XIII congresso nazionale
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GENOVA 30 MAG - 1 GIU 2024

L'Ictus Ischemico

Antonio Voza

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IRCCS Humanitas Research Hospital
Humanitas University

Patologia tempo dipendente

stretta finestra terapeutica

POLICY | November 16, 2021

Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions

Vasu Saini, MD, Luis Guada, MD, and Dileep R. Yavagal, MD | AUTHORS INFO & AFFILIATIONS

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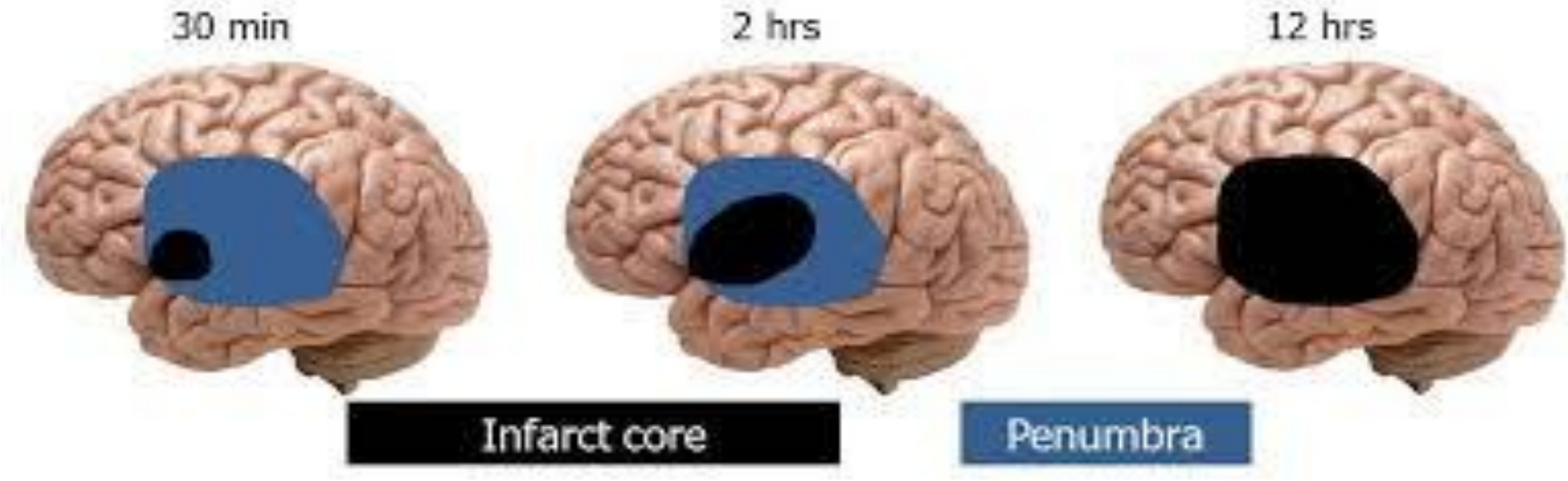
Destino della penombra: Time is brain



In assenza di riperfusione la penombra si trasforma progressivamente in infarto dopo 8-10 ore dall'esordio per fallimento dei meccanismi di compenso (emodinamici e metabolici)

La penombra ischemica può essere presente sino a 24-48 ore dall'esordio dei sintomi

Persistent Target Mismatch Profile >24 Hours after Stroke Onset in DEFUSE 3
S Chiristensen, M Mlynash, S Kemp et al
Stroke 2019; 50: 754-757

ISA-AII
Italian Stroke Association - Associazione Italiana Ictus

Raccomandazione 9.6 **Grado Forte a Favore**

In pazienti adulti con ictus ischemico acuto fra le 4.5 e le 9 ore dall'esordio teorico dei sintomi (incluso l'ictus al risveglio che rientri in questo intervallo di tempo), la trombolisi con r-TPA e.v. è raccomandata qualora la RM DWI/PWI o la TCP evidenzi tessuto ischemico in penombra salvabile.

Sintesi 9.4

Nei trial ECASS IV, EXTEND ed EPITHET il tessuto ischemico in penombra salvabile è stato definito con le seguenti modalità:

- ECASS IV: utilizzo di RM DW e PW; rapporto volumetrico tessuto ipoperfuso/core ischemico > 1.2; volume di ipoperfusione alla PW ≥ 20 ml; lettura visuale
- EXTEND: utilizzo di RM DW e PW o di TCP; volume core ischemico < 70 ml; rapporto volumetrico tessuto ipoperfuso/core ischemico > 1.2; differenza assoluta di volume fra tessuto ipoperfuso e core ischemico > 10 ml; lettura con software automatizzato
- EPITHET: utilizzo di RM DW e PW; rapporto volumetrico PW/DW > 1.2; volume PWI–DWI ≥10 mL; lettura con software automatizzato effettuata centralmente su pazienti selezionati in base ai segni precoci di ischemia alla TC cerebrale

Sintesi 9.5

Nei trial ECASS IV ed EXTEND i pazienti con ictus ischemico acuto al risveglio sono stati inclusi ipotizzando come ora di esordio il tempo medio fra ultima volta in cui erano stati visti/sentiti in benessere e risveglio e qualora il trattamento fosse possibile fra le 4.5 e le 9 ore dal teorico esordio dei sintomi.

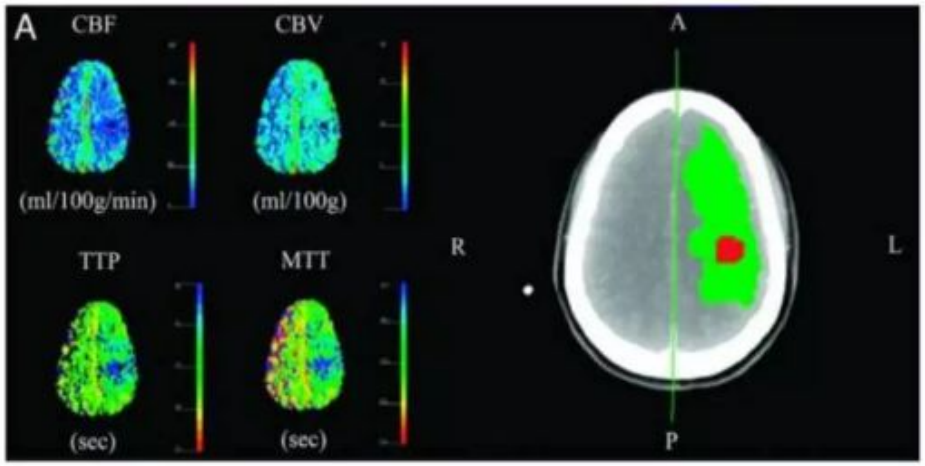
Estendere la finestra temporale per la terapia trombolitica a 9 ore utilizzando l'imaging di perfusione: terapia di riperfusione basata sul tessuto salvabile piuttosto che sul tempo.

Identificazione della penombra

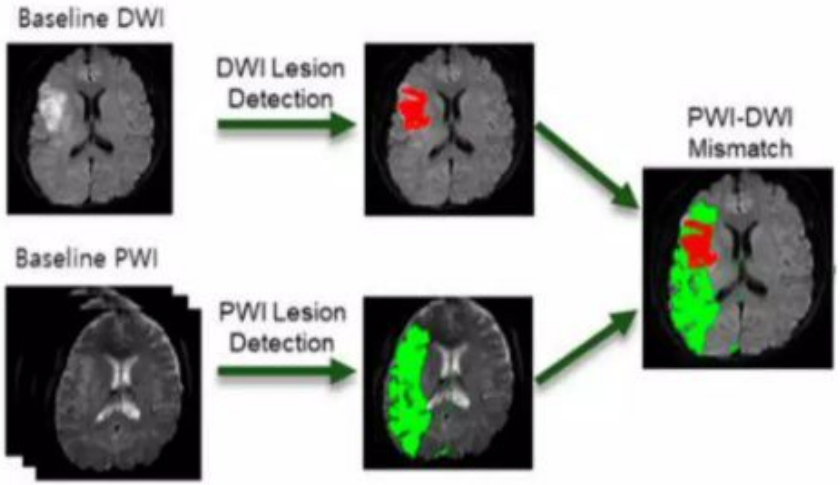
Identificare core infartuale e penombra ischemica nella finestra tardiva

Target mismatch

• TC PERFUSIONALE



• RM: MISMATCH PWI/DWI



Mismatch Tmax – CBF

• ipoperfusione totale (core + penombra) = estensione della lesione nella mappa di tempo al picco massimo della curva di funzione residua (Tmax)

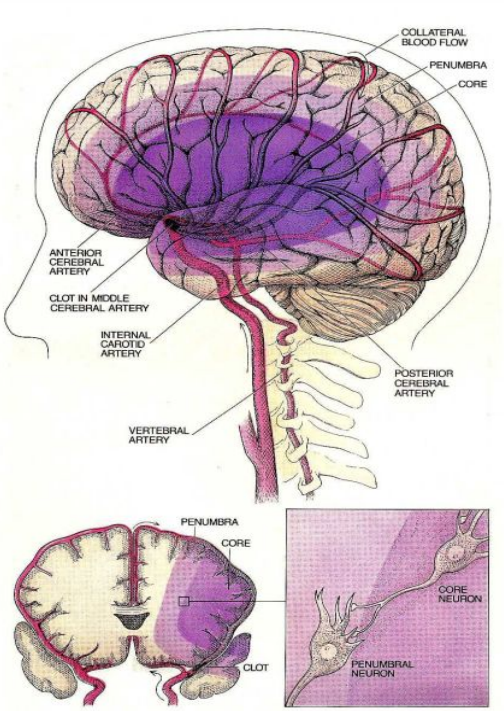
• core infartuale = dimensioni della lesione nella mappa di flusso ematico cerebrale (CBF)

Calcolo del target mismatch: software automatici

forniscono mappe di penombra pixel per pixel attraverso un'analisi volumetrica quantitativa basata sulle soglie: • segmentano sostanza bianca e sostanza grigia

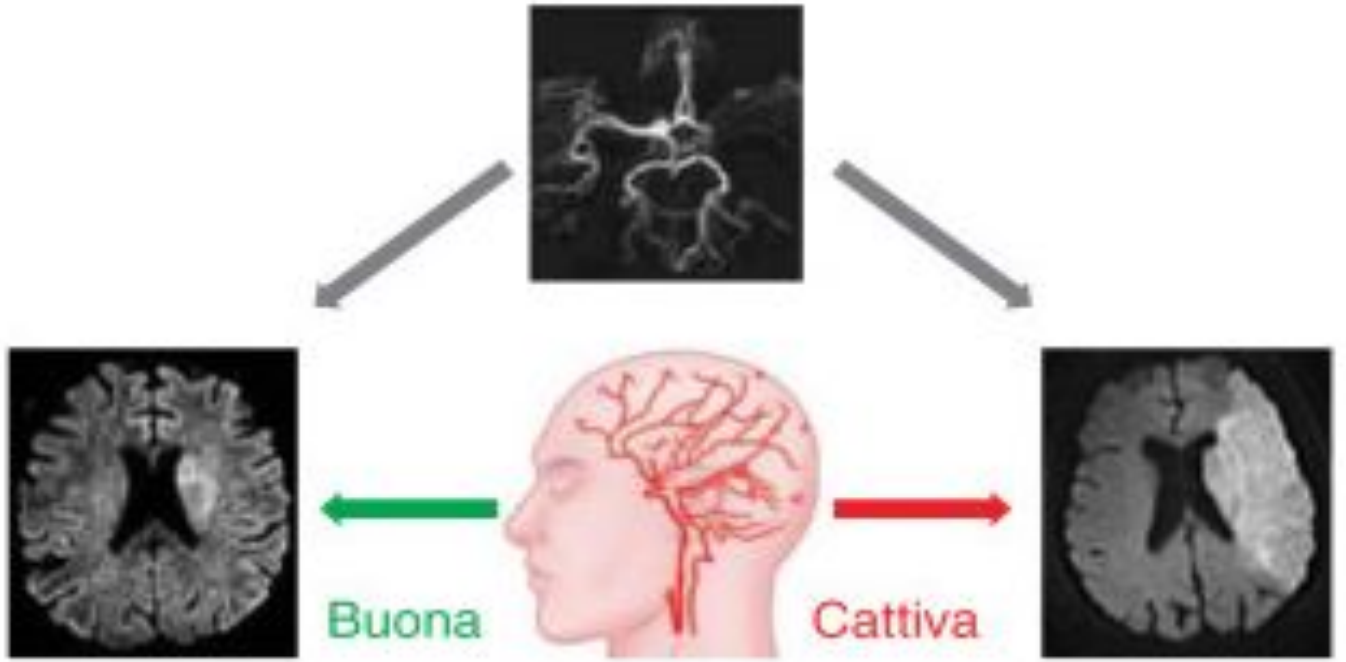
• identificano l'ipoperfusione totale e il core ischemico utilizzando i rispettivi valori soglia prestabiliti

• elaborano mappe che indicano di quanti pixels sono costituiti penombra e core e calcolano automaticamente il volume di queste due aree e il mismatch ratio



Meccanismi di compenso: i circoli collaterali e autoregolazione

vasodilatazione

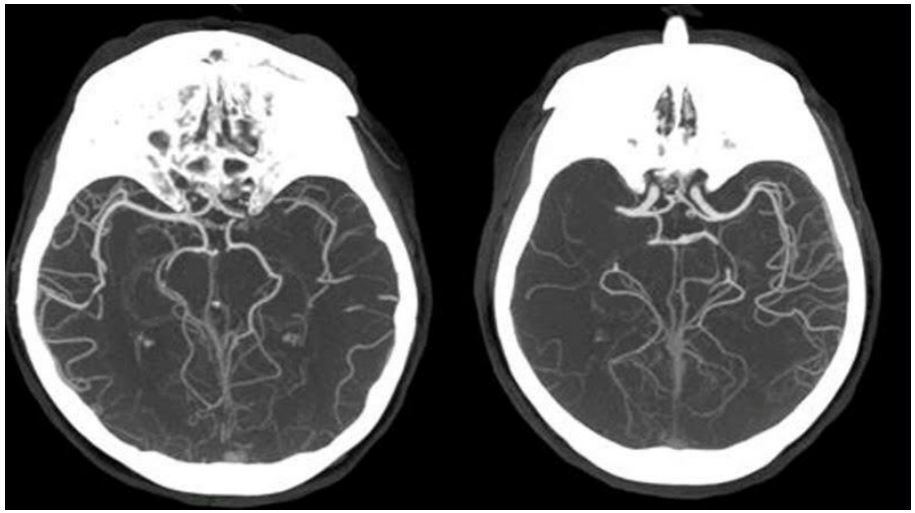


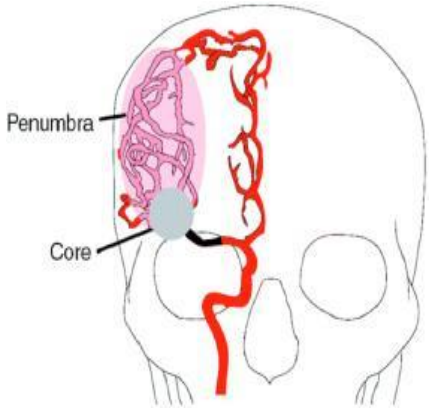
Collateralità leptomeningea

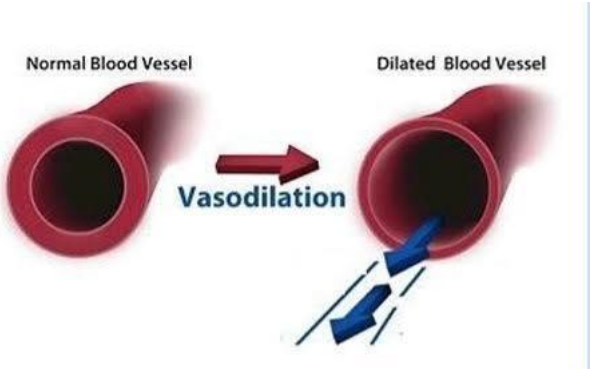
Tempo	=	Tempo
Core	<	*Core*
Penombra ischemica	>	Penombra ischemica

Ruolo dell'a-TC

- identificare la sede e l'estensione dell'occlusione vasale
- valutare l'efficienza dei circoli collaterali







• l'apertura dei circoli collaterali leptomeningei è il principale meccanismo di compenso che mantiene vitale la penombra ischemica attraverso una massiccia vasodilatazione

• l'estensione dei circoli collaterali è associata alla prognosi perché buoni circoli collaterali = outcome favorevole

nelle linee guida l'utilizzo della CTA per la valutazione dei circoli collaterali è fortemente raccomandata nei pazienti

Attuali linee guida

finestra terapeutica precoce e tardiva

ISA-AII
Italian Stroke Association - Associazione Italiana Ictus

Trombolisi ev

- Finestra precoce < 4.5 ore

Uso TC encefalo smdc

- Finestra tardiva 4.5-9 ore o al risveglio

Uso TCsmdc+TC perfusionale

Con o senza occlusione di un grosso vaso

Trattamento endovascolare

- Finestra precoce < 6 ore

Uso TC encefalo smdc + angioTC

- Finestra tardiva 6-24 ore o al risveglio

Uso TCsmdc+TC perfusionale+angioTC

Con occlusione di un grosso vaso

EDITORIALS

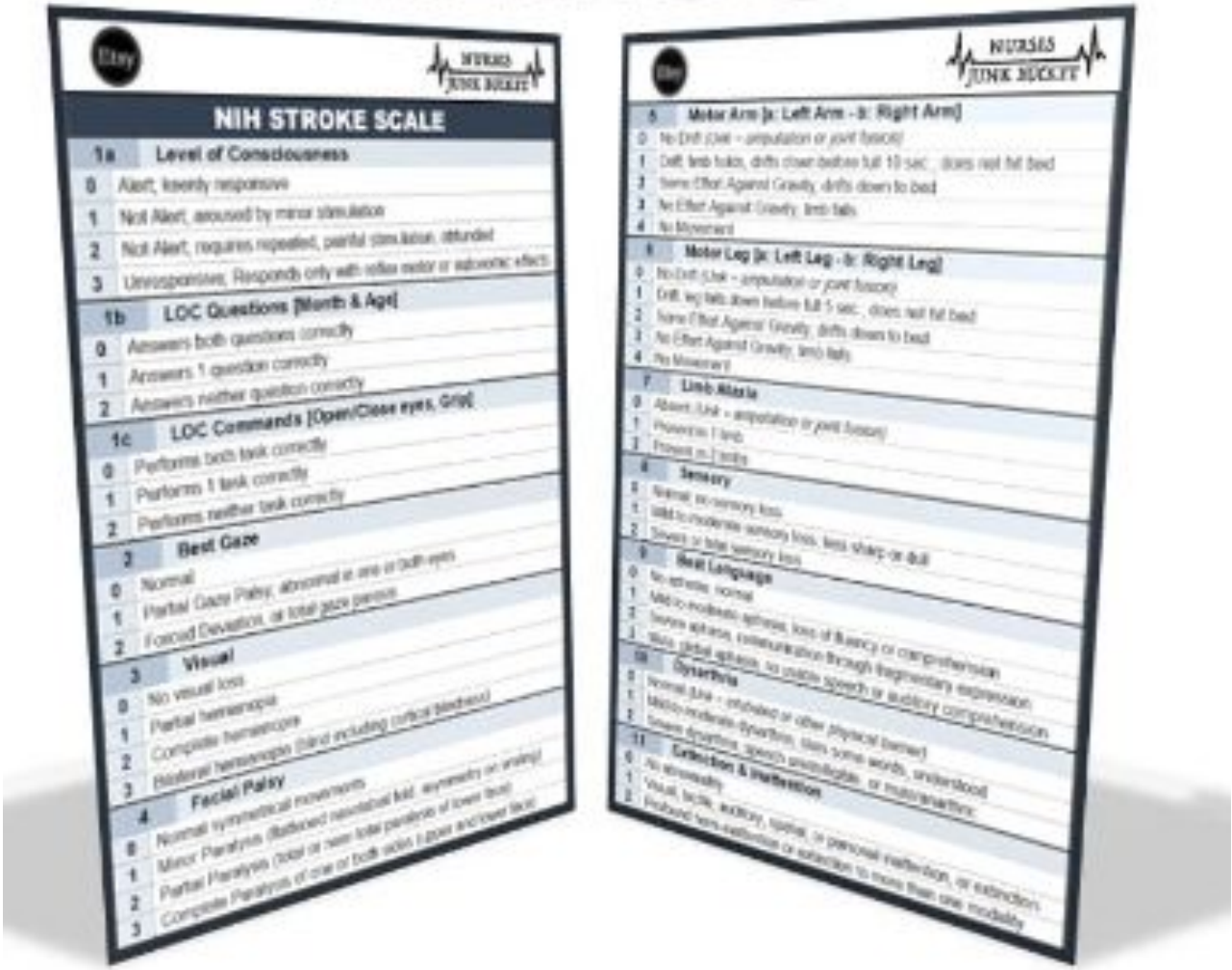
Alteplase and Thrombectomy — Not a Bridge to Dismantle

Alfonso Ciccone, M.D.

MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)–NO IV,[4] the results of which are reported in this issue of the *Journal*, is the fourth trial[5-7] to test whether thrombolysis can be omitted before thrombectomy for stroke. The primary end point in the trial was functional outcome on the modified Rankin scale (with scores ranging from 0 [no symptoms] to 6 [death]) at day 90. The trial was designed to test noninferiority of thrombectomy alone by a margin of 0.8 and also to test superiority. The adjusted common odds ratio across the scores on the modified Rankin scale was 0.84 (95% confidence interval, 0.62 to 1.15), which showed neither noninferiority nor superiority of thrombectomy alone. This result contrasts with those of most previous trials. Mortality at 90 days was 20.5% in the thrombectomy group and 15.8% in the usual-care group, and symptomatic intracerebral hemorrhage occurred in approximately 5% of the patients in each trial group.

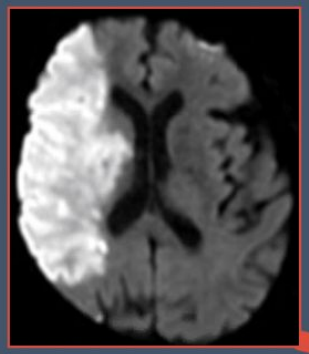
Therefore, on the basis, in part, of the results from the MR CLEAN–NO IV trial, the bridge of intravenous thrombolysis before thrombectomy in acute stroke due to occlusion of a large cerebral vessel is not ready to be dismantled.

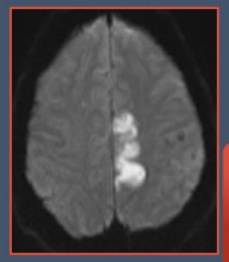
NIHSS


NURSES JUNK BUCKET
NIH STROKE SCALE
1a Level of Consciousness
0 Alert; keenly responsive
1 Not Alert; aroused by minor stimulation
2 Not Alert; requires repeated, painful stimulation, obtunded
3 Unresponsive; Responds only with reflex motor or autonomic effects
1b LOC Questions [Month & Age]
0 Answers both questions correctly
1 Answers 1 question correctly
2 Answers neither question correctly
1c LOC Commands [Open/Close eyes, Grip]
0 Performs both task correctly
1 Performs 1 task correctly
2 Performs neither task correctly
2 Best Gaze
0 Normal
1 Partial Gaze Palsy; abnormal in one or both eyes
2 Forced Deviation, or total gaze paresis
3 Visual
0 No visual loss
1 Partial hemianopia
2 Complete hemianopia
3 Bilateral hemianopia (blind including cortical blindness)
4 Facial Palsy
0 Normal symmetrical movements
1 Minor Paralysis (flattened nasolabial fold, asymetry on smiling)
2 Partial Paralysis (total or near total paralysis of lower face)
3 Complete Paralysis of one or both sides (upper and lower face)
5 Motor Arm [a: Left Arm - b: Right Arm]
0 No Drift (Use = amputation or joint fusion)
1 Drift; limb holds, drifts down before full 10 sec.; does not fall bed
2 Some Effort Against Gravity; drifts down to bed
3 No Effort Against Gravity; limb falls
4 No Movement
6 Motor Leg [a: Left Leg - b: Right Leg]
0 No Drift (Use = amputation or joint fusion)
1 Drift; leg falls down before full 5 sec.; does not fall bed
2 Some Effort Against Gravity; drifts down to bed
3 No Effort Against Gravity; limb falls
4 No Movement
7 Limb Ataxia
0 Absent (Use = amputation or joint fusion)
1 Present in 1 limb
2 Present in 2 limbs
8 Sensory
0 Normal; no sensory loss
1 Mild to moderate sensory loss; less sharp or dull
2 Severe or total sensory loss
9 Best Language
0 No aphasia; normal
1 Mild to moderate aphasia; loss of fluency or comprehension
2 Severe aphasia; communication through fragmentary expression
3 Mute, global aphasia; no useful speech or auditory comprehension
10 Dysarthria
0 Normal (Use = intubated or other physical barrier)
1 Mild to moderate dysarthria; slurs some words, understood
2 Severe dysarthria; speech unintelligible, or mute/anarthric
11 Extinction & Inattention
0 No abnormality
1 Visual, tactile, auditory, spatial, or personal inattention, or extinction
2 Profound hemi-inattention or extinction to more than one modality

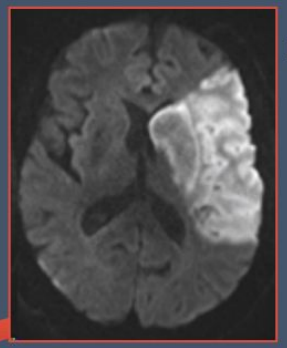
VASTLY OVERSIMPLIFIED BUT CONCISE OVERVIEW OF MAJOR STROKE SYNDROMES

R MCA Syndrome:
- R gaze deviation
- L sided weakness
- L neglect

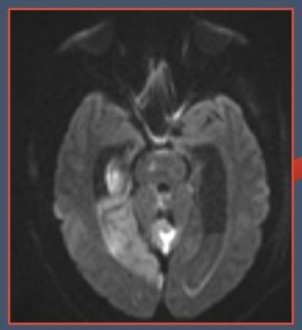




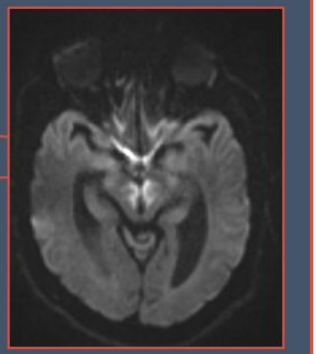
ACA Syndrome:
- Contralateral leg weakness
- Executive disfunction / abulia

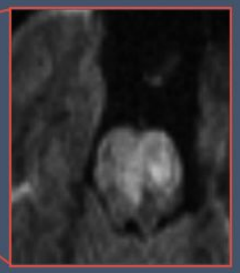


L MCA Syndrome:
- L gaze deviation
- R sided weakness
- Aphasia



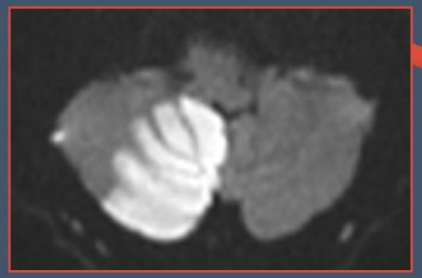
PCA Syndrome:
- Contralateral hemianopsia
- Confusion, amnesia, often w/ disorders of consciousness



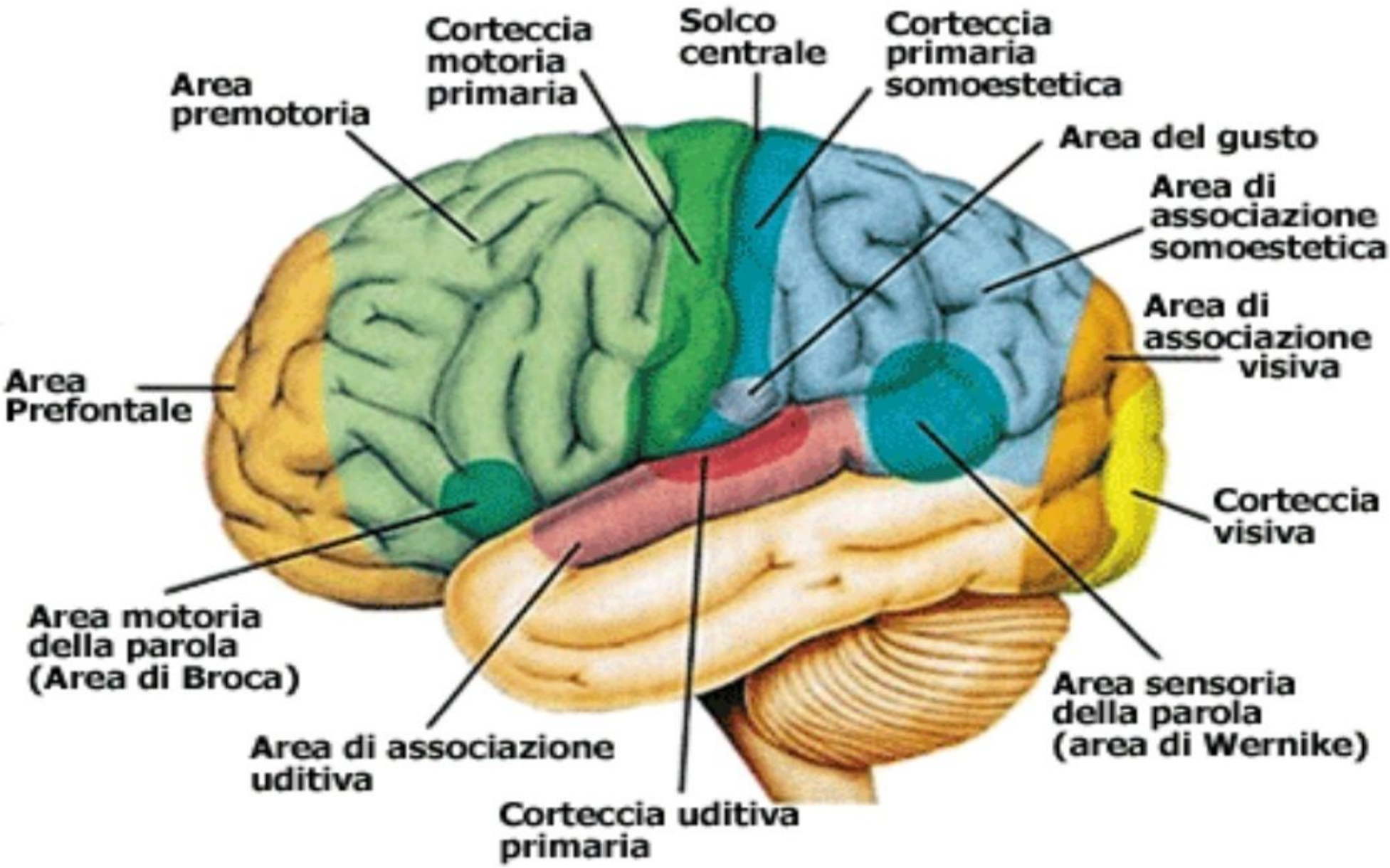


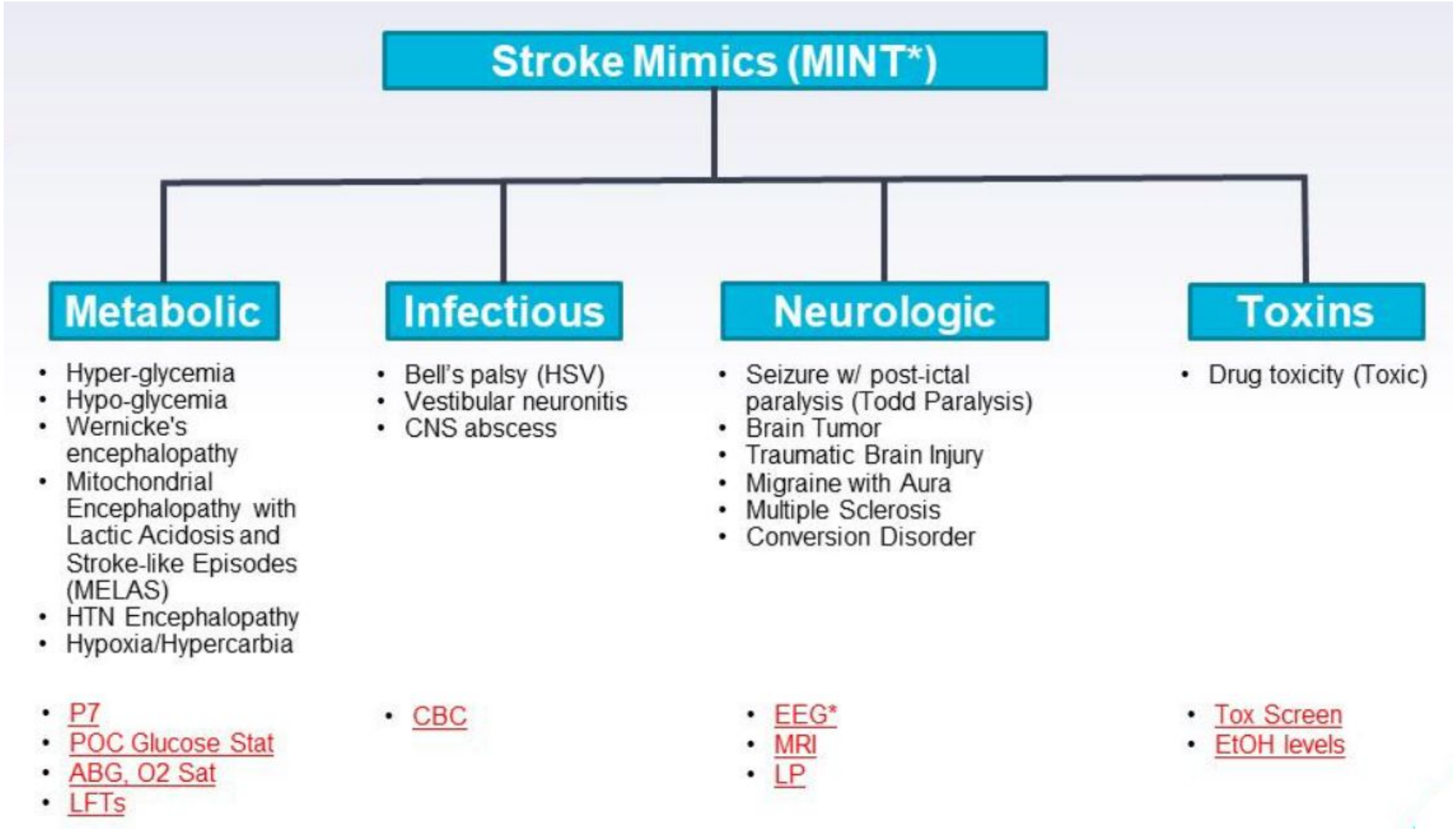
Mid-Basilar Stroke:
- Locked-in state
- "Crossed" symptoms
- Ocular palsies

Top of the Basilar / Thalamic Perforators:
- Acute disorders of consciousness / Coma



Cerebellar Stroke:
(May result from vert, PICA, AICA, SCA occlusions)
- Ipsilateral ataxia
- Nausea, vertigo, nystagmus, imbalance


Area premotoria
Corteccia motoria primaria
Solco centrale
Corteccia primaria somoestetica
Area del gusto
Area di associazione somoestetica
Area di associazione visiva
Area Prefontale
Corteccia visiva
Area motoria della parola (Area di Broca)
Area di associazione uditiva
Corteccia uditiva primaria
Area sensoria della parola (area di Wernike)


Stroke Mimics (MINT*)
Metabolic
Infectious
Neurologic
Toxins
• Hyper-glycemia
• Hypo-glycemia
• Wernicke's encephalopathy
• Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like Episodes (MELAS)
• HTN Encephalopathy
• Hypoxia/Hypercarbia
• Bell's palsy (HSV)
• Vestibular neuronitis
• CNS abscess
• Seizure w/ post-ictal paralysis (Todd Paralysis)
• Brain Tumor
• Traumatic Brain Injury
• Migraine with Aura
• Multiple Sclerosis
• Conversion Disorder
• Drug toxicity (Toxic)
• P7
• POC Glucose Stat
• ABG, O2 Sat
• LFTs
• CBC
• EEG*
• MRI
• LP
• Tox Screen
• EtOH levels

NOVITA’

che hanno modificato o potenzialmente modificheranno nel futuro prossimo la gestione dello stroke

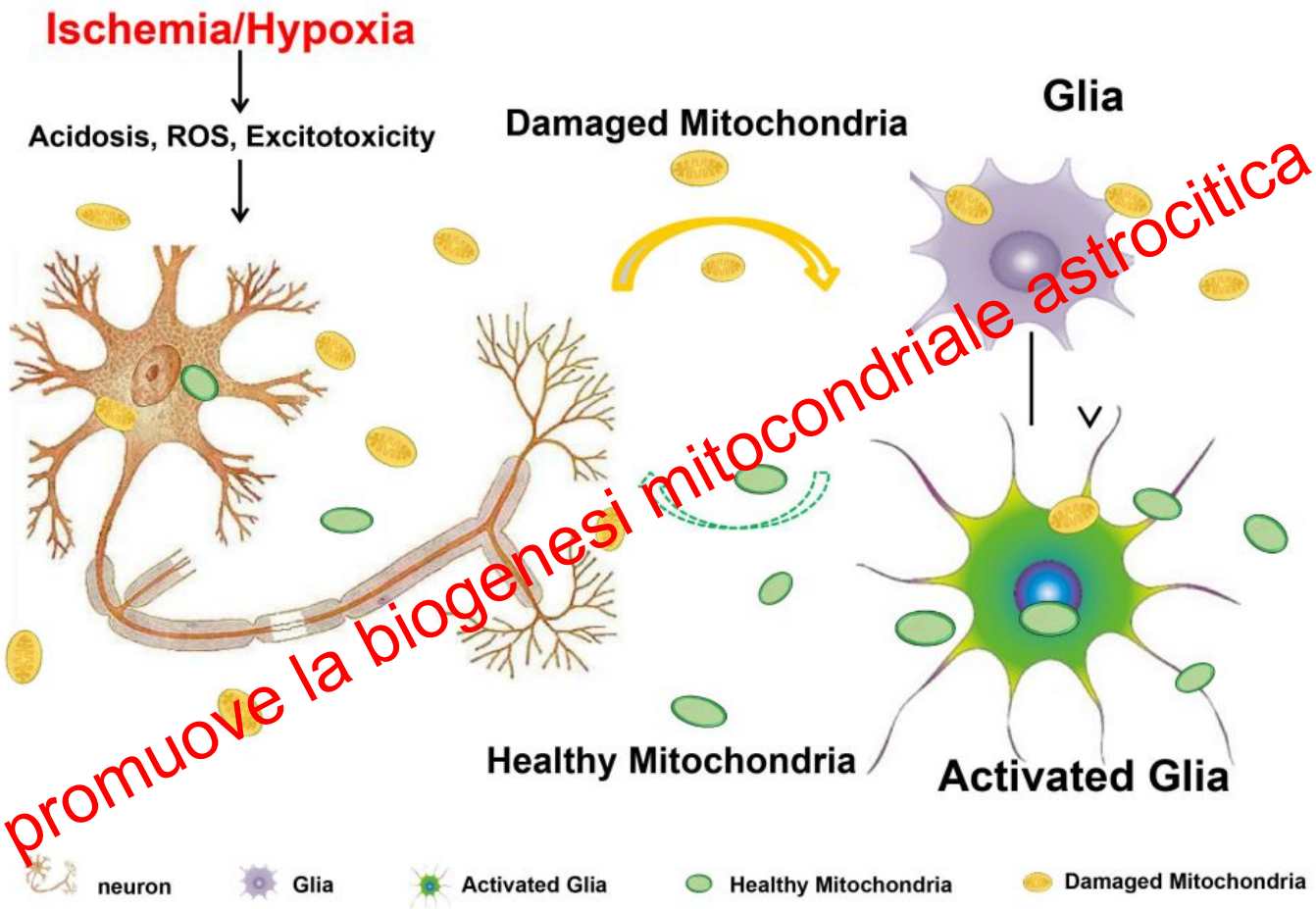
?

frontiers in Aging Neuroscience

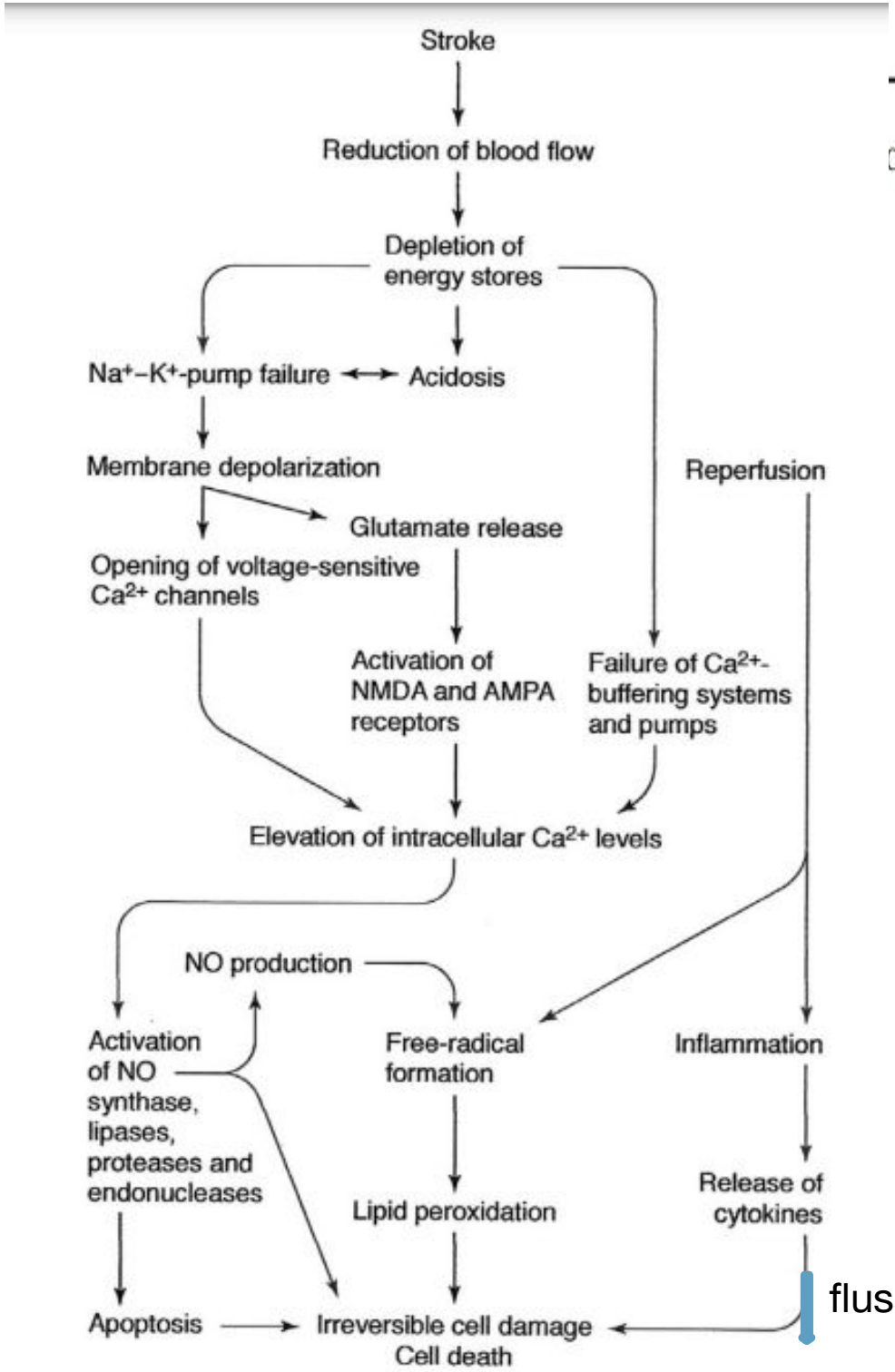
ORIGINAL RESEARCH
published: 03 March 2022
doi: 10.3389/fnagi.2022.785761

Neurons Release Injured Mitochondria as "Help-Me" Signaling After Ischemic Stroke

Li Gao[1,2†], Fan Liu[3†], Pin-Pin Hou[1], Anatol Manaenko[4], Zhi-Peng Xiao[2], Fei Wang[2], Tian-Le Xu[3] and Qin Hu[1*]*

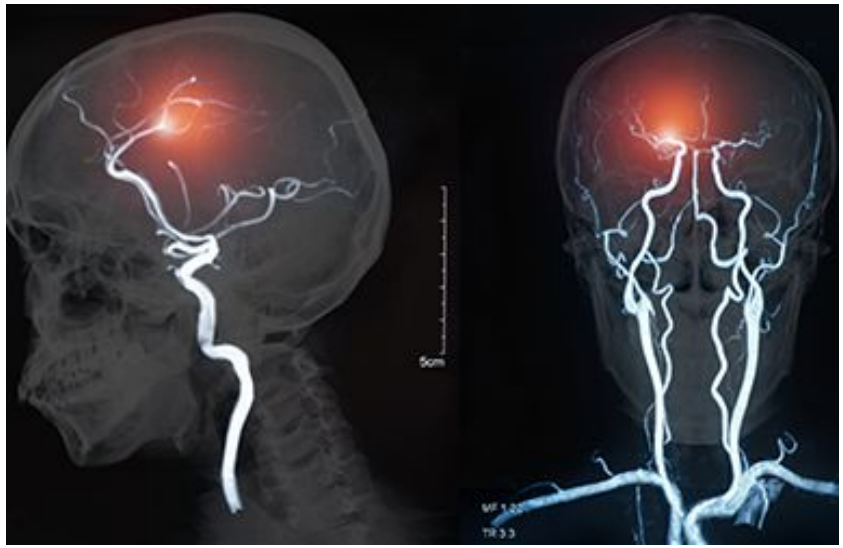


promuove la biogenesi mitocondriale astrocitica



Neuroprotection in Acute Ischemic Stroke: A Brief Review

Alastair M. Buchan, David M. Pelz



flusso sanguigno -> produzione di adenosina 5 trifosfato

The use of dual antiplatelet therapy for ischemic cerebrovascular events in secondary prevention

Features of the three studies: DAPT in TIA or minor-moderate stroke

	CHANCE	POINT	THALES
Number of patients (DAPT vs. controls)	5170 (2584 vs. 2586)	4881 (2432 vs. 2449)	11,073 (5523 vs. 5493)
Median age (years)	62	65	65
Inclusion criteria			
Non-cardioembolic ischemic stroke	NIHSS ≤ 3	NIHSS ≤ 3	NIHSS ≤ 5
Non-cardioembolic high-risk TIA	$ABCD^2$ score ≥ 4	$ABCD^2$ score ≥ 4	$ABCD^2$ score ≥ 6
Treatment			
DAPT group	Day 1: Clopidogrel 300 mg + ASA 75–300 mg Day 2–22: Clopidogrel 75 mg + ASA 75 mg Day 22–90: Clopidogrel 75 mg	Day 1: Clopidogrel 600 mg + ASA 50–325 mg Day 2–90: Clopidogrel 75 mg + ASA 50–325 mg	Day 1: Ticagrelor 90 mg × 2 + ASA 300–325 mg Day 2–30: Ticagrelor 90 mg × 2 + ASA 75–100 mg
Control group	Day 1: ASA 75–300 mg + placebo Day 2–90: ASA + placebo	Day 1 – 90: ASA 50–325 mg + placebo	Day 1: ASA 300–325 mg + placebo Day 2–30: ASA 75–100 mg + placebo

In the last 10 years, the use of dual antiplatelet therapy (DAPT) has been explored in patients with non-cardioembolic ischemic stroke,transient ischemic attack (TIA). CHANCE and POINT clinical trials showed that the addition of clopidogrel to aspirin reduced risk of subsequent stroke in minor stroke or high-risk TIA. THALES showed that the association of

JAMA | Original Investigation

Dual Antiplatelet Therapy vs Alteplase for Patients With Minor Nondisabling Acute Ischemic Stroke
The ARAMIS Randomized Clinical Trial

Hui-Sheng Chen, MD; Yu Cui, PhD; Zhong-He Zhou, MD; Hong Zhang, BSM; Li-Xia Wang, BSM; Wei-Zhong Wang, BSM; Li-Ying Shen, BSM; Li-Yan Guo, MM; Er-Qiang Wang, MM; Rui-Xian Wang, MM; Jing Han, MM; Yu-Ling Dong, BSM; Jing Li, BSM; Yong-Zhong Lin, MD; Qing-Cheng Yang, BSM; Li Zhang, BSM; Jing-Yu Li, MM; Jin Wang, BSM; Lei Xia, BSM; Guang-Bin Ma, BSM; Jiang Lu, BSM; Chang-Hao Jiang, BSM; Shu-Man Huang, BSM; Li-Shu Wan, MM; Xiang-Yu Piao, MD; Zhuo Li, MM; Yan-Song Li, MM; Kui-Hua Yang, BSM; Duo-Lao Wang, PhD; Thanh N. Nguyen, MD; for the ARAMIS Investigators

IMPORTANCE Intravenous thrombolysis is increasingly used in patients with minor stroke, but its benefit in patients with minor nondisabling stroke is unknown.

OBJECTIVE To investigate whether dual antiplatelet therapy (DAPT) is noninferior to intravenous thrombolysis among patients with minor nondisabling acute ischemic stroke.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, open-label, blinded end point, noninferiority randomized clinical trial included 760 patients with acute minor nondisabling stroke (National Institutes of Health Stroke Scale [NIHSS] score ≤5, with ≤1 point on the NIHSS in several key single-item scores; scale range, 0-42). The trial was conducted at 38 hospitals in China from October 2018 through April 2022. The final follow-up was on July 18, 2022.

Conclusions

Among patients presenting with minor nondisabling acute ischemic stroke within 4.5 hours of symptom onset, dual antiplatelet treatment was noninferior to intravenous alteplase with regard to excellent functional outcome at 90 days.

JAMA. 2022;328(24):2427-2436

Battaglini *et al. Critical Care* (2020) 24:163
https://doi.org/10.1186/s13054-020-02885-8

Critical Care

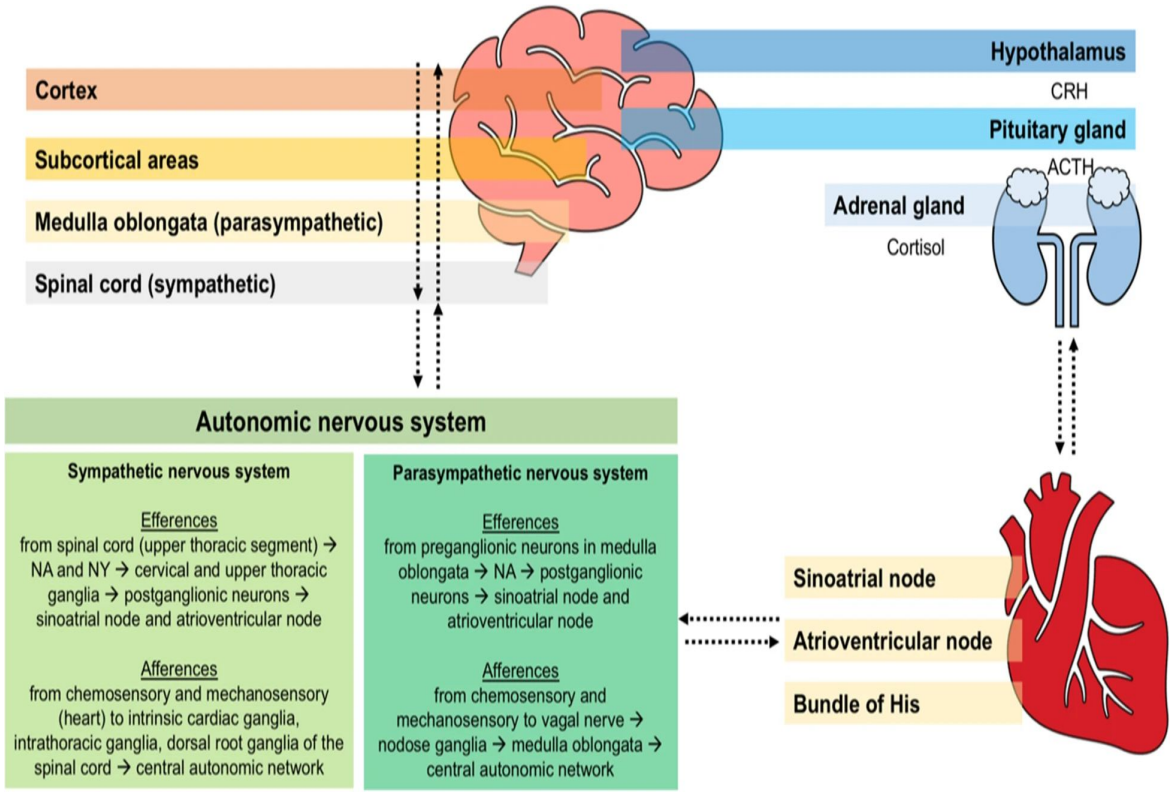
REVIEW Open Access

Brain–heart interaction after acute ischemic stroke

Denise Battaglini[1,2], Chiara Robba[1], Adriana Lopes da Silva[3], Cynthia dos Santos Samary[3,4], Pedro Leme Silva[3], Felipe Dal Pizzol[5], Paolo Pelosi[1,2†] and Patricia Rieken Macedo Rocco[3,6*†]

Cardiovascular disease is regarded as the main predisposing risk factor for acute ischemic stroke

Brain damage can modify the autonomic and neurohormonal pathways involved in the control of heart function so patients affected by stroke are extremely vulnerable to severe cardiac adverse events



3% myocardial infarction

50% asymptomatic coronary stenosis

4% autonomic dysfunction

17% heart failure

28% left ventricular ejection fraction

13–29% systolic dysfunction

60-85% Electrocardiographic abnormalities

T wave inversion (35%), ST depression (33%), prolonged QTc interval (29%), U waves (28%).

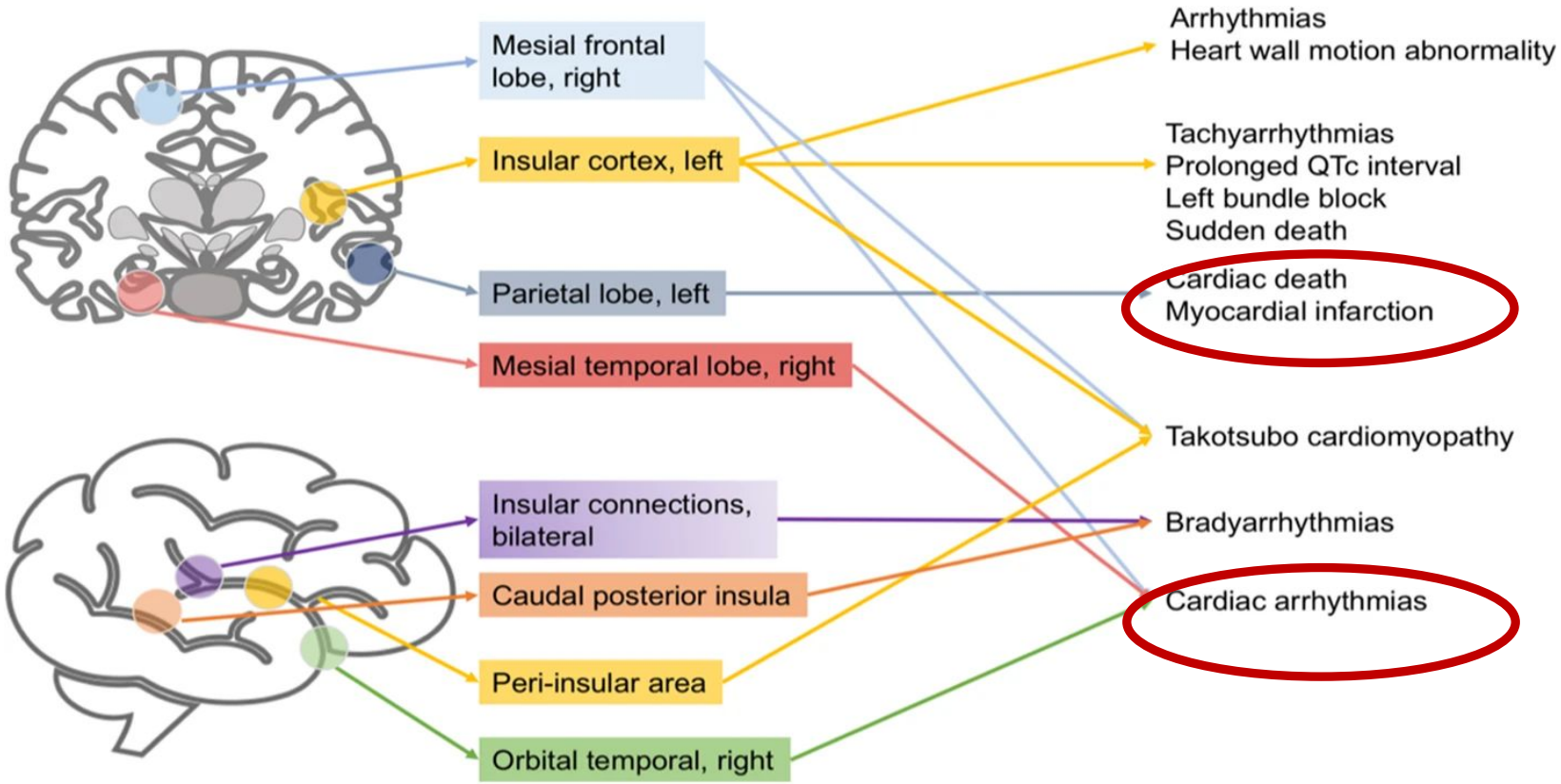
Atrial fibrillation, supraventricular tachycardia, ven-

The main mechanisms involved in the so-called stroke- heart crosstalk include:

- hypothalamic–pituitary–ad- renal axis (HPA)
- the immune and inflammatory responses

Brain-heart interaction after acute ischemic stroke

Brain <-> Heart



Activation of different brain areas during stroke followed by specific cardiovascular complications.

Depending on the extent of subsequent brain damage, stroke triggers different central regulatory regions, thus activating corresponding pathways that depend on the injured area.

Post-stroke cardiac dysfunctions may be referred to specific brain areas.

Right-side stroke is usually associated with more cardiac complications than left-side stroke

Brain-heart interaction after acute ischemic stroke
Battaglini et al. Critical Care (2020) 24:163

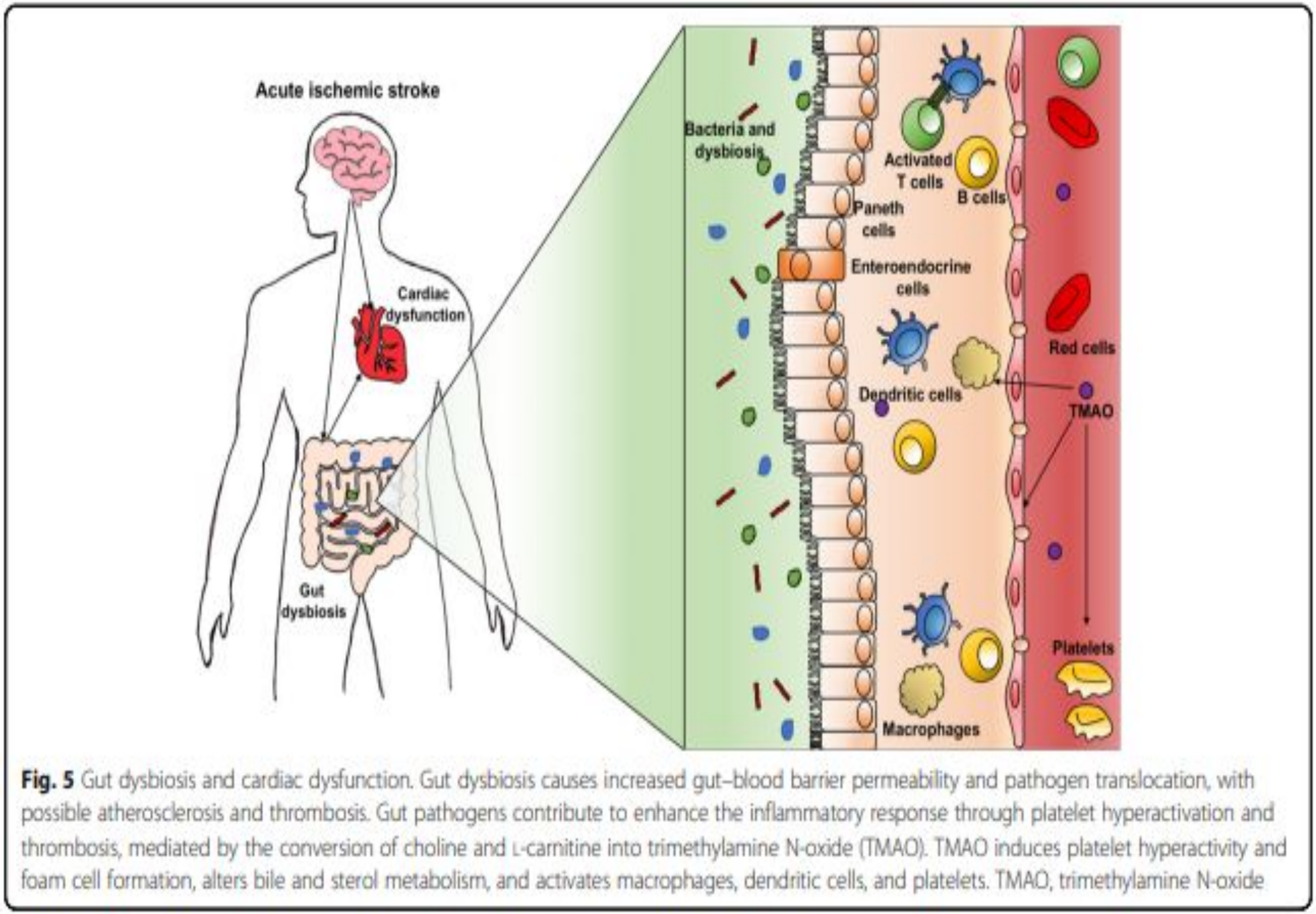


Fig. 5 Gut dysbiosis and cardiac dysfunction. Gut dysbiosis causes increased gut–blood barrier permeability and pathogen translocation, with possible atherosclerosis and thrombosis. Gut pathogens contribute to enhance the inflammatory response through platelet hyperactivation and thrombosis, mediated by the conversion of choline and L-carnitine into trimethylamine N-oxide (TMAO). TMAO induces platelet hyperactivity and foam cell formation, alters bile and sterol metabolism, and activates macrophages, dendritic cells, and platelets. TMAO, trimethylamine N-oxide

Brain-heart interaction after acute ischemic stroke Battaglini et al. Critical Care (2020) 24:163


How is
stroke different
between
MEN and WOMEN?

Circulation Research

WOMEN AND CARDIOVASCULAR HEALTH COMPENDIUM

The Impact of Sex and Gender on Stroke

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ABSTRACT: Women face a disproportionate burden of stroke mortality and disability. Biologic sex and sociocultural gender both contribute to differences in stroke risk factors, assessment, treatment, and outcomes. There are substantial differences in the strength of association of stroke risk factors, as well as female-specific risk factors. Moreover, there are differences in presentation, response to treatment, and stroke outcomes in women. This review outlines current knowledge of impact of sex and gender on stroke, as well as delineates research gaps and areas for future inquiry.

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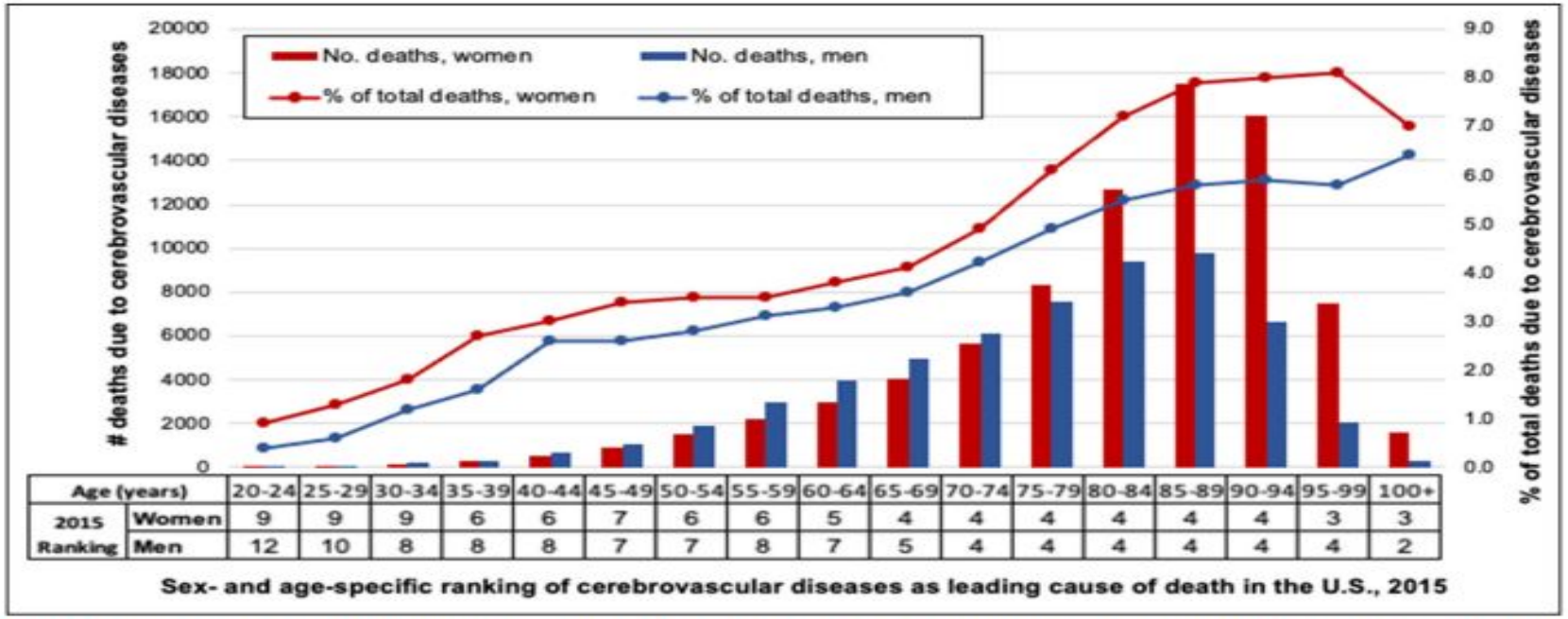

Age (years)		20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99	100+
2015 Ranking	Women	9	9	9	6	6	7	6	6	5	4	4	4	4	4	4	3	3
	Men	12	10	8	8	8	7	7	8	7	5	4	4	4	4	4	4	2

Sex- and age-specific ranking of cerebrovascular diseases as leading cause of death in the U.S., 2015

Figure 1. Sex- and age-specific ranking, percentage, and total number of deaths attributed to cerebrovascular diseases in 2015.
Data derived from National Vital Statistics System (NVSS), 2015. LCWK1: deaths, percent of total deaths, and death rates for the 15 leading causes of death in 5-year age groups, by race and sex: United States, 2015. Accessed October 13, 2021. https://www.cdc.gov/nchs/data/dvs/LCWK1_2015.pdf

American Stroke Association.
A division of the American Heart Association.

American Heart Association.
Go Red for women.

Women face higher risk of stroke

STROKE IN U.S. WOMEN BY THE NUMBERS

One in 5 women will have a stroke.

About 55,000 more women than men have a stroke each year.

#3 cause of death

Stroke is the No. 3 cause of death in women.

Stroke kills over 90,000 women a year.

Among women, Black women have the highest prevalence of stroke.

STROKE RISK **INCREASES** IN WOMEN WHO:

Are pregnant

Pregnant women are three times more likely to have a stroke as non-pregnant women of the same age.

Have preeclampsia

This dangerous condition of high blood pressure during pregnancy doubles stroke risk later in life.

Take birth control pills

These can double the risk of stroke, especially in women with high blood pressure.

Use hormone replacement therapy

It doesn't lower stroke risk if postmenopausal, as once thought.

Have migraines with aura and smoke

Strokes are more common in women who have migraines with aura and smoke, compared with other women.

Have atrial fibrillation

This quivering or irregular heartbeat can increase stroke risk fivefold.

STROKE RISK **DECREASES** IN WOMEN WHO:

Talk to their health care professional to **determine safest medication** if pregnant with high blood pressure.

Discuss with their health care professional **low-dose aspirin guidelines** starting in the second trimester (week 12) to lower preeclampsia risk.

Get their blood pressure checked before taking birth control pills and monitor every six months.

Review the risk and benefits of hormone replacement therapy with their health care professional and discuss if the benefit outweighs the risks. For some women, it might not.

Quit smoking. All women who experience migraines and smoke should avoid smoking, nicotine use, vaping and e-cigarettes.

Get screened for atrial fibrillation if over the age of 75 as this condition then becomes more common in women.

STROKE SYMPTOMS: WOMEN VS. MEN

Men and women share a common set of stroke symptoms. But women also can experience more subtle warning signs.

WOMEN

- Face drooping
- Arm weakness
- Speech difficulty
- Vision problems
- Trouble walking or lack of coordination
- Severe headache without a known cause
- **General weakness**
- **Disorientation & confusion or memory problems**
- **Fatigue**
- **Nausea or vomiting**

MEN

- Face drooping
- Arm weakness
- Speech difficulty
- Vision problems
- Trouble walking or lack of coordination
- Severe headache without a known cause

American Heart Association.
Go Red for women.

Source: American Stroke Association; Gender Medicine; Journal of Neuroscience Nursing
Published May 31, 2019 |
By American Heart Association News

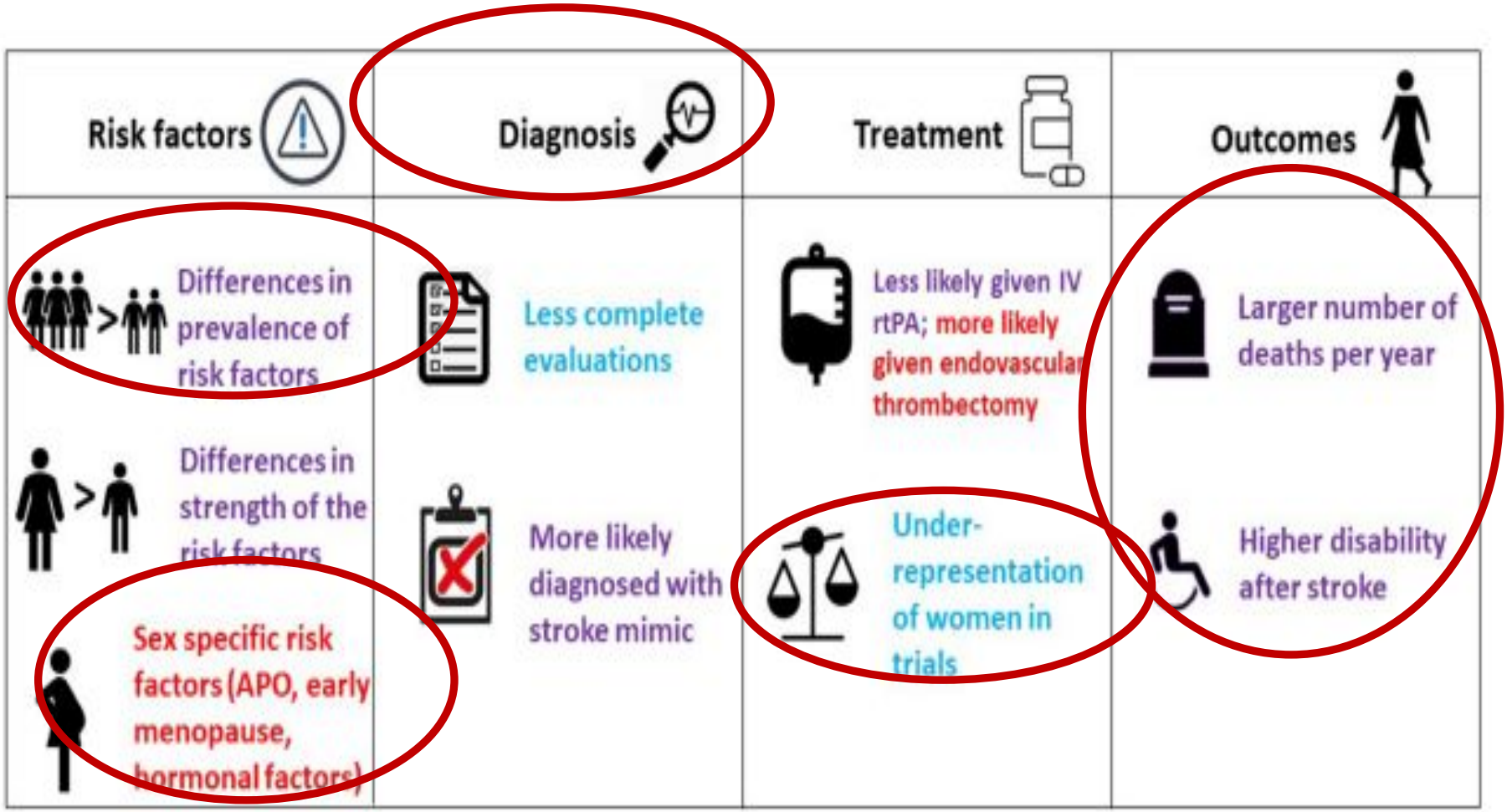

Figure 5. Central Illustration, the impact of sex and gender on stroke.

APO indicates adverse pregnancy outcomes; IV rtPA, intravaneous recombinant tissue plasminogen activator. Biologic sex is shown in red, gender in blue, combined in purple.

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There is no sun without the shadow and it is essential to know the night.

Albert Camus, The Myth of Sisyphus, 1942