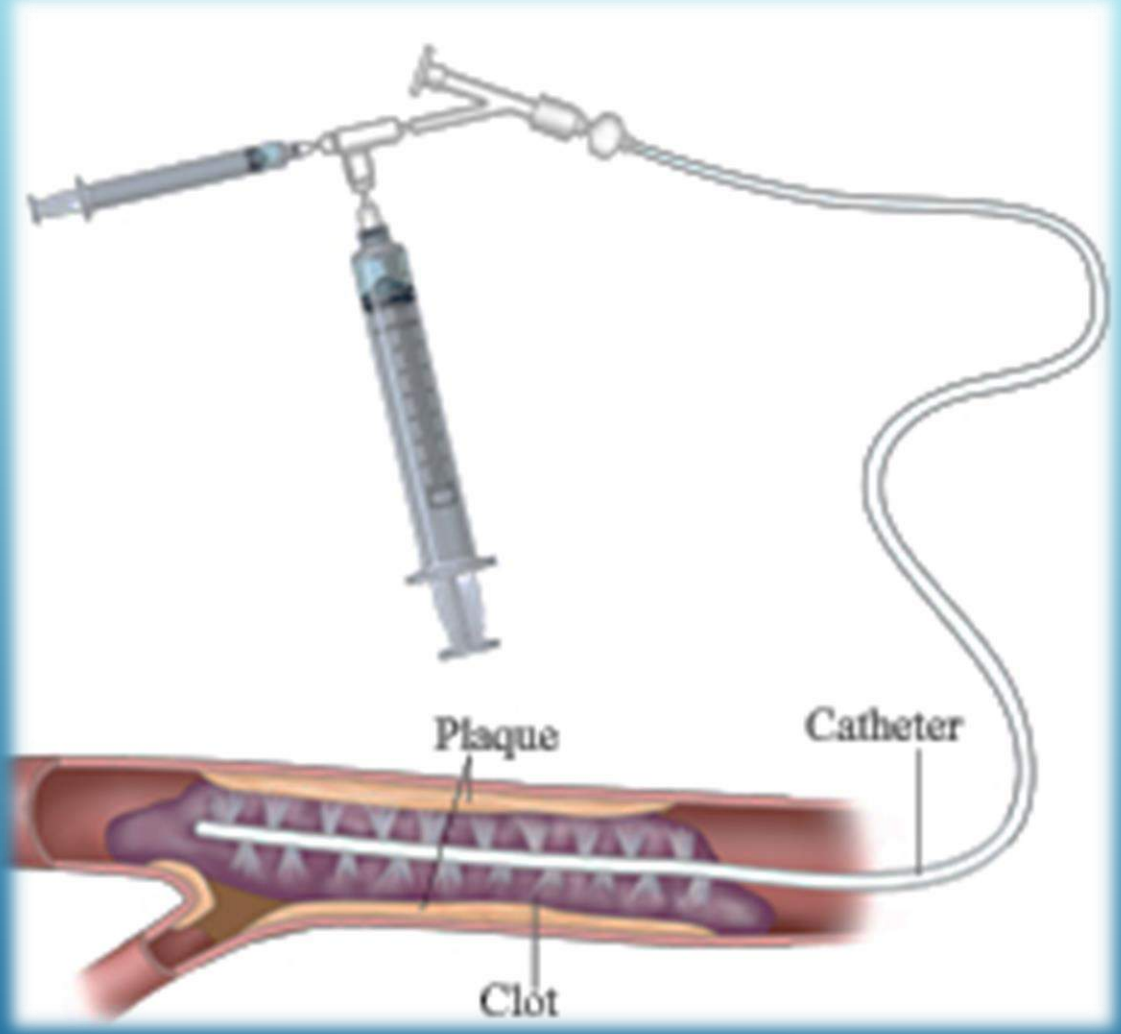
EVOLUTION OF IA AIS TREATMENT

TECHNOLOGICAL AND CLINICAL MILESTONES

1980s INTRA-ARTERIAL THROMBOLYSIS

Administering the clot busting pharmacological agent at the site of blockage

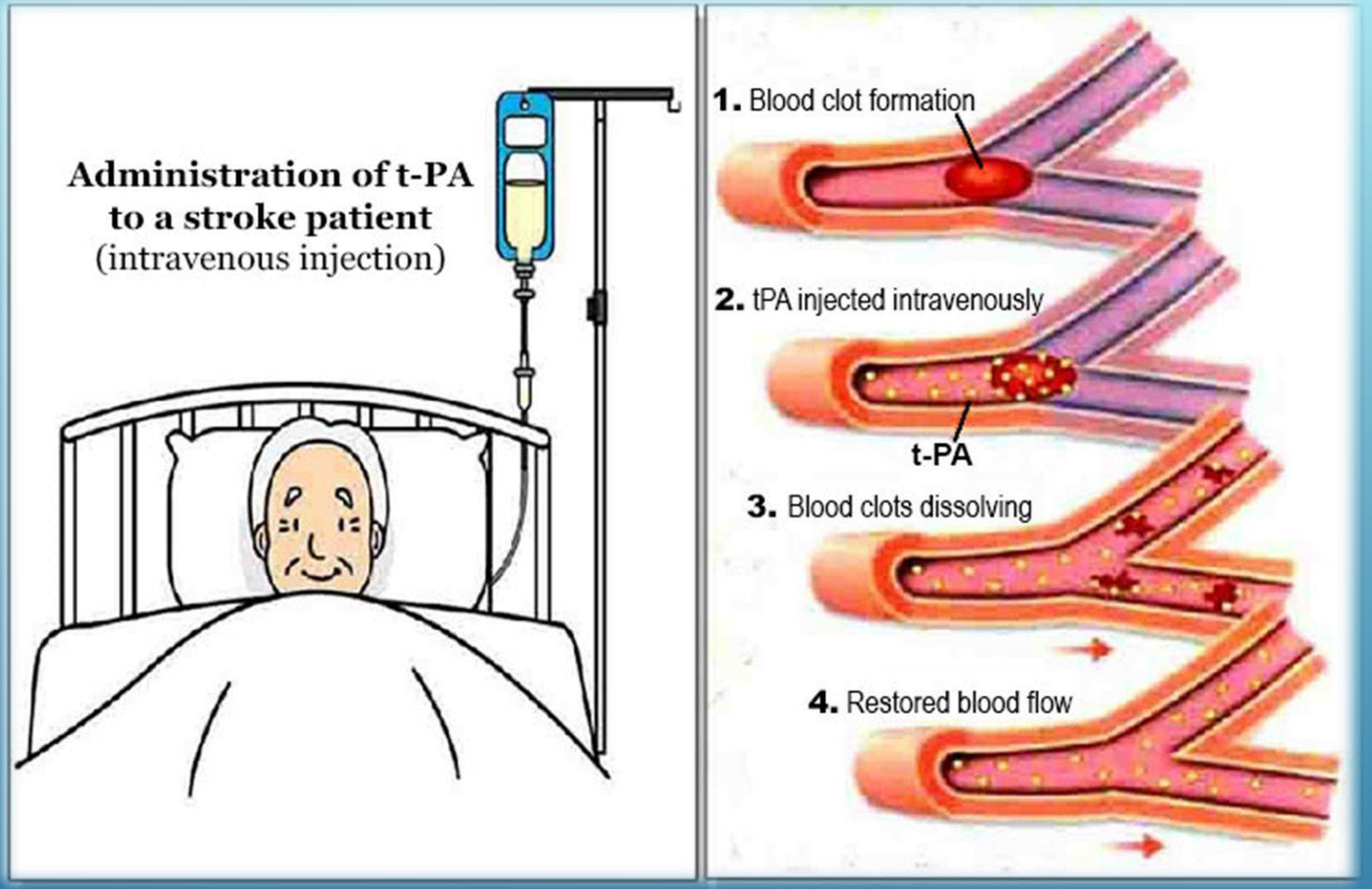
It made sense, but did not produce better outcomes versus IV lysis



1990s INTRA-VENOUS THROMBOLYSIS ESTABLISHED AS GOLD STANDARD

NINNDS (‘95) & ECASS (’96) established IV thrombolysis as the gold standard treatment of AIS

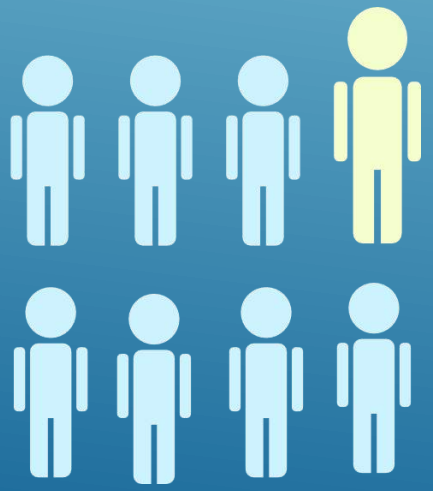
Problems:
Does not work well in proximal, large vessel occlusions
& Counter-indicated for some patients



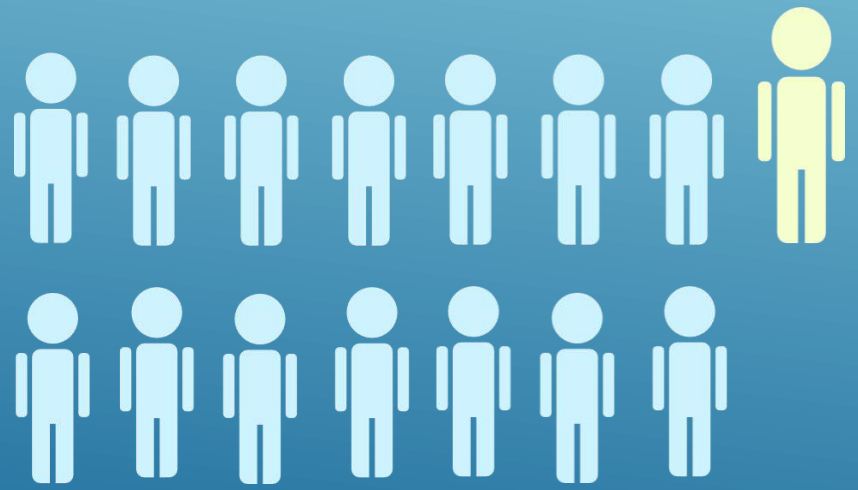
1990s INTRA-VENOUS THROMBOLYSIS ESTABLISHED AS GOLD STANDARD

Outcomes were far from satisfactory but it was the best treatment available

Time to treatment: **<3 hrs from onset**
Need to treat 8 patients with IV thrombolysis to have 1 good outcome (no deficit or almost no deficit)



Time to treatment: **3 - 4.5 hrs from onset**
Need to treat 15 patients with IV thrombolysis to have 1 good outcome (no deficit or almost no deficit)



2000

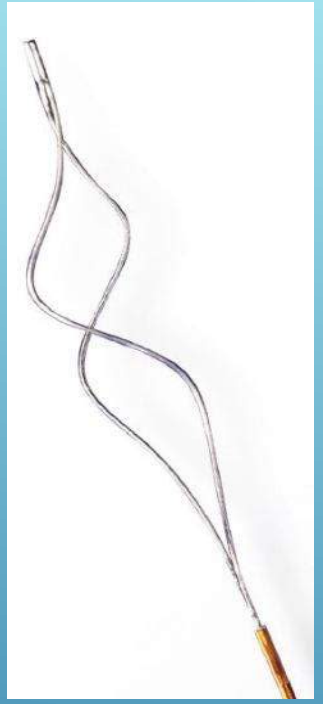
THEN, SOMEBODY HAD THIS IDEA !

Use the catheter delivering the pharmacological agent for manipulating and breaking the clot

Problem: Distal emboli!

2000

THEN, SOMEBODY HAD THIS IDEA !

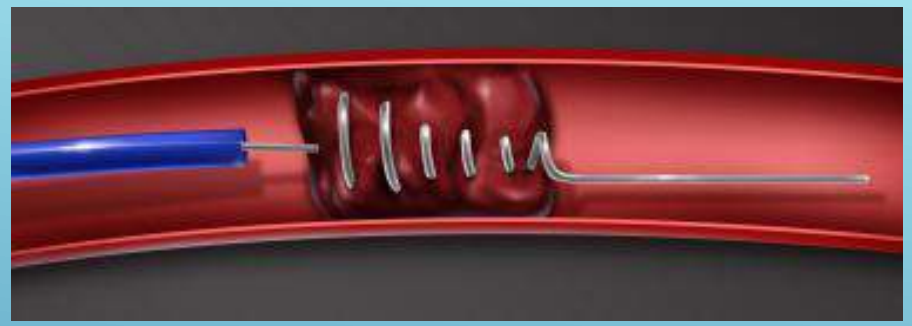


Use a snare like device to capture and pull away pieces of the clot out

Problem: It did not remove all of the clot, & often lost pieces of it!

2004

THEN, SOMEBODY HAD THIS IDEA !



Introduction of the MERCI retriever: And it worked – to some extent…

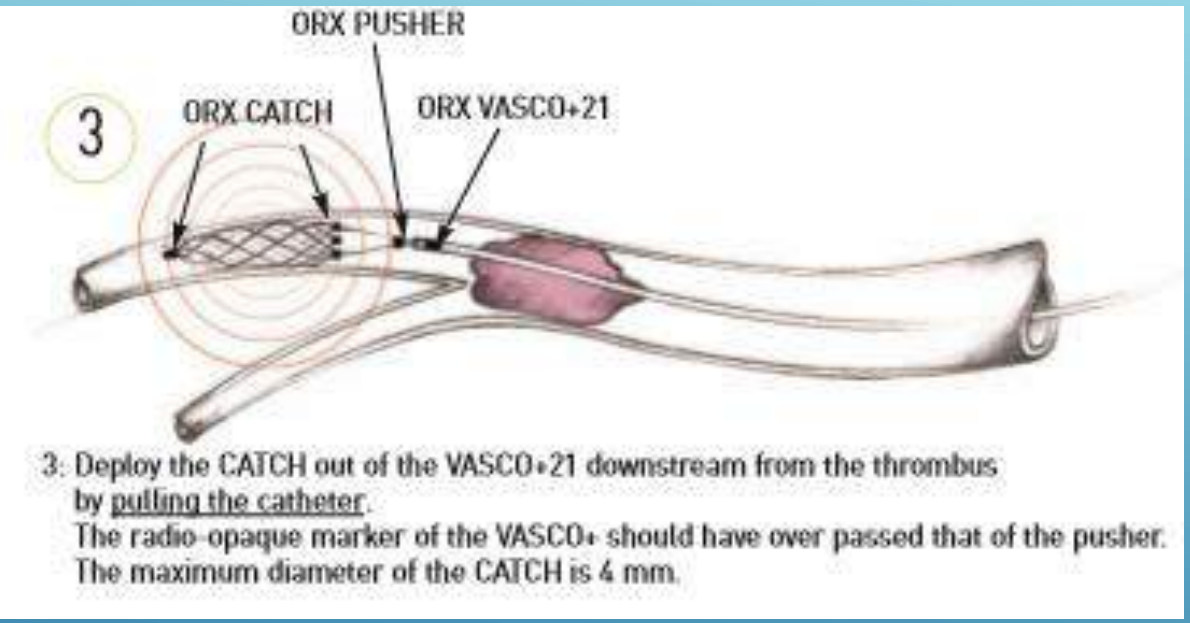
Problem: increased intra cranial hemorrhage

2006 ASPIRATING CLOT INTO A LARGE BORE CATHETER

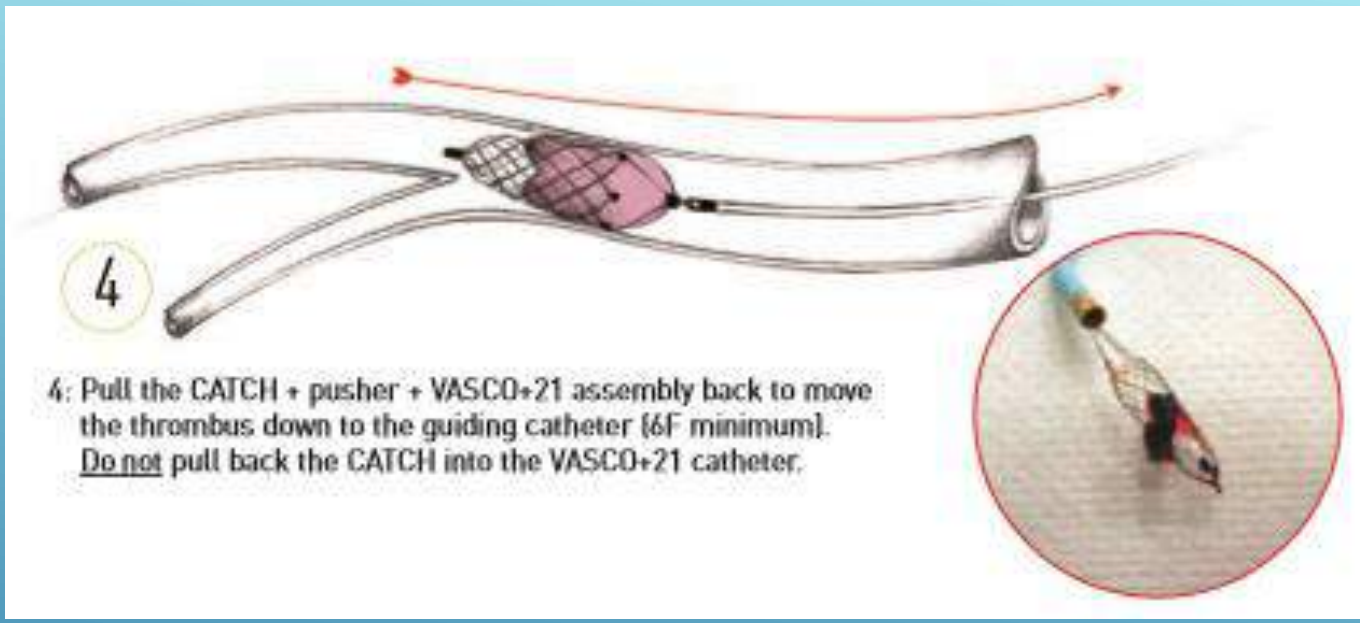
Launch of the first Penumbra aspiration catheter system

Problem: Navigability of large bore catheters into distal territory

2007 USING A STENT TO RETRIEVE CLOT



3: Deploy the CATCH out of the VASCO+21 downstream from the thrombus by pulling the catheter.
The radio-opaque marker of the VASCO+ should have over passed that of the pusher.
The maximum diameter of the CATCH is 4 mm.



4: Pull the CATCH + pusher + VASCO+21 assembly back to move the thrombus down to the guiding catheter (6F minimum).
Do not pull back the CATCH into the VASCO+21 catheter.

Dr. R. Chapot used the Balt catch system and the idea got many adepts in the following years

Problem: lack of evidence & skepticism in the neurology community

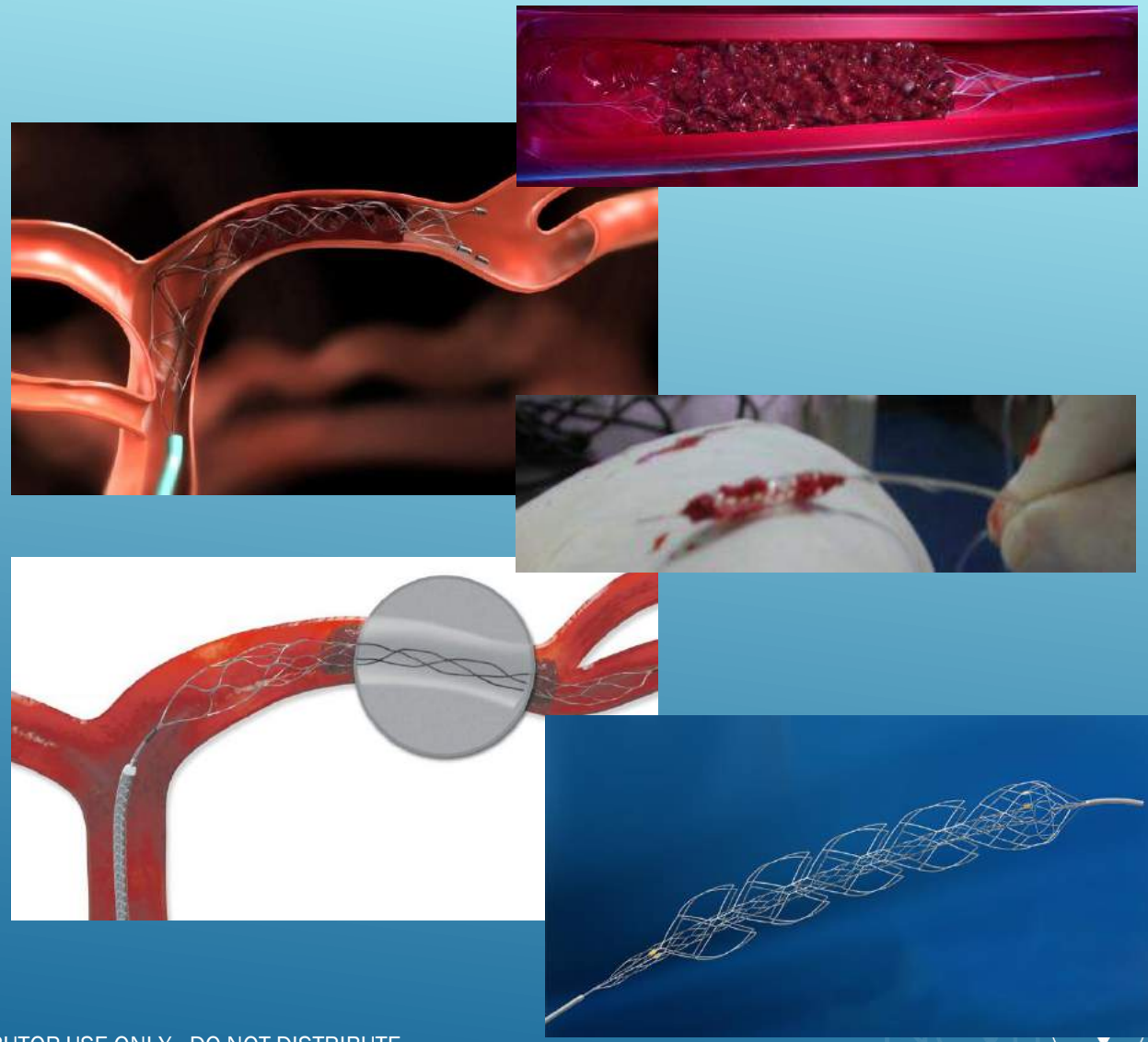
2007 to 2012 BIRTH OF A NEW TERM: STENT RETRIEVER

Use of stents as clot retrievers became popular AND new products flooded the market

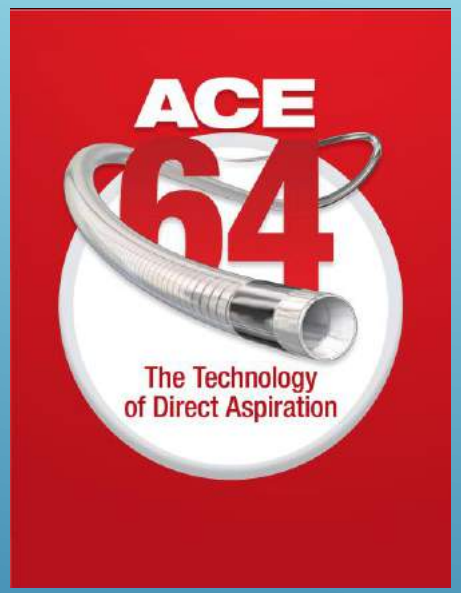
Aspiration with Penumbra lost popularity

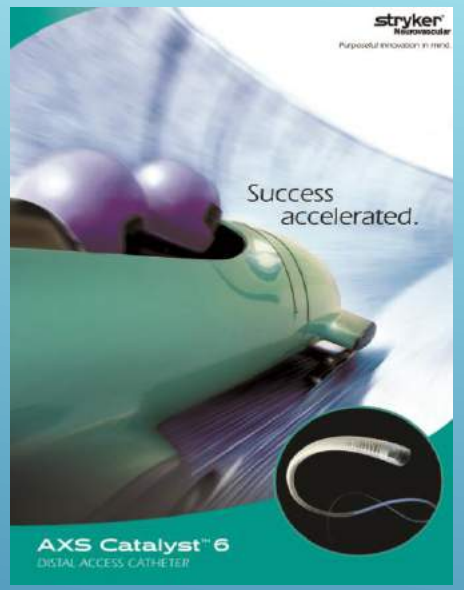
Stent retrievers were used employing several techniques:

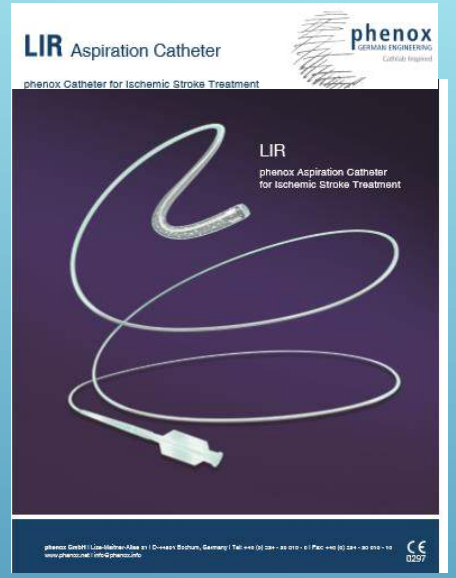
- FLOW ARREST
- LOCAL ASPIRATION
- even simple retrieval into a guide catheter (CO-AXIAL)

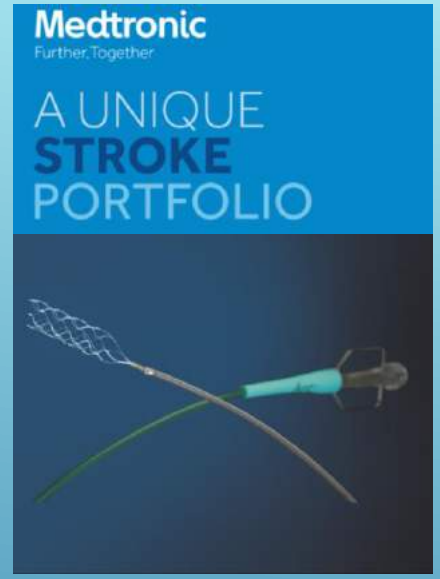


2015 ASPIRATION STRIKES BACK









Penumbra launched the new ACE 64 that resolved the previous navigability issues of large bore aspiration catheters & started Promoting ADAPT technique. This launch was followed by other aspiration catheters.

2015 CLOT STUDIES AND DISCUSSIONS

Red blood cell dominant clots

Fibrin dominant clots

- Mr Clean study group saves clots for research
- Neuravi clot lab
- The notion that clot properties may influence revascularisation rates

"We need to develop techniques and devices that make it possible to more safely and efficiently remove the clot. Ideally, this should be possible with 1-2 attempts and the total time of the procedure, from groin puncture to revascularization, should not exceed 15–20 minutes. The final TICI-score is less important if the procedure takes 90 minutes!

....future thrombectomy devices should be designed to be able to manage all types of clots, or, there should be different devices specifically designed for a certain type of clot...."

Tommy Andersson

AZ Groeninge Kortrijk, Belgium and Karolinska University Hospital, Stockholm, Sweden

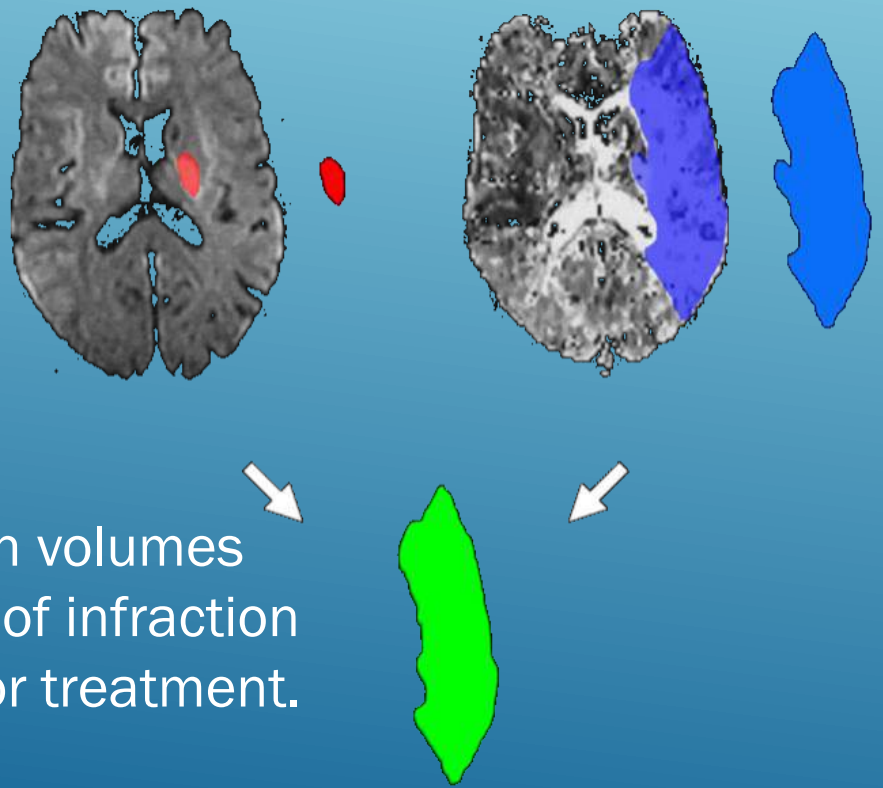
LANDMARK STUDIES

1995 1996	NINNDS2 & ECASS3 established IV thrombolysis as the gold standard treatment of AIS PROACT 2 showed positive results for intra-arerial tX for the first time
2009 2010	PENUMBRA & POST established aspiration as a valid technique for creating successful recanalization
Aug. 2012	SWIFT & TREVO established the new generation stentrievers as the new standard in creating successful recanalization
Feb 2013	IMS3, MR RESCUE & SYNTHESIS showed no additional benefit to doing endovascular intervention, even as add on, even when thrombolysis time window was passed
Dec 2014	MR CLEAN, SWIFTPRIME, ESCAPE, EXTEND IA, REVASCAT, THRACE & PISTE trials provided proof of significant added value of thrombectomy with the new generation stentrievers (Even in elderly patients, even more/less severe strokes)
Dec 2017	DAWN trial disproved the dogma of a time window for treatment. Every patient has an individual course of infarct evolution and thrombectomy can be initiated as late as 1 day after stroke onset

RECAP: STROKE TREATMENT GOAL

The goal of stroke treatment is saving salvageable brain tissue (Penumbra) that is not yet dead thanks to collateral flow. Achieving recanalization is necessary but not an end goal in itself.

The small lesion on diffusion weighted imaging (DWI) represents the infarct core,



The much larger area in the time-to-peak map calculated from perfusion imaging (PWI) identifies the area of critically hypo-perfused tissue.

The MISMATCH between both volumes represents the tissue at risk of infraction and thus, the target tissue for treatment.

RECAP: STROKE TREATMENT OPTIONS

Treatment options have evolved significantly over the past 20 years.

- Intra-venous treatment (i.e. use of clot busting pharmacological agent) is still used up to 4.5 hours from symptom onset.
- Intra-arterial or endovascular treatment of AIS means something very different today than what it meant in the beginning of the millennium.

The most recent thrombectomy technologies are:

- stent retrievers – accepted as the new gold standard
- large bore aspiration catheters – which have tagged along

Landmark studies have proven the effectiveness of thrombectomy up to 24 hours from symptom onset.

WHAT HAPPENS WHEN A STROKE PATIENTS COMES IN?

THE AIS DISEASE STATE

3.1. Introduction to AIS	3.2. Treatment of AIS	3.3. Patient Selection & Guidelines
• What is AIS • AIS facts & figures in Europe • Time is Brain • Acting FAST	• Penumbra & the goal of AIS treatment • Overview of AIS treatment methods • Evolution of AIS treatment: Technological and clinical milestones	• Assessment scales used in AIS • Patient selection for thrombectomy procedures • AIS treatment guidelines and current debates

NeVa™

NEXT GENERATION STROKE TREATMENT

Designed for first pass success

3.3. PATIENT SELECTION & GUIDELINES

ASSESSMENT IN AIS

FOR IMPROVEMENT, MEASUREMENT IS NEEDED

1. How was the patient when admitted?

- What was the neurological status of the patient?
- Was there penumbra to save on the imaging?
- Is it worthwhile to treat the patient?

NIHSS | **ASPECTS**

2. How well did we do with the treatment?

- How good was the angiographic outcome?
- Did we achieve good recanalization?

Success of the operation:

- the difficulty of the case
- performance of the device/ devices
- the technique used
- the experience/talent operator

TIMI & TICI

- How well did the patient do? (Functional outcome)
- How much neurological recovery was possible?

Success of treatment:

- How severe was the stroke to begin with? How much penumbra was there to save?
- How fast could we treat?
- Did we have complications?

mRS

TO ASSESS SEVERITY OF STROKE AT ADMISSION: NATIONAL INSTITUTE FOR HEALTH STROKE SCALE (NIHSS)

- A measure of neurological deficit
- Used to establish a baseline: incoming stroke severity
- Cognitive, speech, visual and motor-sensory
- 0 (excellent) – 45 (near dead)
- “8-10” is considered minimum severity for endovascular treatment to be indicated
- Not a measure of disability nor a measure of independence

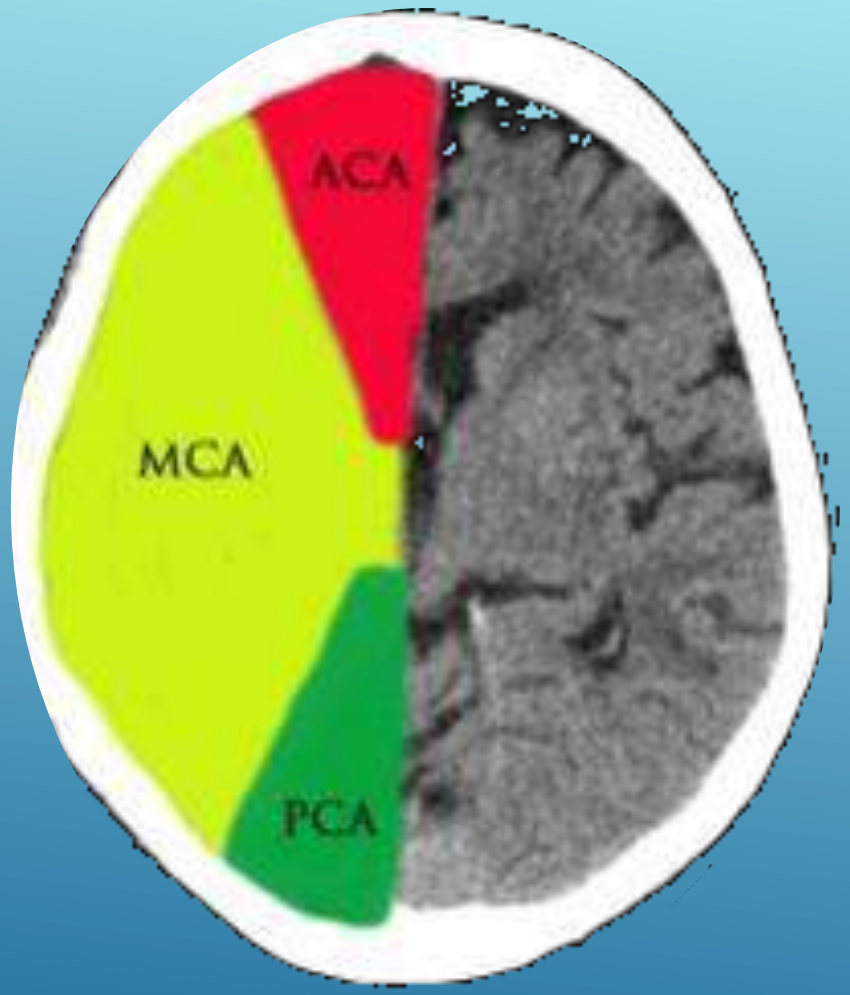
TO ASSESS EXISTENCE OF ENOUGH PENUMBRA: 1/3 MCA RULE

Patient classification system initially used in stroke studies such as ECASS

Unenhanced CT scan:

IF more than 1/3rd of MCA territory involved: eliminate patient from therapy

WHY: Belief that risk for hemorrhage is higher

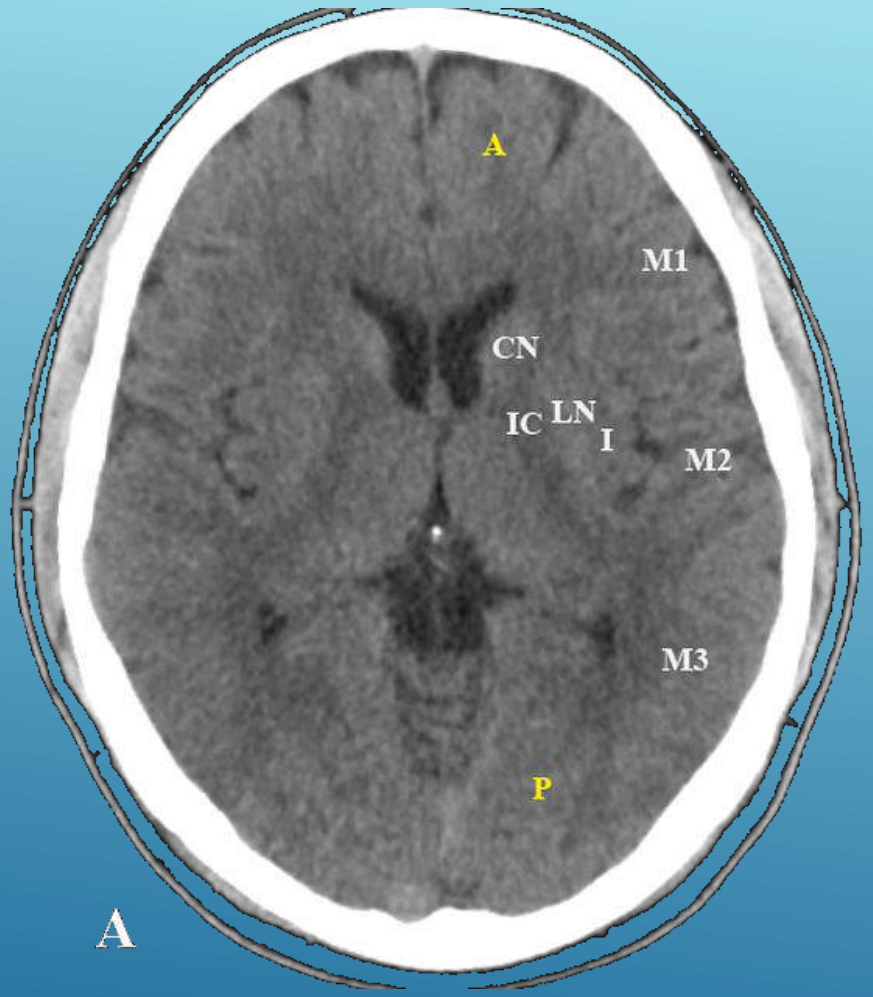


TO ASSESS EXISTENCE OF ENOUGH PENUMBRA: ASPECTS: ALBERTA STROKE PROGRAM EARLY CT SCORE

Patient classification system currently used in stroke patient selection

A 10-point quantitative topographic CT scan score

- Segmental assessment of the MCA vascular territory
- 1 point deducted from the initial score of 10 for every region involved
- ASPECTS score ≤ 7 predicts worse functional outcome @ 3 months as well as symptomatic hemorrhage
- ASPECTS score < 8 treated with thrombolysis did not have a good clinical outcome



TO ASSESS ANGIOGRAPHIC OUTCOME: THROMBOLYSIS IN CEREBRAL INFARCTION (TICI):

From TICI to Revised TICI for a finer definition of recanalization success

Dissatisfactory outcome

Satisfactory outcome

0	No perfusion
1	Penetration but not perfusion
2	Incomplete perfusion (slower or incomplete)
2a	Some perfusion with distal branch filling of <50% of territory visualized
2b	Substantial perfusion with distal branch filling of ≥50% of territory visualized
3	Complete perfusion with normal filling of all distal branches

TO ASSESS ANGIOGRAPHIC OUTCOME: THROMBOLYSIS IN CEREBRAL INFARCTION (TICI):

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0	No perfusion
1	Penetration but not perfusion
2	Incomplete perfusion (slower or incomplete)
2a	Some perfusion with distal branch filling of <50% of territory visualized
2b	Substantial perfusion with distal branch filling of ≥50% of territory visualized
2c	Near-complete perfusion (slow flow in a few distal vessels or presence of distal emboli)
3	Complete perfusion with normal filling of all distal branches

TO ASSESS FUNCTIONAL OUTCOME: MODIFIED RANKIN SCALE (MRS)

	Score	Description
Satisfactory outcome with good recovery	0	No symptoms at all
	1	No significant disability despite symptoms; able to carry out all usual duties and activities
	2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
Unfavorable outcome	3	Moderate disability; requiring some help, but able to walk without assistance
	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
	6	Dead

TO ASSESS FUNCTIONAL OUTCOME: MODIFIED RANKIN SCALE (MRS)

- Scale for **measuring the degree of disability or dependence** in the daily activities of people who have suffered a stroke.
- Studies use mRS scores to measure outcome
  - Dichotomous mRS = either “good” (mRS ≤ 2) or “bad” (mRS 3-6)
  - “Shift” mRS = assesses outcomes across the entire 7 point ordinal scale.

Satisfactory outcome with good recovery

Unfavorable outcome

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
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6	Dead

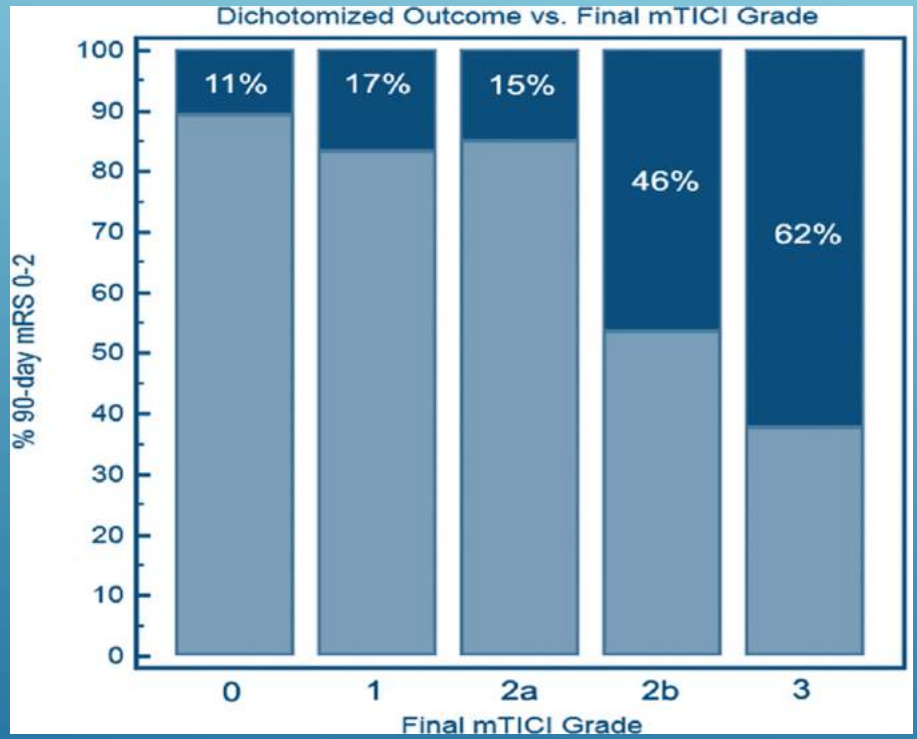
PATIENT SELECTION TODAY

RECANALIZATION QUALITY AND FUNCTIONAL OUTCOMES

BETTER RECANALIZATION CORRELATES WITH BETTER FUNCTIONAL OUTCOMES

Proportion of good outcomes by mTICI grade (P<0.0001 for overall comparison)

- Good outcome (mRS 0 - 2)
- Poor outcome (mRS 3 - 6)



THE INITIAL CENTRAL BELIEF OF ENDOVASCULAR AIS TREATMENT WAS "RECANALIZATION = RECOVERY"

BUT NOT EVERY PATIENT HAS THE SAME CHANCE OF FUNCTIONAL INDEPENDENCE

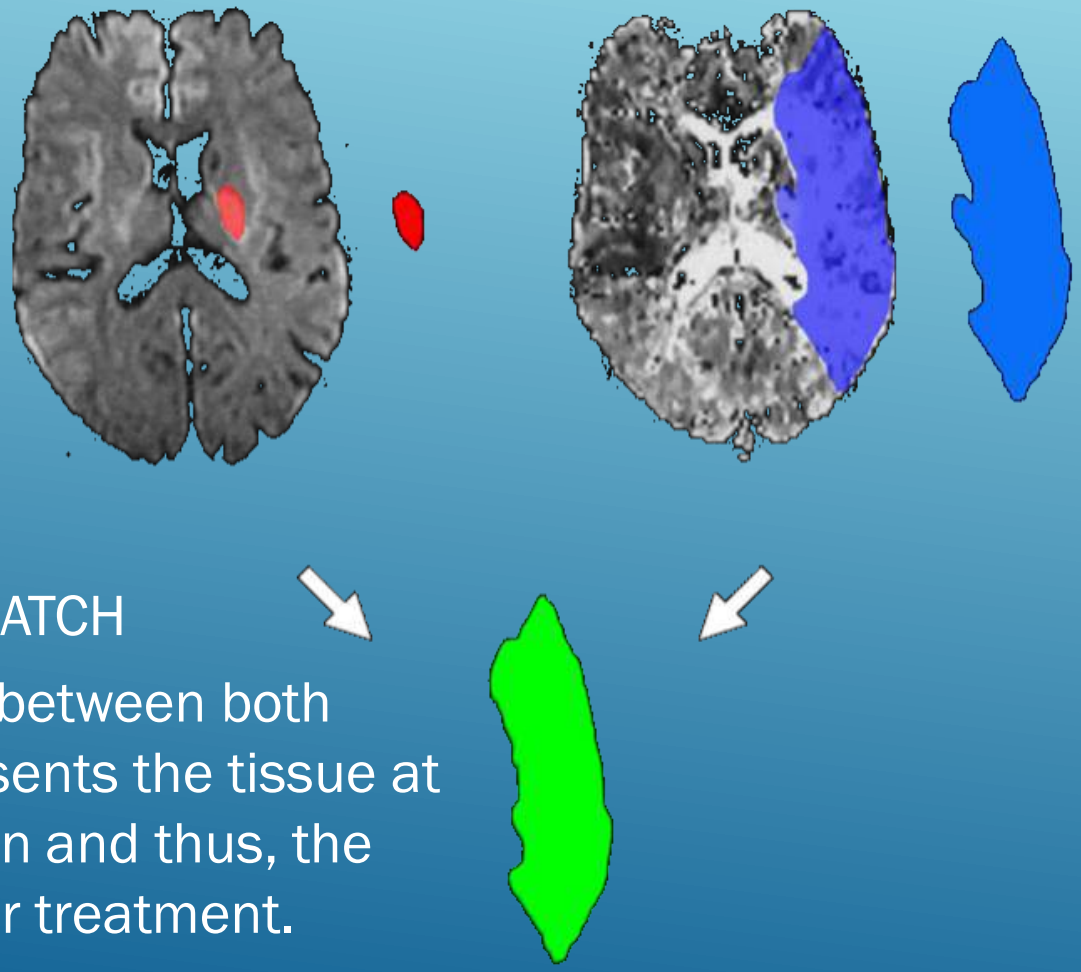
- Severity of stroke
- Size of infarct and penumbra
- Neurological condition prior to stroke
- Anatomy
- Other present disease states
- …

THE MISMATCH CONCEPT TO IDENTIFY SALVAGEABLE PENUMBRA

MRI perfusion–diffusion mismatch

DWI

The small lesion on diffusion weighted imaging (DWI) represents the infarct core,



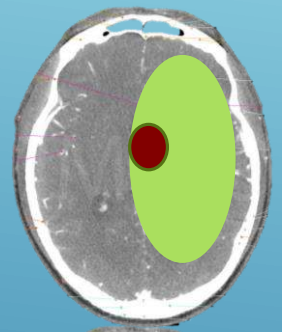
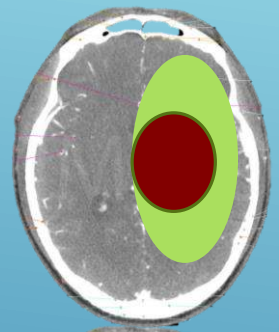
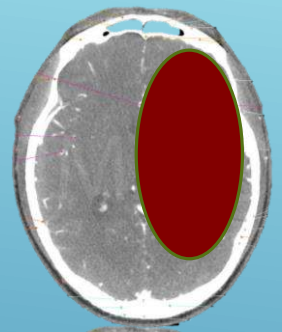
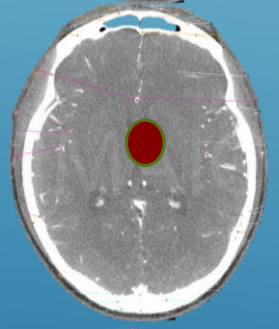
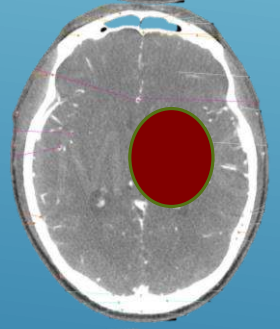
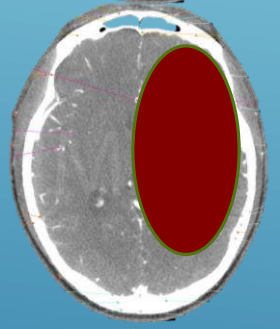
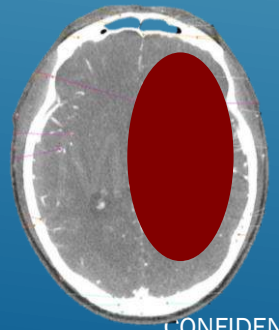
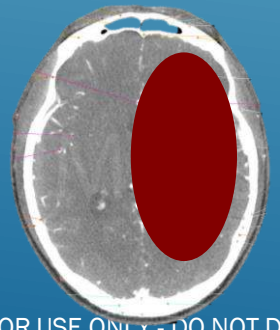
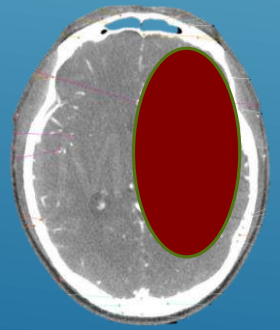
PWI

The much larger area in the time-to-peak map calculated from perfusion imaging (PWI) identifies the area of critically hypo-perfused tissue.

PWI-DWI MISMATCH

The mismatch between both volumes represents the tissue at risk of infraction and thus, the target tissue for treatment.

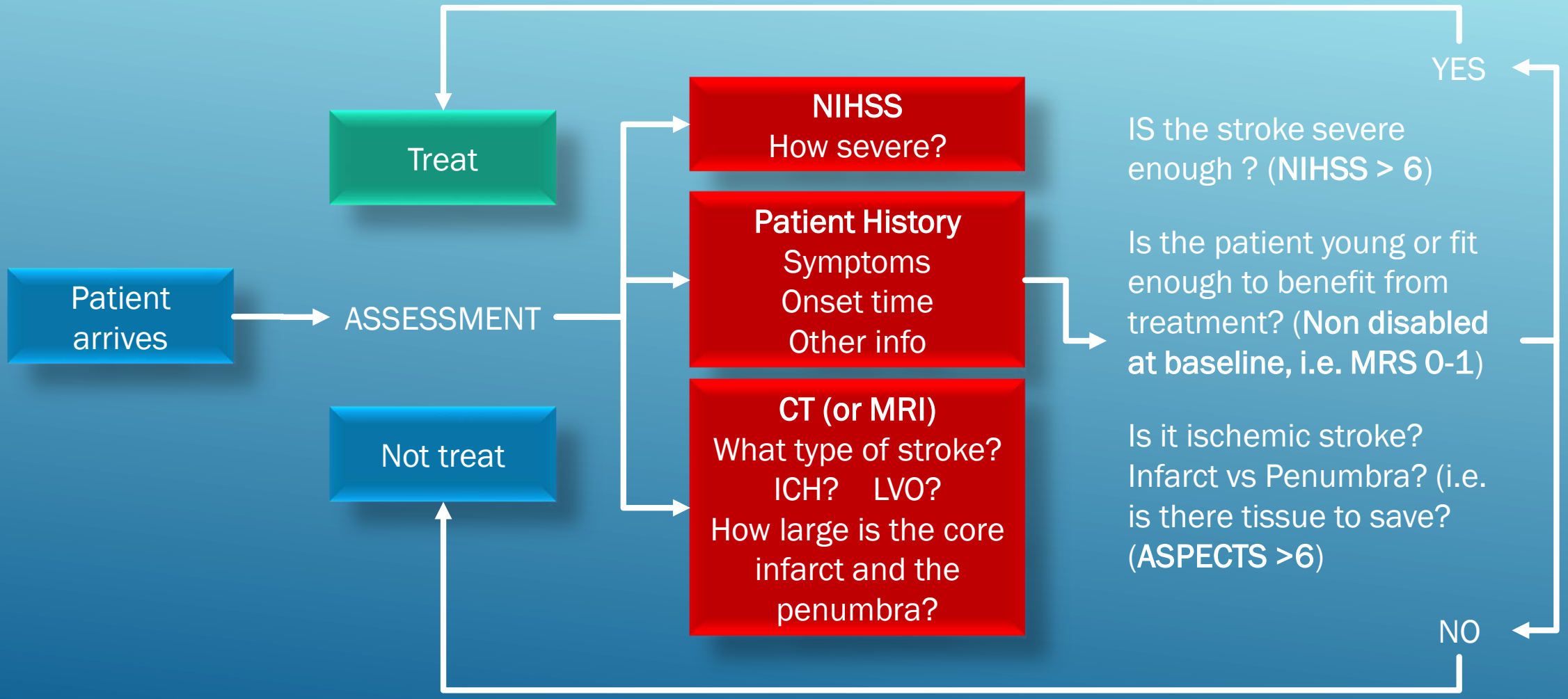
THE MISMATCH CONCEPT USED FOR PATIENT SELECTION

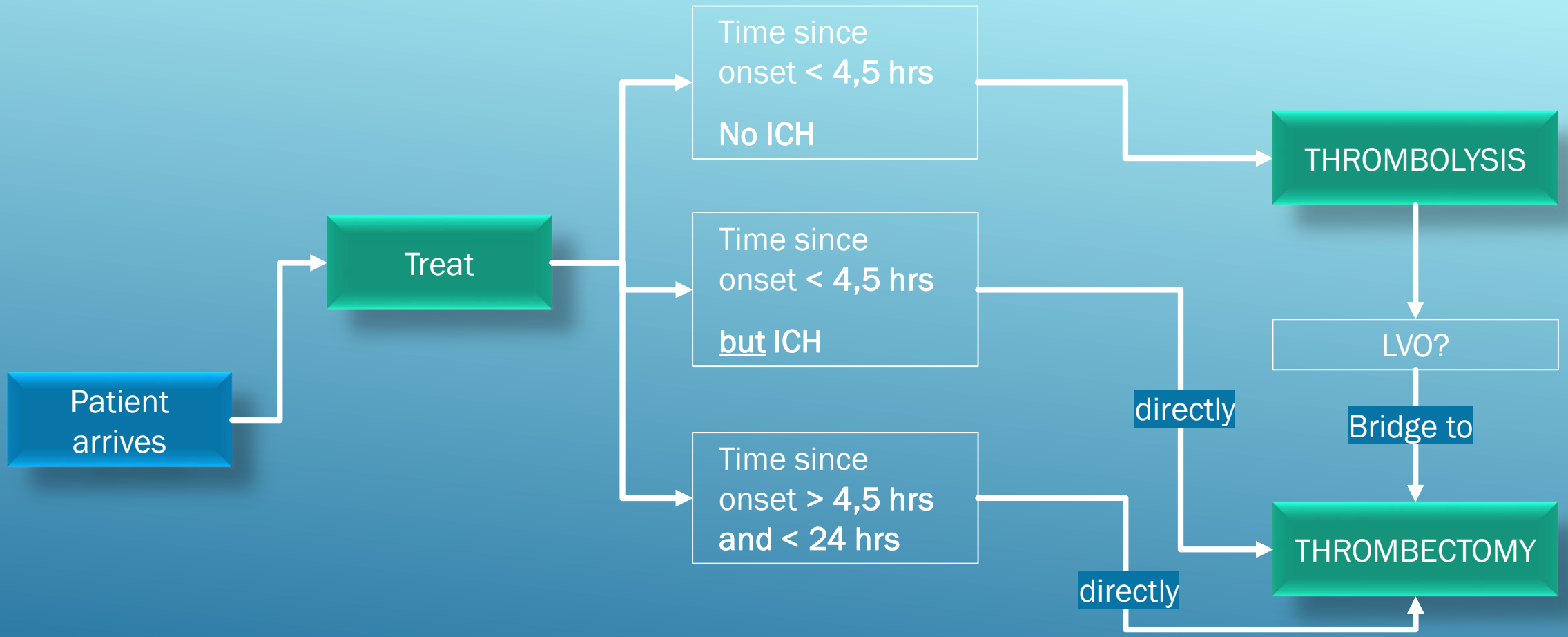
	Patient 1: Small core infarct	Patient 2: Medium size core infarct	Patient 3: Large core infarct
What the imaging will show prior to treatment			
What happens if treated			
What happens if NOT treated			

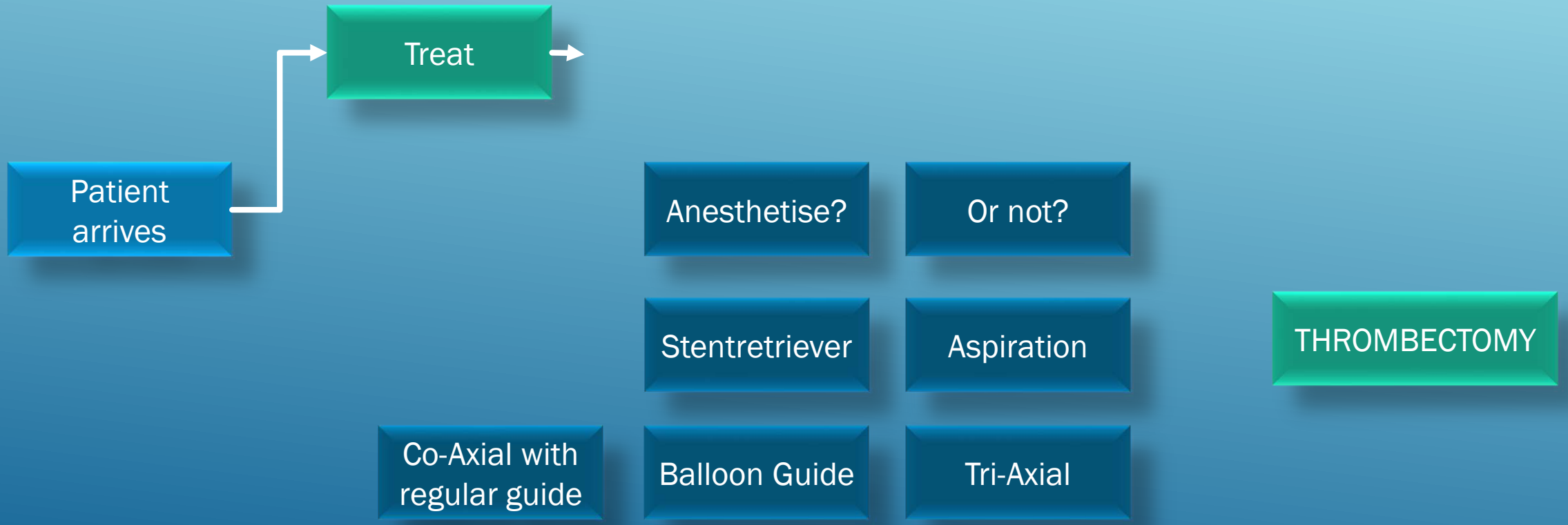
Treat?

Patient arrives

Not treat?







TREATMENT GUIDELINES AND DEBATES

DEBATES HAVE EVOLVED OVER THE PAST YEARS

Pre MR CLEAN Question:

Is thrombectomy a viable treatment option?

Should it be used:

- systematically after thrombolysis?
- as first line if thrombolysis is counter-indicated?

What is the cut-off time from onset

Up until DAWN:

- What about patients that arrive after 6 hours?
- What about wake-up strokes (40% of strokes)?
- What about posterior circulation strokes?
- Is “time from onset” the right selection criterium or should we use other criteria (eg. To take into account the viability of collateral flow)?

Ongoing debates:

- What about aspiration?
- What type of stroke organization could bring the best overall patient outcomes, DRIP & SHIP vs LOAD & GO (MOTHERSHIP)?
- Is it worthwhile to spend more time to get better imaging? MRI instead of CT? Vaso-CT for distal territory visualization?
- Should we do thrombectomy under local or general anesthesia?
- Should we treat distal occlusions (M3) / should we treat cases with mild symptoms?
- Should we bypass thrombolysis altogether for LVOs?
- Should we do lysis “after” thrombectomy for distal vessel occlusion?
- Should cardiologists be allowed to do thrombectomy? How to cater to training needs?

END 2014: PARADIGM CHANGE WITH THE EMERGENCE OF BULLET PROOF EVIDENCE (MR CLEAN & OTHERS)

“There aren’t many things in the history of medicine that show this dramatic effect size for treatment.”

Dr Mayank GOYAL
PI of ESCAPE

“These trials change everything. The data are consistent and convincing. We are now obligated to use this technology in eligible stroke patients with a large vessel occlusion”

Dr Kyra Becker
International Stroke Conference program chair, who confessed to having been a skeptic about endovascular treatment of AIS

“These data are even more impressive than the rumors have suggested. Excellent efficacy and safety has been shown across different trials and different countries. There is absolutely no question that mechanical thrombectomy should now be the standard of care.”

Dr Patrick Lyden
Co-author of NINDS,
who also confessed to having been a skeptic about endovascular treatment of AIS

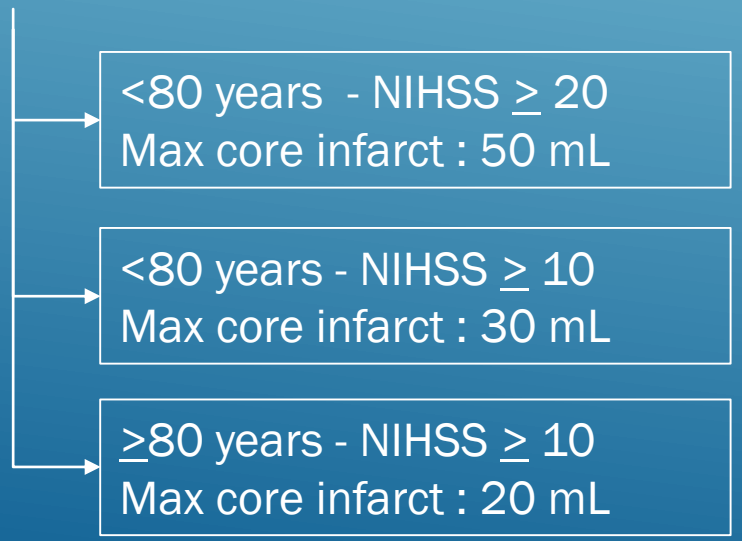
"This is sea change — a new day in stroke,"

Dr Joseph Broderick
PI of IMS-III

END 2017: FURTHER PROOF THAT EXPANDS USE OF THROMBECTOMY TO LATE WINDOW PATIENTS (DAWN & DEFUSE 3)

Patient Selection:

- last known well 6 to 24 hrs earlier
- proximal MCA or ICA occlusions
- IV-tPA failed or ineligible
- Pre-mRS 0-1
- Min Age = 18
- Max Age, NIHSS & Max core infarct:



- **Recan**: 77% in the thrombectomy & 36% in the control arm
- **Functional independence** scores compared to the trials involving patients within 6h of onset:
  - In the thrombectomy arm: Similar rates (49% x 46%)
  - In the control arm: lower rates (13% x 26%)
    - rTpa might have been the explanation, used in 14% of DAWN patients vs 88% of patients in the pooled trials
- Patients treated from 6-12h had better mRs shift (0-2) than patients treated from 12-24h of onset
- Similar ICH and death rates between tX & control arms
- Regarding the literature data, 1/3 of patients outside the trial may meet the radiological pattern used for eligibility criteria in the study and may be selected for recanalization with good outcomes.

FEB 2019: NEW ESO / ESMINT GUIDELINES

If LVO in the anterior circulation within 6hrs:

- Thrombectomy in addition to IV lysis within 4.5 hours when eligible
- Thrombectomy as first line if IV lysis is contraindicated
- Quality of evidence: **High** ⨁⨁⨁⨁; strength of recommendation: **Strong** ↑↑

If M2 occlusion:

- Expert opinion: thrombectomy reasonable

If acute basilar artery occlusion:

- Expert opinion: given grim natural course, strongly consider IV-lysis and thrombectomy

https://jnis.bmj.com/content/early/2019/02/28/neurintsurg-2018-014569

FEB 2019: NEW ESO / ESMINT GUIDELINES

If LVO in the anterior circulation between 6-24 hrs from last known well

and fulfilling the selection criteria of DEFUSE-3 or DAWN:

- Thrombectomy + BMM
- Quality of evidence: **Moderate** ⊕⊕⊕; strength of recommendation: **Strong** ↑↑

and not fulfilling the selection criteria of DEFUSE-3 or DAWN:

- Thrombectomy + BMM up to 7h18 min after stroke onset, without the need for perfusion imaging-based selection
- 10/11 Experts agree: patients can be treated in the 6–12 hour time window if they fulfil the ESCAPE criteria (ASPECTS ≥6 and moderate-to-good collateral circulation)
- Preferably treated in the context of clinical studies

SELECTION CRITERIA OF DEFUSE-3 & DAWN:

Age ≤ 80 years and NIHSS ≥ 6:

- infarct core volume <70 mL
- penumbra volume >15 mL
- penumbra volume /core volume >1.8

Age < 80 years:

- infarct core ≤30 mL if NIHSS ≥10
- infarct core ≤51 mL if NIHSS ≥20

Age ≥ 80 years:

- infarct core ≤20 mL and NIHSS ≥10

https://jnis.bmj.com/content/early/2019/02/28/neurintsurg-2018-014569

FEB 2019: NEW ESO / ESMINT GUIDELINES

- **If LVO and eligible for both IV thrombolysis and thrombectomy**
  - Do both rather than thrombectomy alone
  - Perform both as early as possible
  - Thrombectomy should not prevent the initiation of IV thrombolysis
  - IV thrombolysis should not delay thrombectomy
  - Quality of evidence: **Very low** ⨁; strength of recommendation: **Strong** ↑↑

- **If LVO and NOT eligible for IV thrombolysis**
  - Do thrombectomy as stand-alone treatment
  - Quality of evidence: **Low** ⨁⨁; strength of recommendation: **Strong** ↑↑

https://jnis.bmj.com/content/early/2019/02/28/neurintsurg-2018-014569

DEBATES HAVE EVOLVED OVER THE PAST YEARS

Pre MR CLEAN Question:

Is thrombectomy a viable treatment option? YES

Should it be used:

- systematically after thrombolysis? YES
- as first line if thrombolysis is counter-indicated? YES

What is the cut-off time from onset

24hrs dependiong on...

Up until DAWN:

- What about patients that arrive after 6 hours? YES
- What about wake-up strokes (40% of strokes)? YES
- What about posterior circulation strokes?
- Is "time from onset" the right selection criterium or should we use other criteria (eg. To take into account the viability of collateral flow)? YES

Not alone

Current debates:

- What about aspiration?
- What type of stroke organization could bring the best overall patient outcomes, DRIP & SHIP vs LOAD & GO (MOTHERSHIP)?
- Is it worthwhile to spend more time to get better imaging? MRI instead of CT? Vaso-CT for distal territory visualization?
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- Should we bypass thrombolysis altogether for LVOs? NO
- Should we do lysis "after" thrombectomy for distal vessel occlusion?
- Should cardiologists be allowed to do thrombectomy? How to cater to training needs?

INCONCLUSIVE

DEBATE #1: STENT RETRIEVING OR ASPIRATION… IN 2015

Retrieving clot using stents is the only proven technology with good outcome data. So, INRs should be using stent retrievers only!

VS

Look at all our great recanalization data with aspiration! It is only a matter of time before we collect better evidence to support this technique

DEBATE #1: STENT RETRIEVING OR ASPIRATION?
THE ASTER TRIAL: IS ASPIRATION A BETTER 1ST LINE OPTION?

Stroke patients with similar baseline characteristics were randomized to either stent retriever or contact aspiration treatment groups.

	aspiration group	stent retriever group	p value
TICI 2b3 AFTER 1st LINE THERAPY ALONE: *Scores achieved after 3 passes*	63,0%	67,7%	.53
TICI 2b3 AT THE END OF ALL PROCEDURES:	85.4%	83.1%	.34
Rescue used in	~33% of cases	~24% of cases	.05
TOTAL # of ATTEMPTS	Median : 2 - IQR: 1 – 4 Range: 0 - 11	Median : 2 - IQR: 1 – 3 Range: 0 - 15	.84
TIME from puncture to Revascularization	Median : 38 min. IQR: 24 – 60 min.	Median : 45 min. IQR: 31 – 60 Min.	.10

- The study was designed to look for superiority (of aspiration), not equivalence or non inferiority. BUT, no significant differences were found between the two groups.
- ASTER 2 is ongoing & is finalizing recruitment of 480 patients: Comparing Stent-retriever with contact aspiration to Stent-retriever alone (balloon guide)

FEB 2019: NEW ESO / ESMINT GUIDELINES

Aspiration Alone

- No evidence that contact aspiration alone improves functional outcome vs BMM
- No evidence that contact aspiration alone increases the rate of reperfusion vs stent retrievers
- **Therefore, we suggest the use of a stent retriever over contact aspiration alone for thrombectomy**
- Quality of evidence: **Very low** ⨁; strength of recommendation: **Weak** ↑

Aspiration first + SR Rescue (A Direct Aspiration first Pass Technique)

- Experts (9/11) believe that **ADAPT may be used as standard first-line treatment, followed by stent retriever thrombectomy as rescue therapy if needed**
- Could not reach a majority vote on the proposal that distal aspiration should be used only in combination with a stent retriever (3/11 experts)

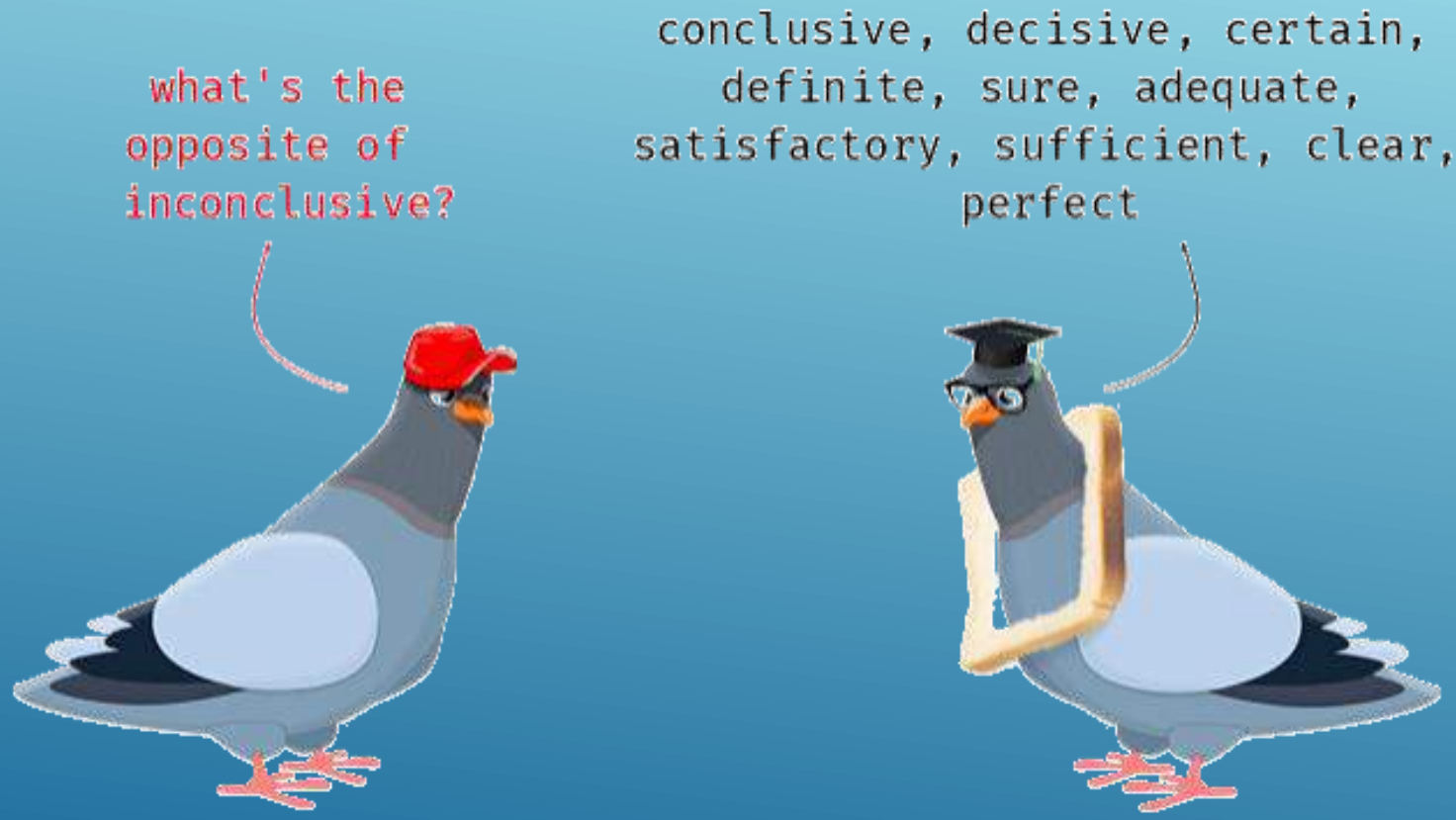
Use of BGC

- 8/11 experts believe that thrombectomy should **preferably be performed with a proximal balloon guide catheter**

https://jnis.bmj.com/content/early/2019/02/28/neurintsurg-2018-014569

DEBATE #1: STENT RETRIEVING OR ASPIRATION?

INCONCLUSIVE



DEBATE #2: DRIP & SHIP VS LOAD & GO

For thrombectomy to successful happen, these three elements need to get together:

The Patient

Trained Interventionalist

Cath Lab

Which organizational solution willyield the best patient results?

DEBATE #2: DRIP & SHIP vs LOAD & GO

Primary Stroke Center

- Has designated beds, complex imaging capabilities and cath lab

- Has specific stroke-trained staff and follows stroke protocols
- Has the ability to perform neurovascular intervention

- +/- 24hr/ 7days

Acute Stroke Ready Hospital

- Provides diagnosis and non-interventional treatment to AIS patients
- Has imaging capabilities, does patient triage (sometimes via telemedicine)
- Administers IV thrombolytics where appropriate & transfers to a Primary Stoke Center

DEBATE #2: DRIP & SHIP VS LOAD & GO

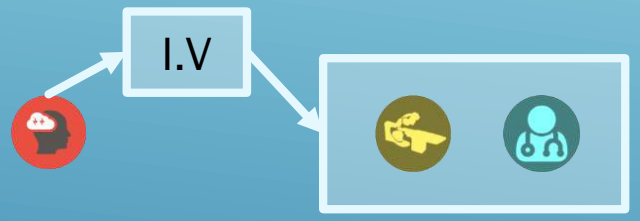
The Patient

Trained Interventionalist

Cath Lab

Mothership (Load & Go)

Drip & Ship



Drip & Drive

Tele Mentoring

DEBATE #2: DRIP & SHIP VS LOAD & GO

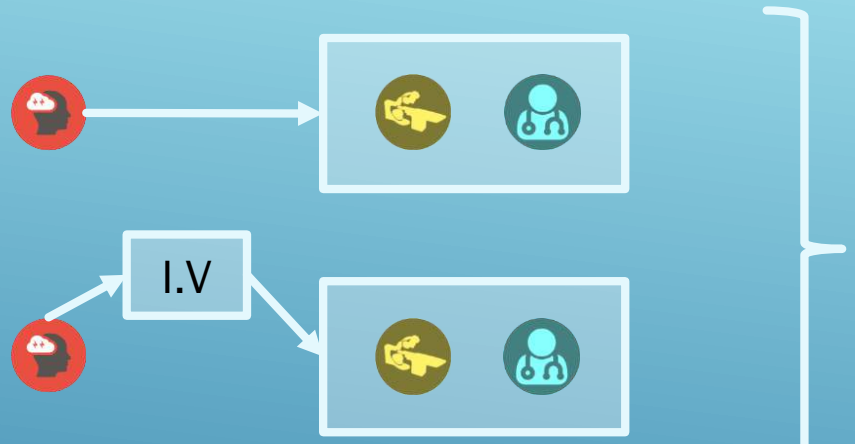
The Patient

Trained Interventionalist

Cath Lab

Mothership (Load & Go)

Drip & Ship



Decision to bypass the STROKE READY HOPISTAL to go directly to the PRIMARY STROKE CENTER is dependent on many variables

- Financial Resources,
- Case load capabilities at primary centers,
- Transportation possibilities – geography & weather

Drip & Drive

Drip & Drive seems to be a good option in metropolitan areas (saves 2 hours in different studies)

Tele Mentoring

Remote Support via online streaming had good results in simulation, will be real life tested (EastMINT)

DEBATES HAVE EVOLVED OVER THE PAST YEARS

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INCONCLUSIVE

GUIDELINES, PROTOCOLS, CLASSIFICATION OF STROKE CENTERS EXIST FOR ONE REASON:

PROVIDE THE BEST AVAILABLE CARE AND CONTINUOUSLY IMPROVE

1. Select the right patients to treat
2. Treat them with the best available tools and in a timely manner
3. Continuously improve

CHALLENGES/ GOALS OF STROKE TEAMS TODAY

Door-to-imaging < 30 minutes

Picture-to-puncture < 30 minutes

Door-to-groin puncture < 60 minutes

Groin puncture-to-recan < 20-30 minutes

Door-to-recan < 90 minutes

"Every 30 minutes of delay from symptom onset to reperfusion translates to roughly 10% decrease in the likelihood of a good outcome."

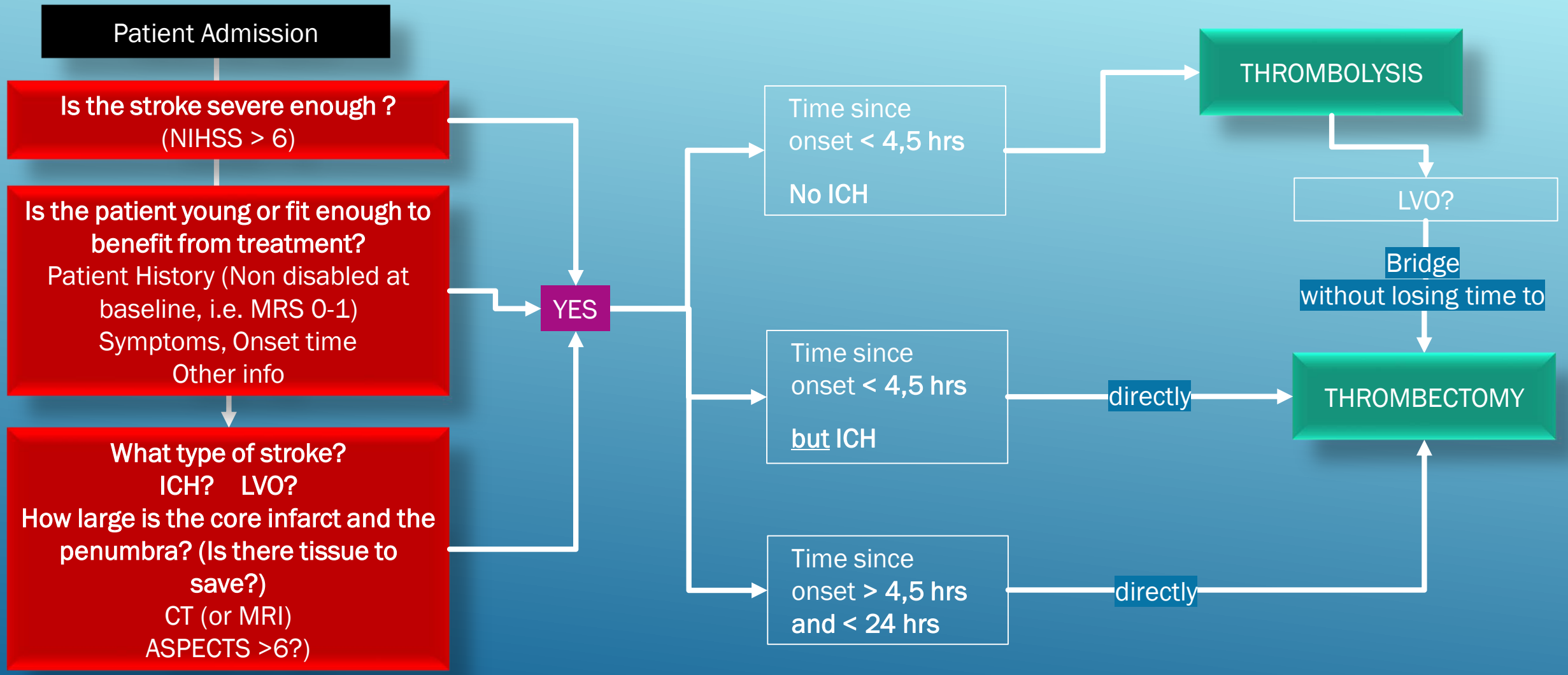
Tudor Jovin
University of Pittsburgh School of Medicine, Pittsburgh, USA

RECAP: STROKE SCALES

The scales used for patient and treatment assessment are:

NIHSS	ASPECTS	TICI	mRS
Scale for **measuring the severity of stroke at admission.** • How was the patient when s/he arrived? • 0-45 (0:perfect, 45:near dead) • AIS tX indicated after min 8-10	Scale for **assessing infarct core & penumbra size** • How large is the penumbra? • 10-point CT scan score • 1 point deducted for every region involved • < 7 predicts worse functional outcome	Scale for **measuring the degree of recanalization.** • How good was the angiographic outcome? • Did we achieve good recanalization? • 0,1,2a,2b,3 • 2c-3 near complete or complete recanalization	Scale for **measuring the degree of disability or dependence** in the daily activities of people who have suffered a stroke. • How well did the patient do? (Functional outcome) • How much neurological recovery was possible? • 0 – 6 (0:perfect, 6: dead) • 0 – 2: good outcome

RECAP: STROKE PATIENT PATHWAY TODAY



RECAP: GUIDELINES AND ONGOING DEBATES

Thrombectomy is the new gold standard for treatment of LVO AIS patients that present up to 24 hours from onset. (ESO/ESMINT Guidelines 2019)

Aspiration alone → not a viable option

Aspiration alone as a first line vs. Using SR systematically as first line → in discussion

Using local aspiration vs. BCG or both → in discussion

The challenge stroke teams face today is to shorten time from onset to recanalization!

FURTHER MATERIAL TO READ OR WATCH ON YOUR OWN TIME

European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke

Guillaume Turc,[1,2,3,4] Pervinder Bhogal,[5] Urs Fischer,[6] Pooja Khatri,[7] Kyriakos Lobotesis,[8] Mikaël Mazighi,[3,9,10,11] Peter D. Schellinger,[12] Danilo Toni,[13] Joost de Vries,[14] Philip White,[15] Jens Fiehler[16]

STROKE UPDATE AT NEUROSCIENCE NURSING SYMPOSIUM

Jeffrey Sunshine walks through of his hospital's stroke protocol, demonstrates the impact of modern AIS treatment through 3 patient cases and walks through the history of stroke treatment to the end of 2016.

This presentation was made while DAWN trial was ongoing and not yet published.

ACTING FAST CAN SAVE LIVES - WATCH

PATIENT STORIES - WATCH

- Identifying stroke & responding fast can save a person's life and avoid them debilitating neurological deficit