La sindrome cuore-cervello dopo stroke ischemico: narrazione o realtà clinica?

Enrico Natale

UOSD Diagnostica Cuore,
Dipartimento Cardio-Toraco-Vascolare
Ospedale S. Camillo, Roma

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERA
SAN CAMILLO FORLANINI

CHINI VIRGILIO

Bassano del Grappa 1901-1983

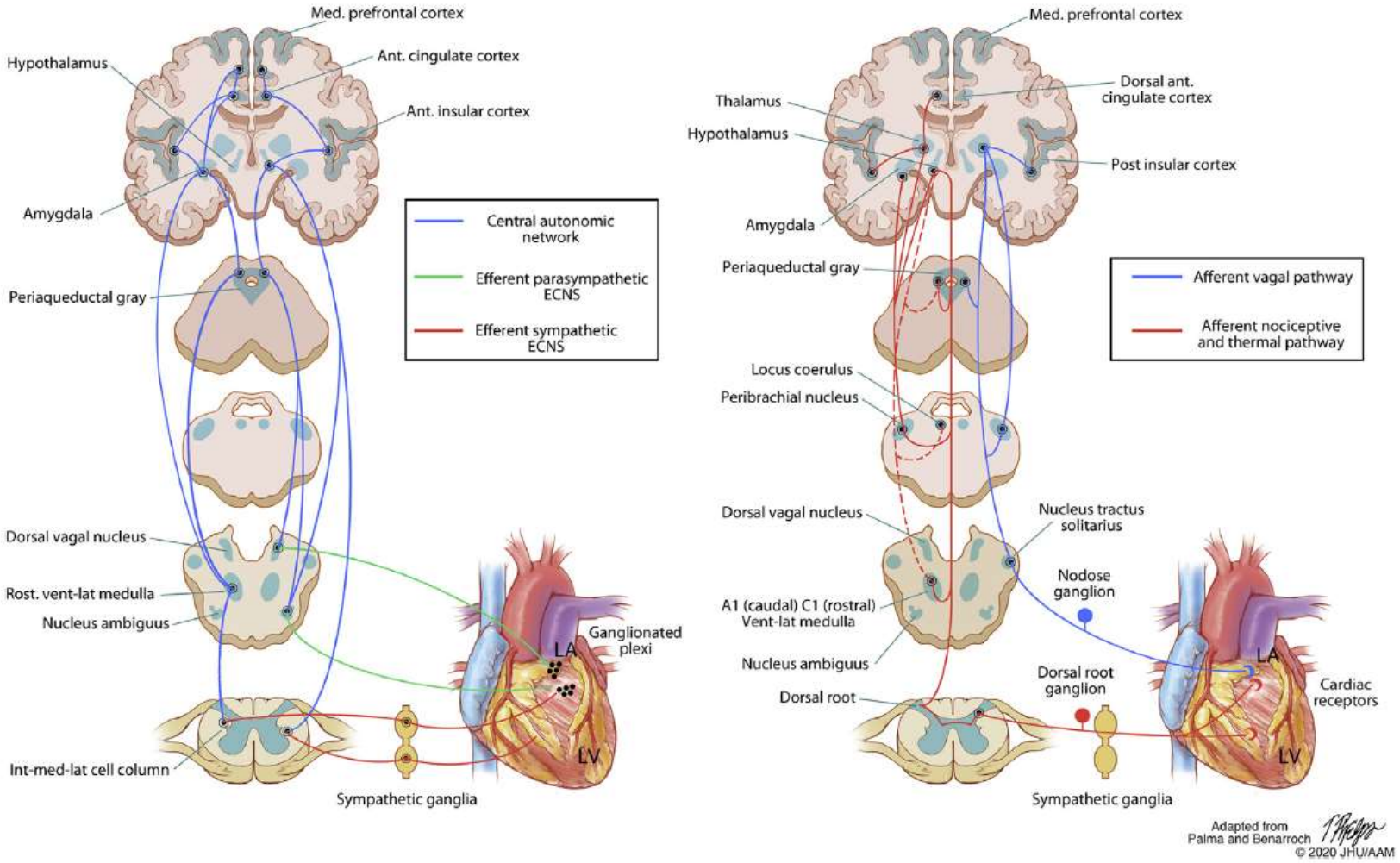
Il clinico-archeologo

"Era Maestro di scienza ma anche Maestro di deontologia e di comportamento medico. Aveva avuto, e lo ricordava, subito dopo la laurea un periodo di attività come medico di prima linea, in condotta", nota un commentatore. Virgilio Chini, anche da direttore dell'Istituto di Clinica medica, avrebbe infatti mantenuto grande rispetto per il sempre problematico agire dell'operatore sanitario. Avrebbe così considerato: "Chi sa per giovanile personale esperienza, cosa vuol dire trovarsi improvvisamente da solo di fronte ad un caso che richiede per la tragedia incombente pronta ed il più possibile esatta terapia, conosce bene l'angoscia di quel sentirsi paurosamente solo e conserva nel cuore comprensione profondamente umana".

In campo cardiologico, richiamò l'importanza sui rapporti tra circolazione coronarica e cerebrale, parlando di "sindrome associata coronarico-cerebrale", la cosiddetta sindrome di Chini, in cui la patologia coronarica si associa a disturbi del circolo cerebrale, fino all'attacco ischemico transitorio e all'ictus.

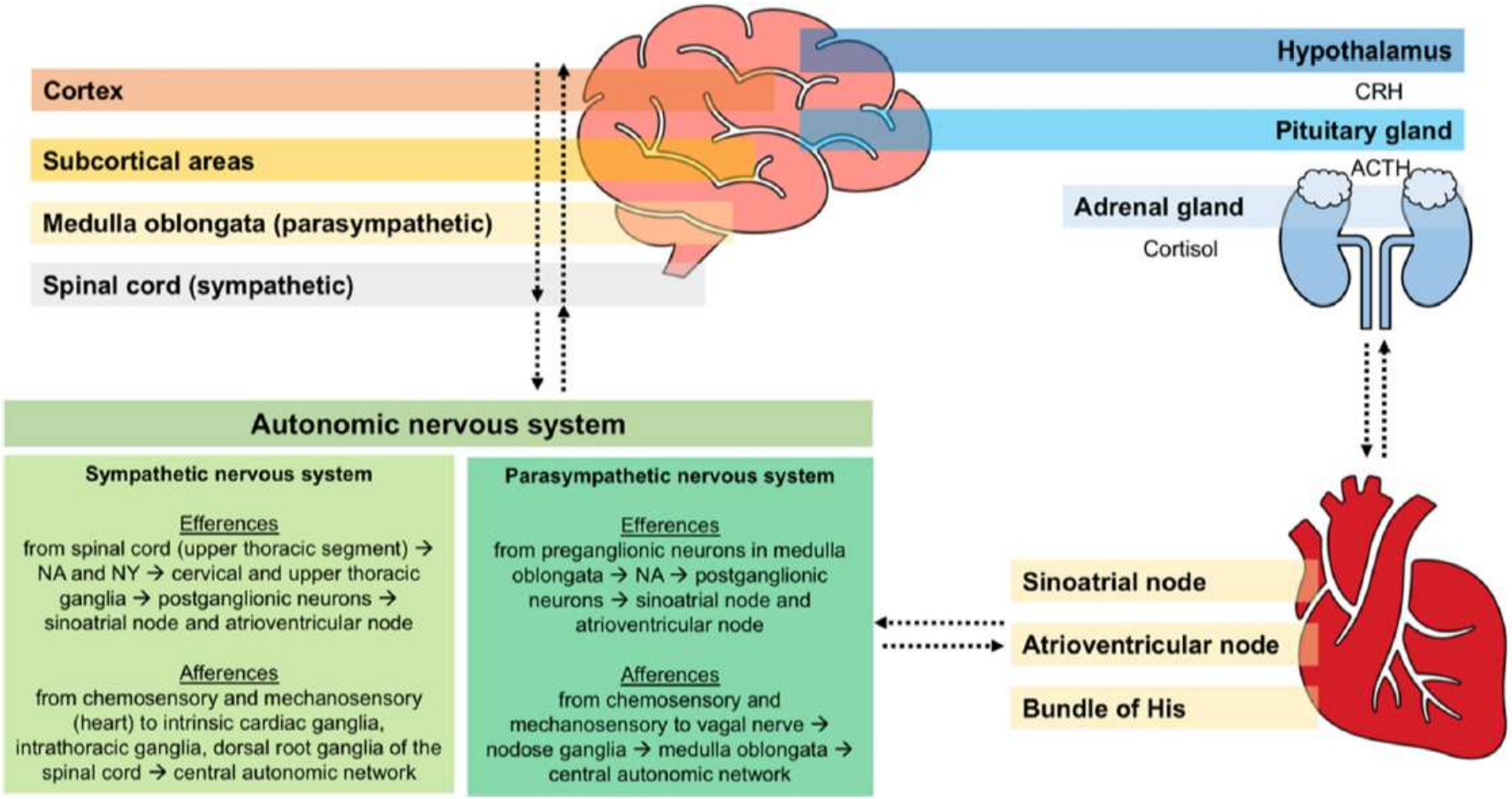
Central Autonomic Network and Extrinsic Cardiac Nervous System

Neural control of the heart



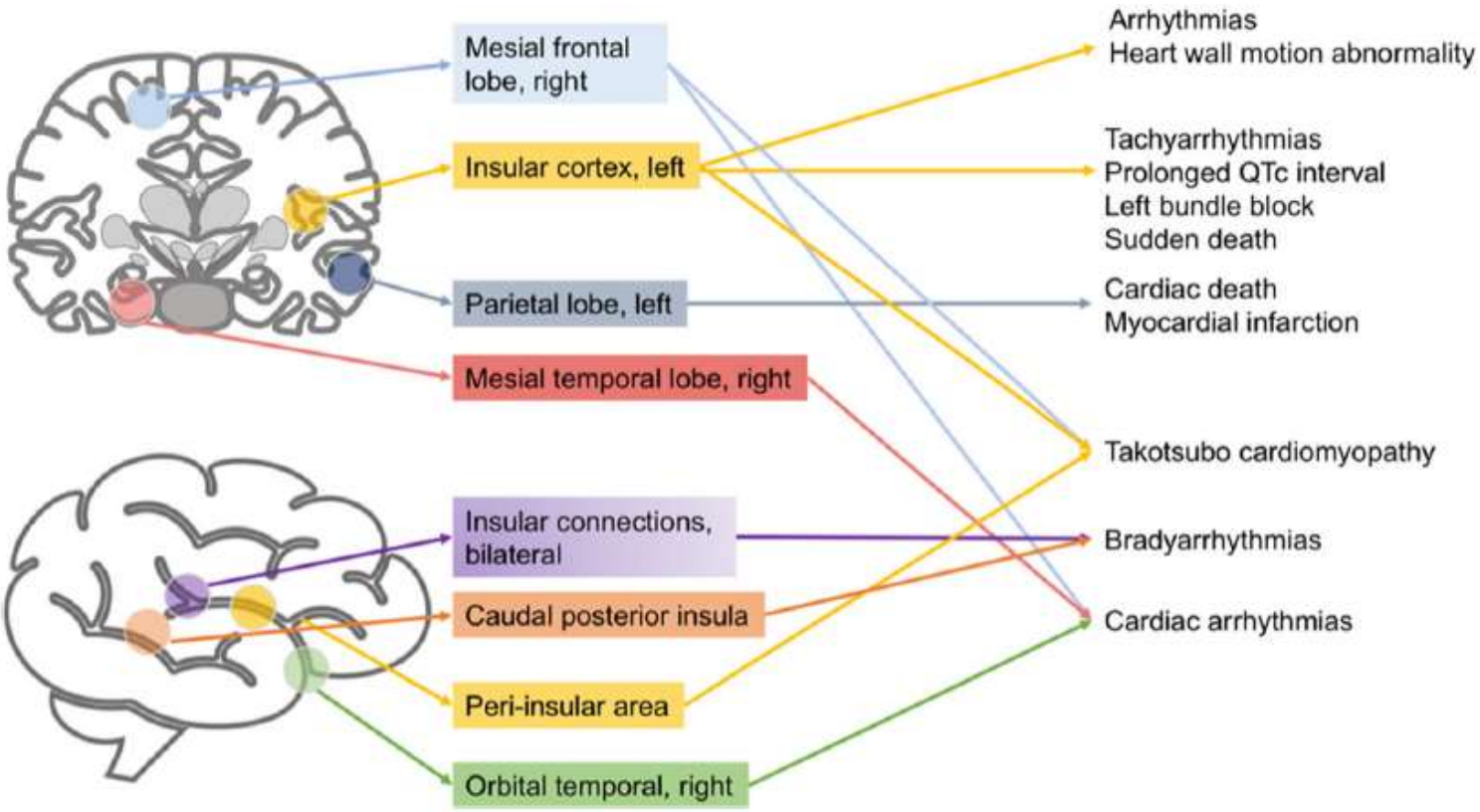
Palma JA, Benarroch EE. Neurology 2014;83:261–71. Sposato LA, et al. J Am Coll Cardiol 2020; 76:2768–85

Neural connections: from the brain to the heart and from the heart to the brain



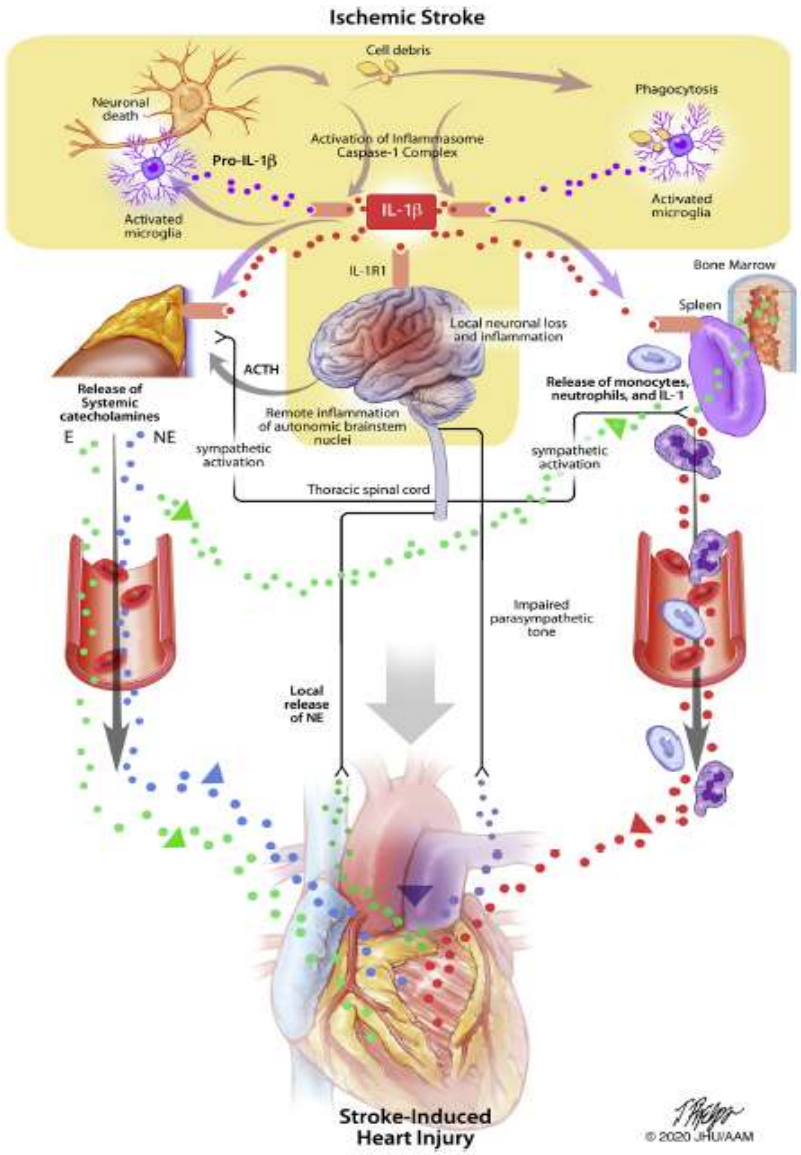
Battaglini D, et al. Critical Care 2020; 24:163-175

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



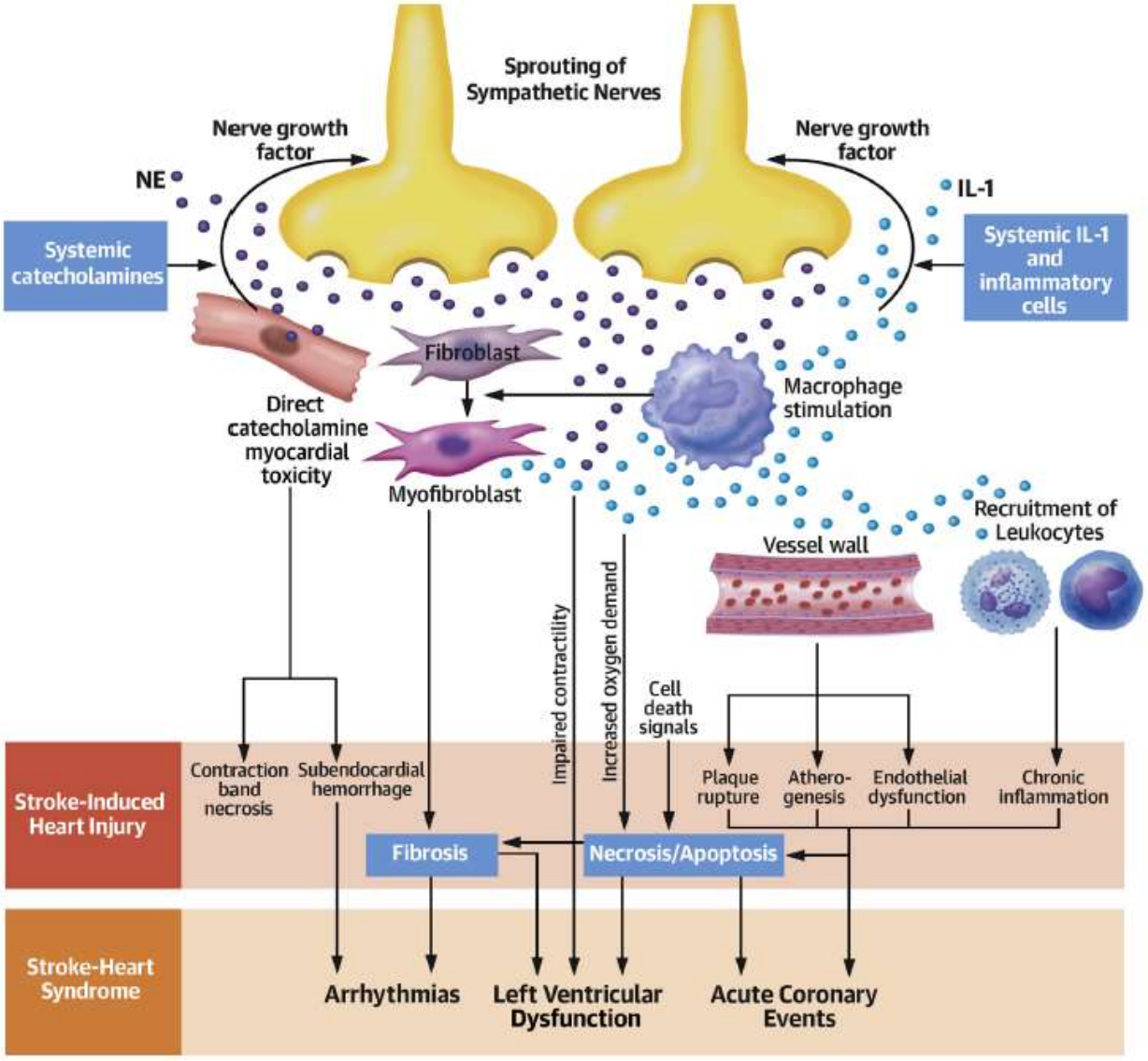
Battaglini D et al. Critical Care 2020; 24:163-175

Systemic Mechanisms of Stroke-Induced Heart Injury



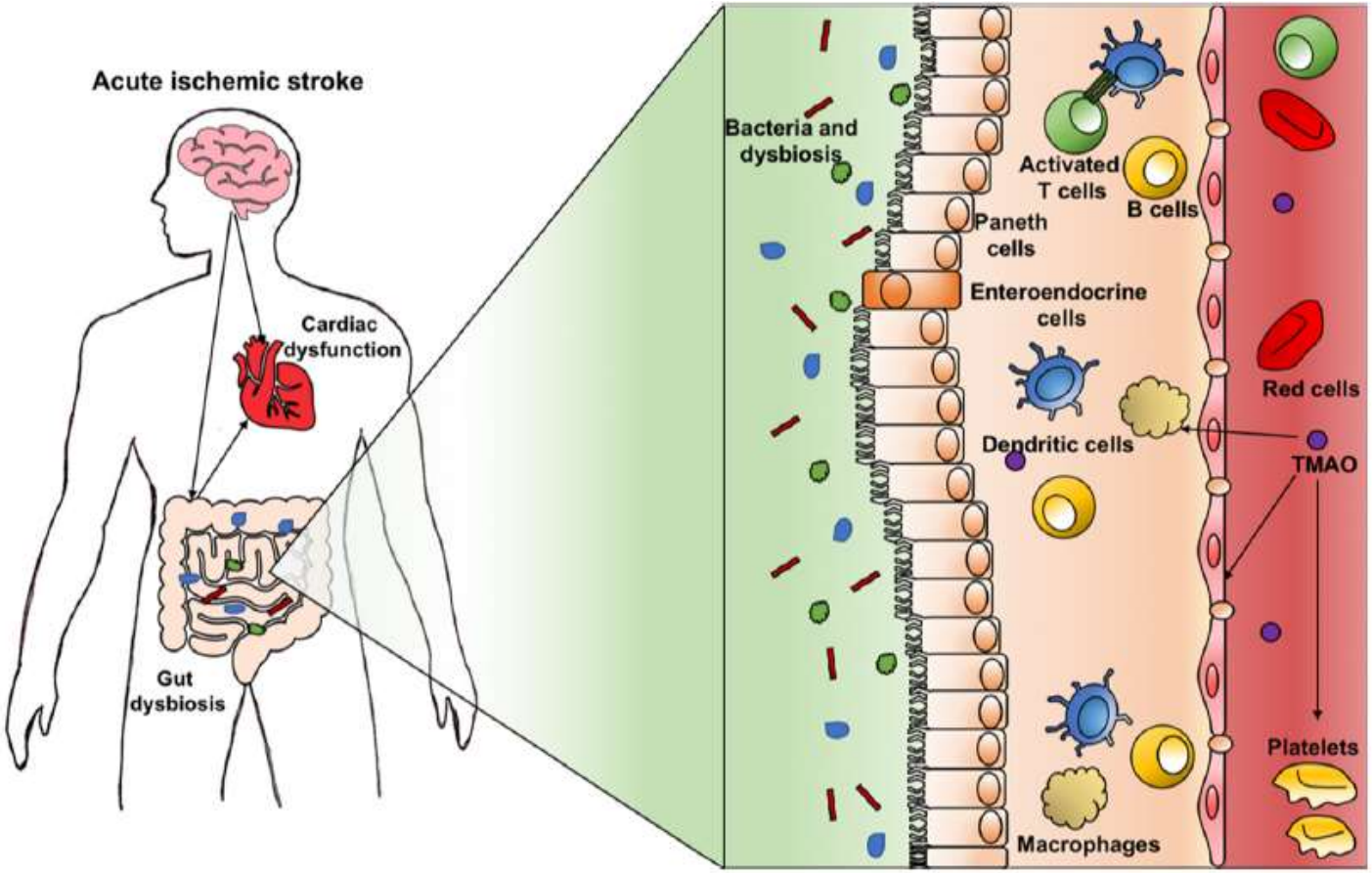
Sposato LA, et al.
J Am Coll Cardiol
2020; 76:2768–85

Local Mechanisms of Stroke-Induced Heart Injury



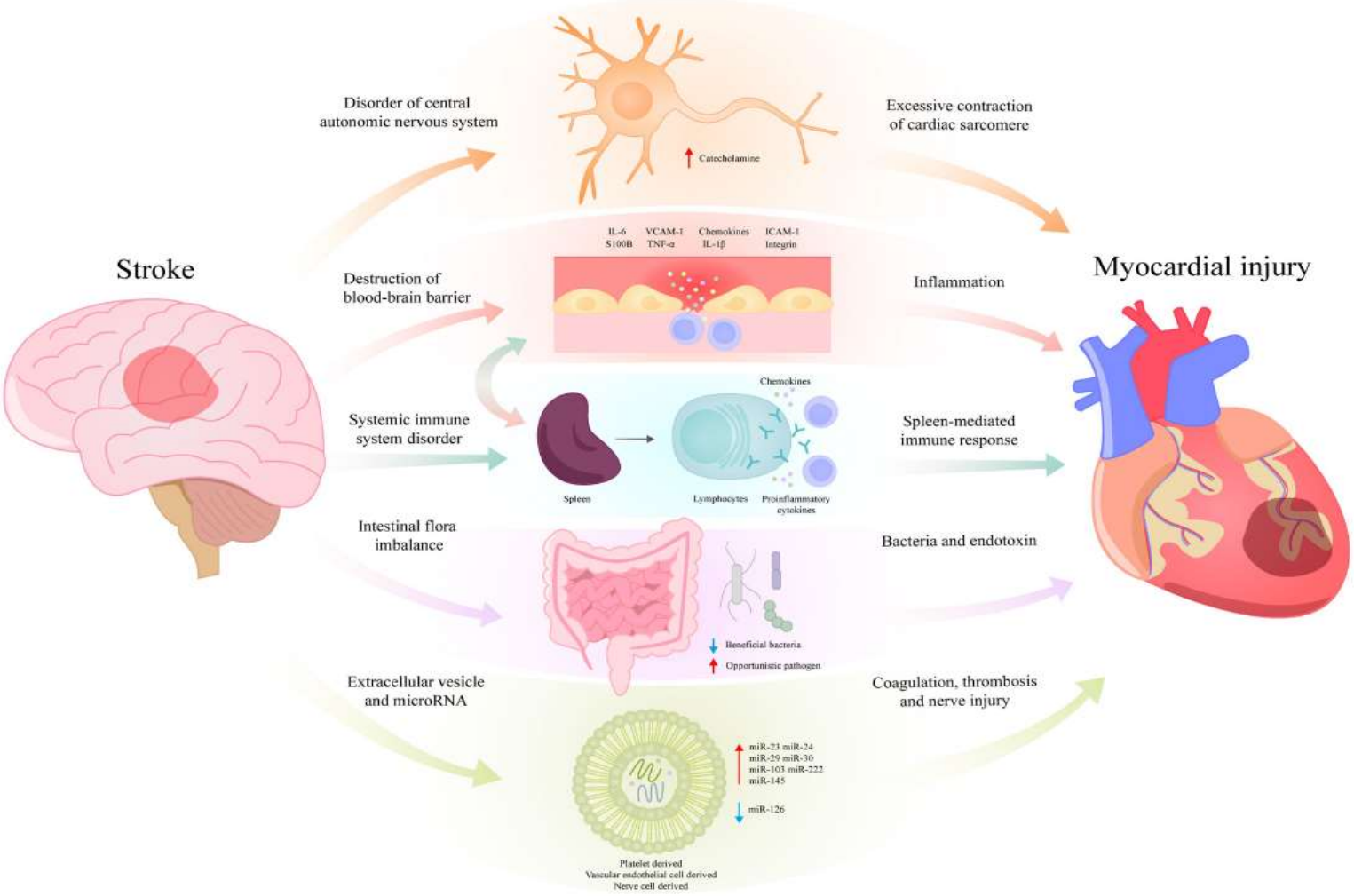
Sposato LA, et al.
J Am Coll Cardiol
2020; 76:2768–85

Gut dysbiosis and cardiac dysfunction



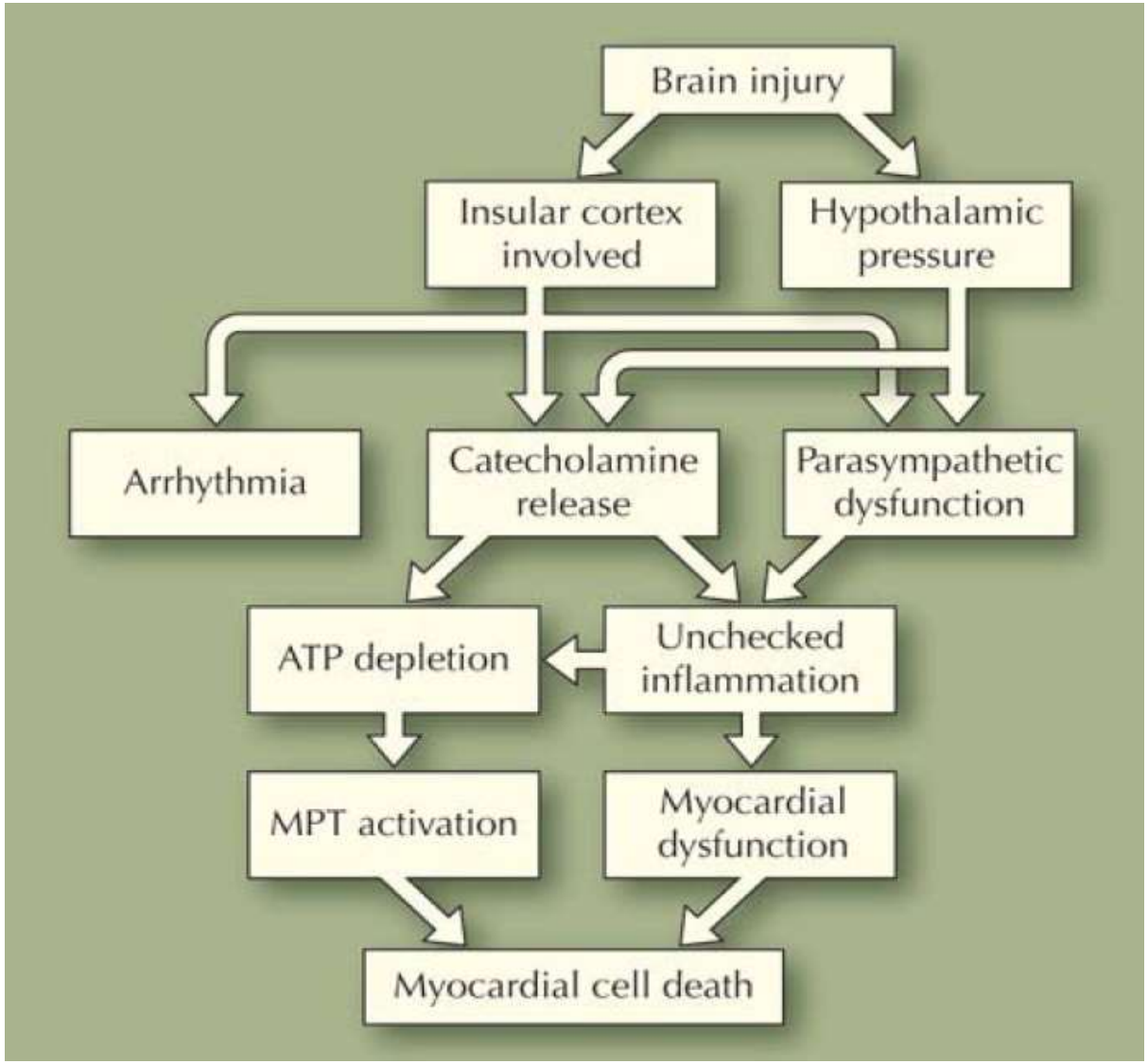
Battaglini D et al. Critical Care 2020; 24:163-175

Molecular mechanisms of stroke-heart syndrome



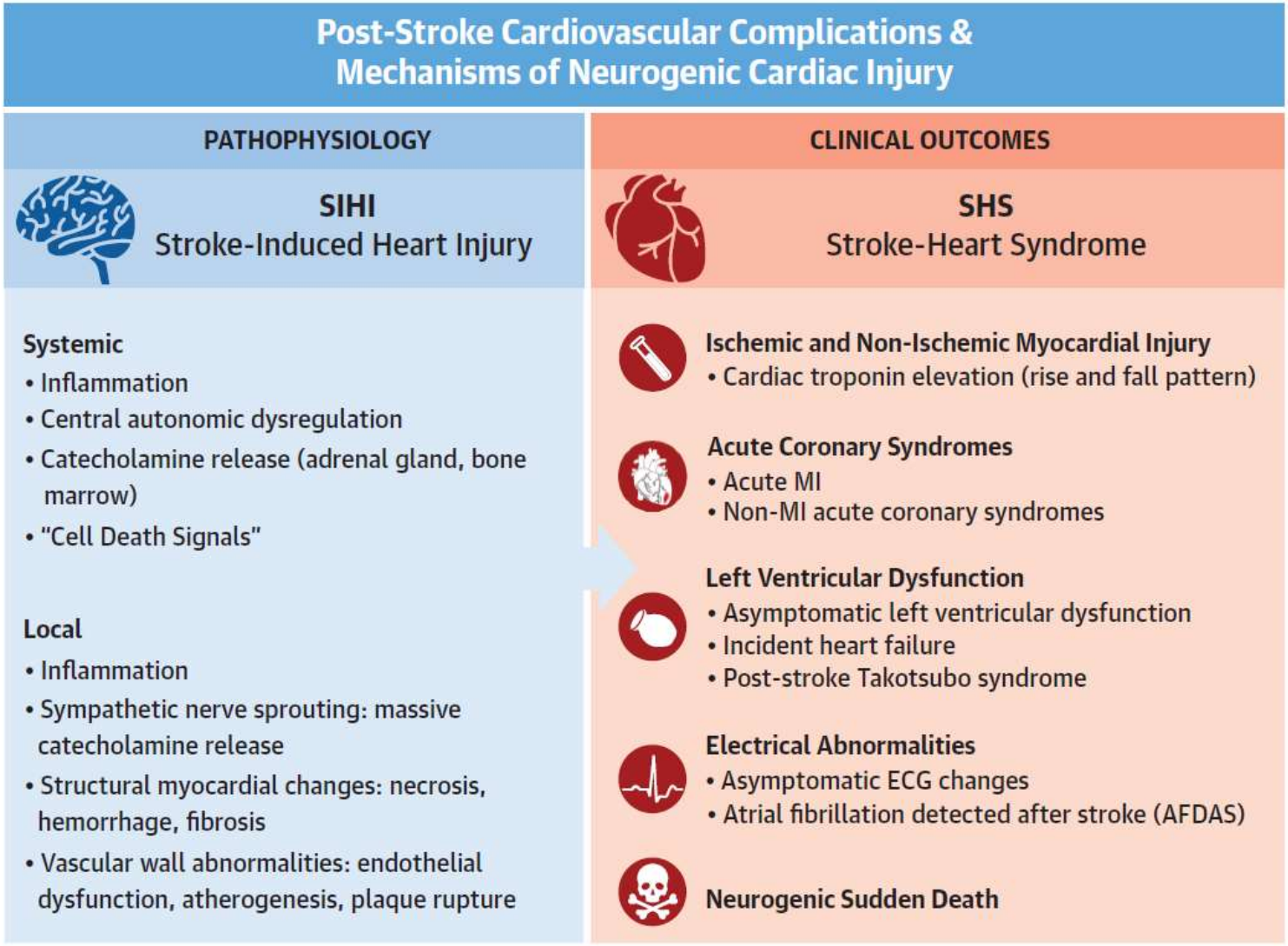
Wang M and Peng Y. Front. Mol. Neurosci 2022; 15:1053478

Neurogenic Stunned Myocardium



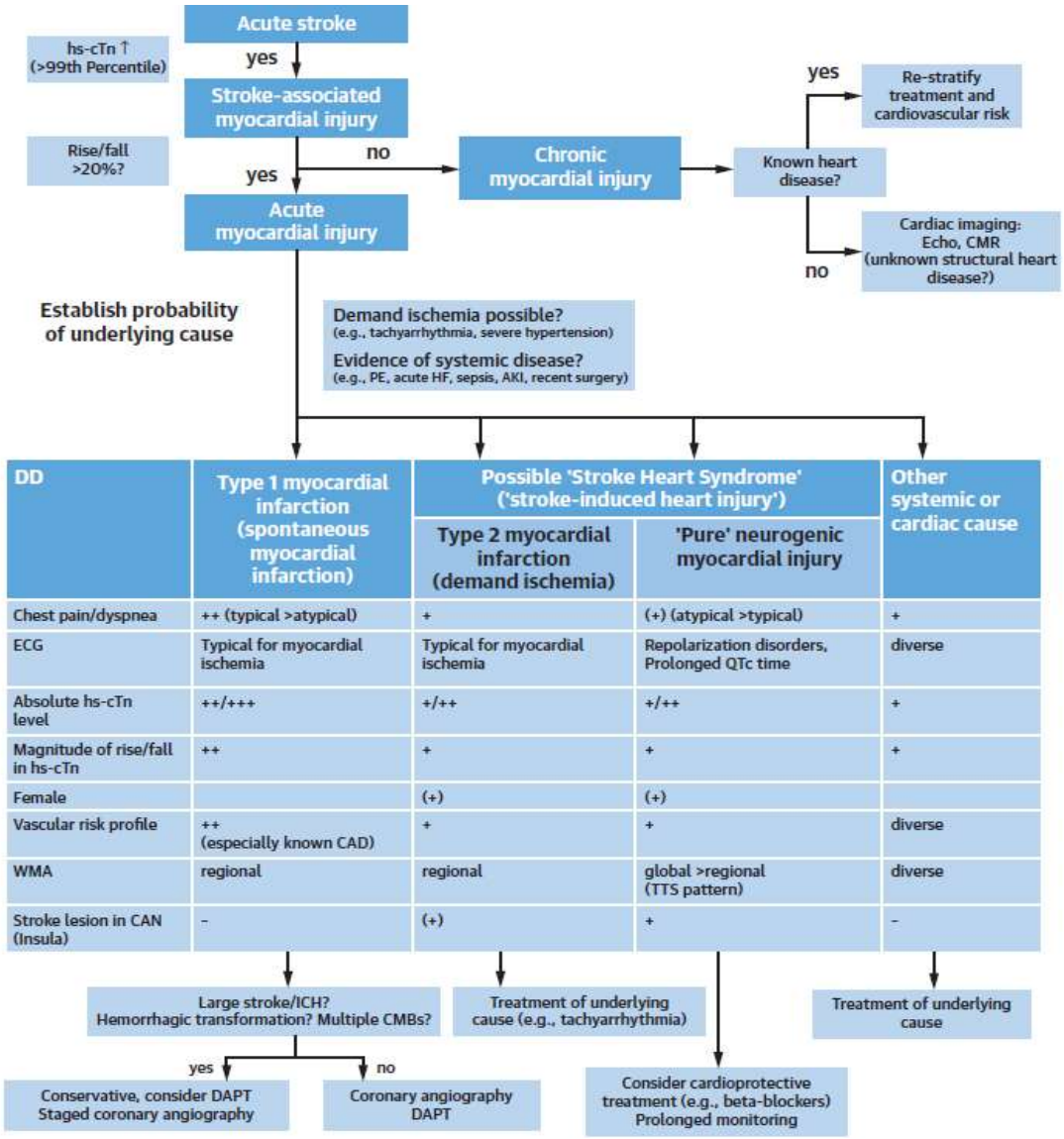
Nguyen and Zaroff. Current Neurology and Neuroscience Reports 2009, 9:486–491

5.5 million deaths each year are related to stroke worldwide. **One-fifth** of deaths in stroke pts have a cardiovascular cause. **Over 1 million post-stroke cardiovascular deaths** occur each year among survivors of cerebrovascular events.



Sposato LA, et al. J Am Coll Cardiol 2020; 76:2768–85

Interpretation and Management of Elevated Troponin Levels After Stroke



DD	Type 1 myocardial infarction (spontaneous myocardial infarction)	Possible 'Stroke Heart Syndrome' ('stroke-induced heart injury')		Other systemic or cardiac cause
		Type 2 myocardial infarction (demand ischemia)	'Pure' neurogenic myocardial injury	
Chest pain/dyspnea	++ (typical >atypical)	+	(+) (atypical >typical)	+
ECG	Typical for myocardial ischemia	Typical for myocardial ischemia	Repolarization disorders, Prolonged QTc time	diverse
Absolute hs-cTn level	++/+++	+/++	+/++	+
Magnitude of rise/fall in hs-cTn	++	+	+	+
Female		(+)	(+)	
Vascular risk profile	++ (especially known CAD)	+	+	diverse
WMA	regional	regional	global >regional (TTS pattern)	diverse
Stroke lesion in CAN (Insula)	-	(+)	+	-

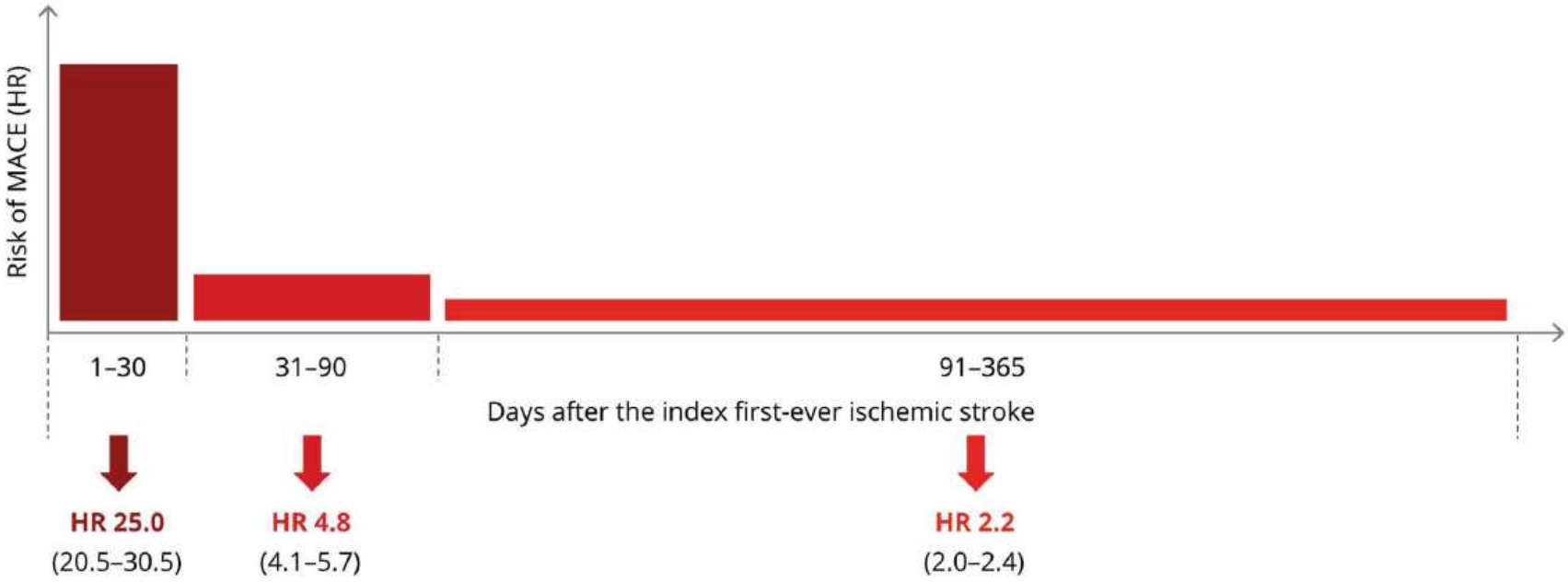
Sposato LA, et al.
J Am Coll Cardiol
2020; 76:2768–85

Time-dependent risk of MACE for first-ever ischemic stroke relative to no stroke

21,931 patients with first-ever ischemic stroke and 71,696 propensity-matched individuals ≥66 years

First-ever ischemic stroke was associated with increased unadjusted incident MACE risk at 1-yr (**HR 4.5**, 95% CI 4.3–4.8)

MACE: myocardial infarction, unstable angina, congestive HF, CAD, coronary artery revascularization, or cardiovascular death

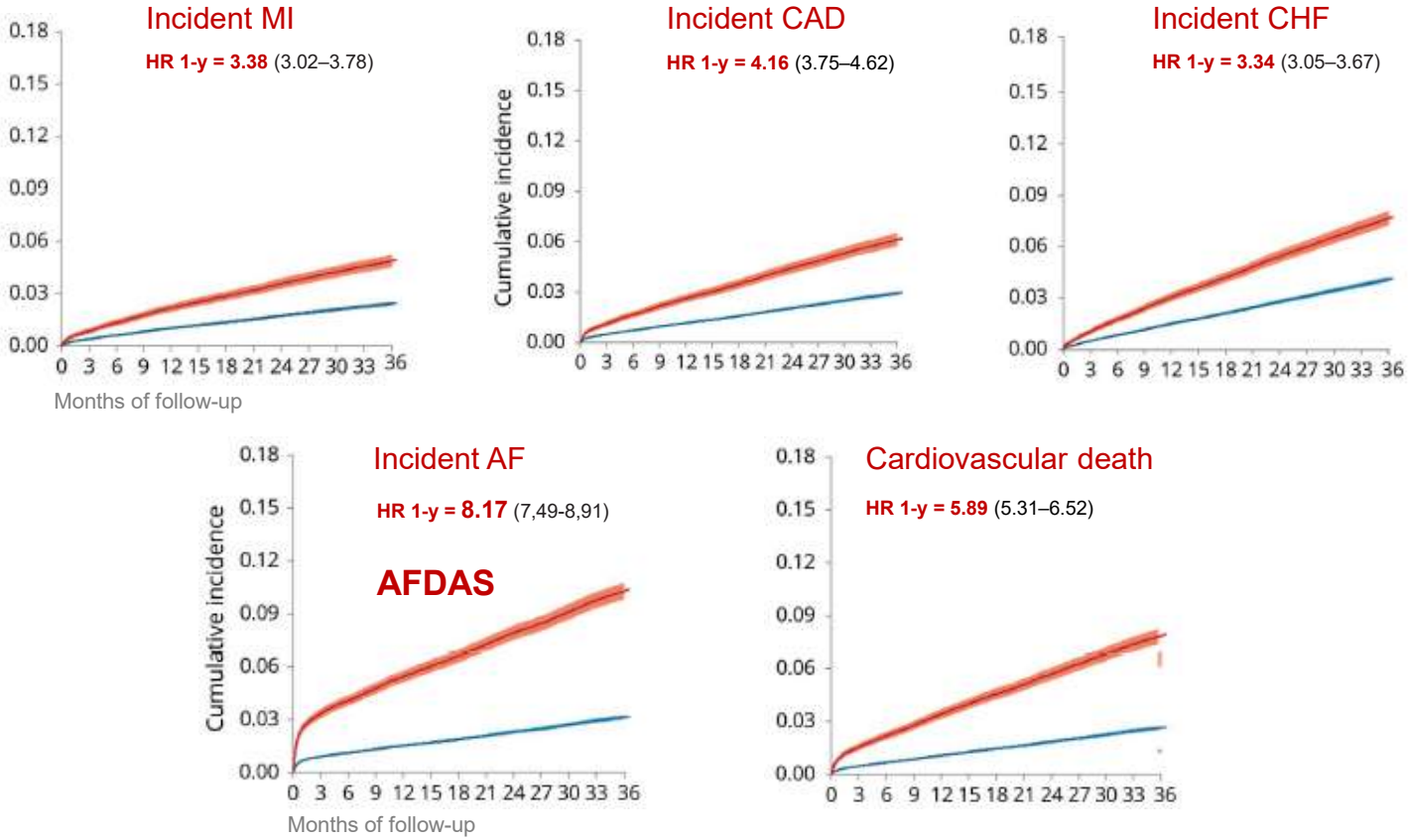


Sposato LA, et al. Neurology 2020; 94:e1559-70

enrico natale

Cumulative index function curves for secondary outcomes

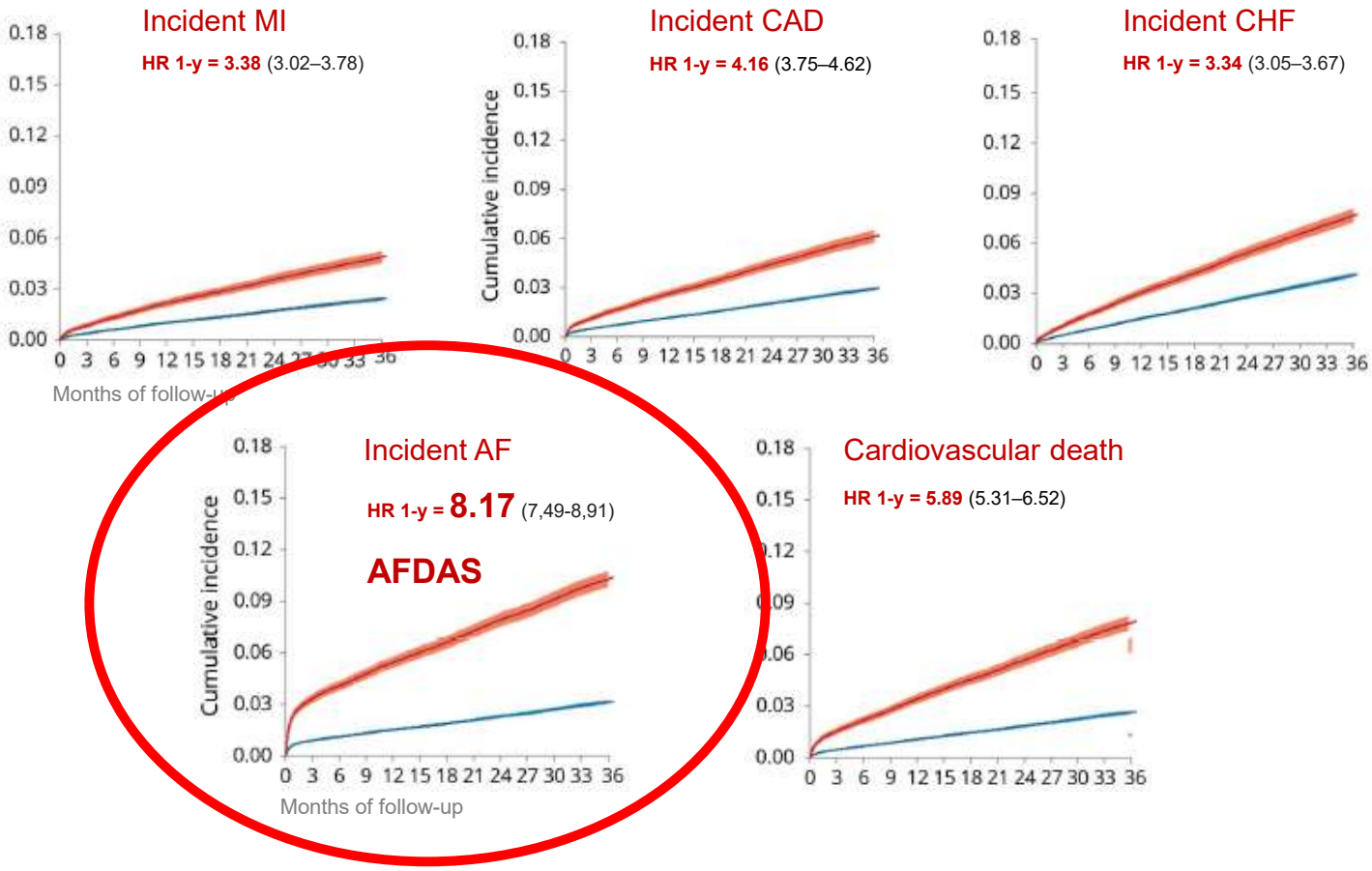
21,931 patients with first-ever ischemic stroke and 71,696 propensity-matched individuals ≥66 years



Sposato LA, et al. Neurology 2020; 94:e1559-70

Cumulative index function curves for secondary outcomes

21,931 patients with first-ever ischemic stroke and 71,696 propensity-matched individuals ≥66 years



Sposato LA, et al. Neurology 2020; 94:e1559-70

enrico natale

AFDAS "atrial fibrillation detected after stroke"

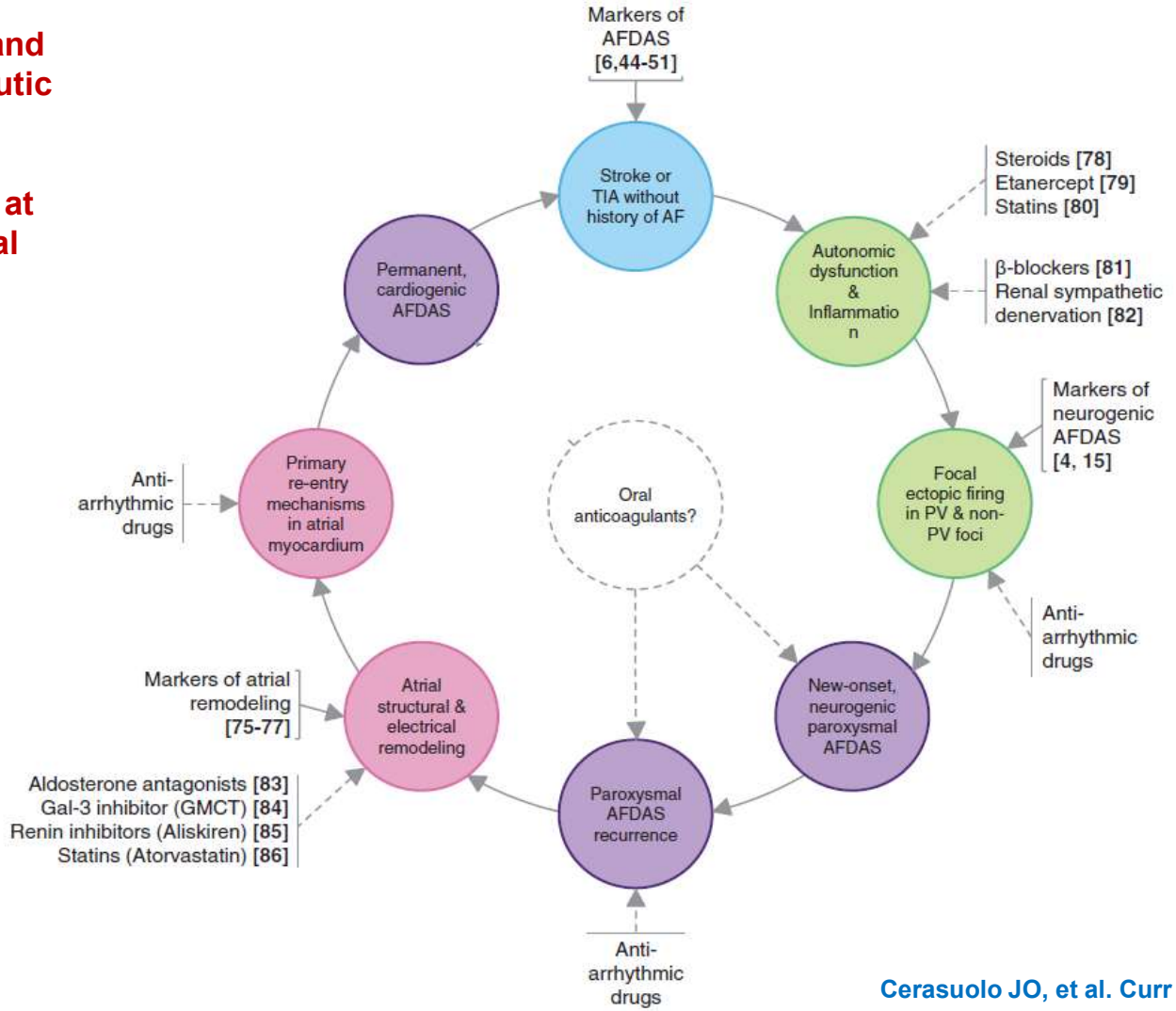
Recommendations for the search for AF in patients with cryptogenic stroke

Recommendations	Class[a]	Level[b]
In patients with acute ischaemic stroke or TIA and without previously known AF, monitoring for AF is recommended using a short-term ECG recording for at least the first 24 h, followed by continuous ECG monitoring for at least 72 h whenever possible.[1113–1116]	I	B
In selected[c] stroke patients without previously known AF, additional ECG monitoring using long-term non-invasive ECG monitors or insertable cardiac monitors should be considered, to detect AF.[1112]	IIa	B

© ESC 2020

high C2HEST score: CAD/COPD (1 point each), Hypertension (1 point), Elderly (≥75 yrs, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point)

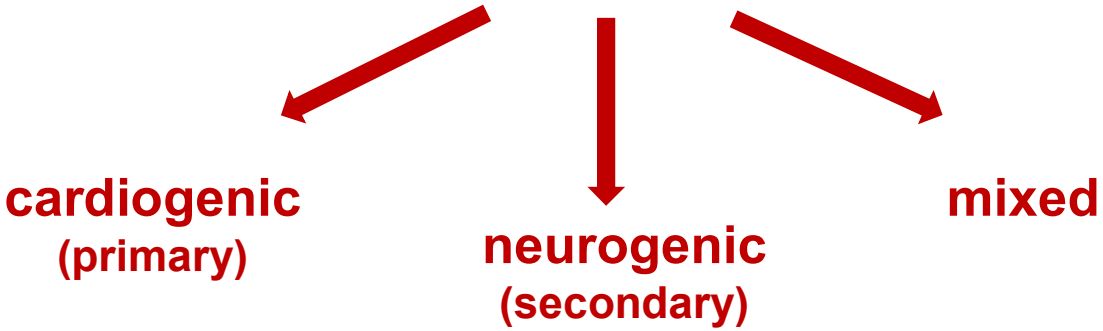
Role of markers and potential therapeutic interventions to prevent stroke recurrence in pts at risk of paroxysmal AFDAS or TIA



Cerasuolo JO, et al. Curr Opin Neurol 2017;30:28–37

AFDAS "atrial fibrillation detected after stroke"

AF can be newly detected in **up to one-fourth of AIS and TIA patients** after applying a sequential strategy of prolonged cardiac monitoring



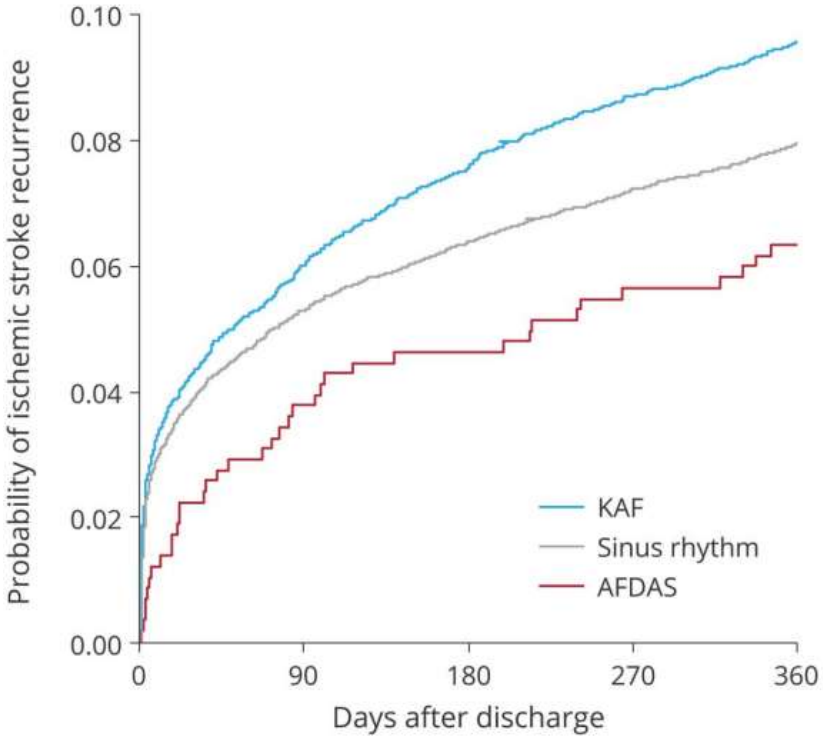
The paradigm of neurogenic AFDAS:
low-burden paroxysmal AF
occurring early after a stroke
involving cerebral regions within the CAN,
in a young patient without AF in previous ECG recordings
and without pre-existing structural heart disease or
cardiovascular comorbidities (e.g., LA enlargement, CAD, or HF)

Cerasuolo JO, et al. Curr Opin Neurol 2017;30:28–37

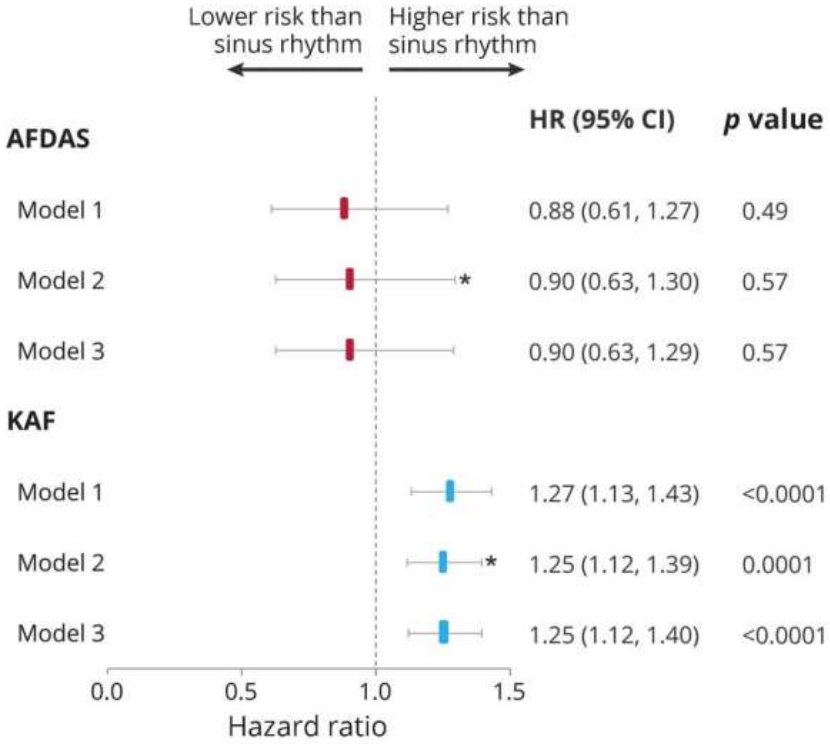
AFDAS is related to a low risk of ischemic stroke recurrence?

23.376 ischemic stroke patients, 15.885 had SR, 587 AFDAS, and 6.904 KAF

Cumulative incidence function curve for recurrent ischemic stroke in AF known prior to the stroke (KAF), AFDAS, and sinus rhythm

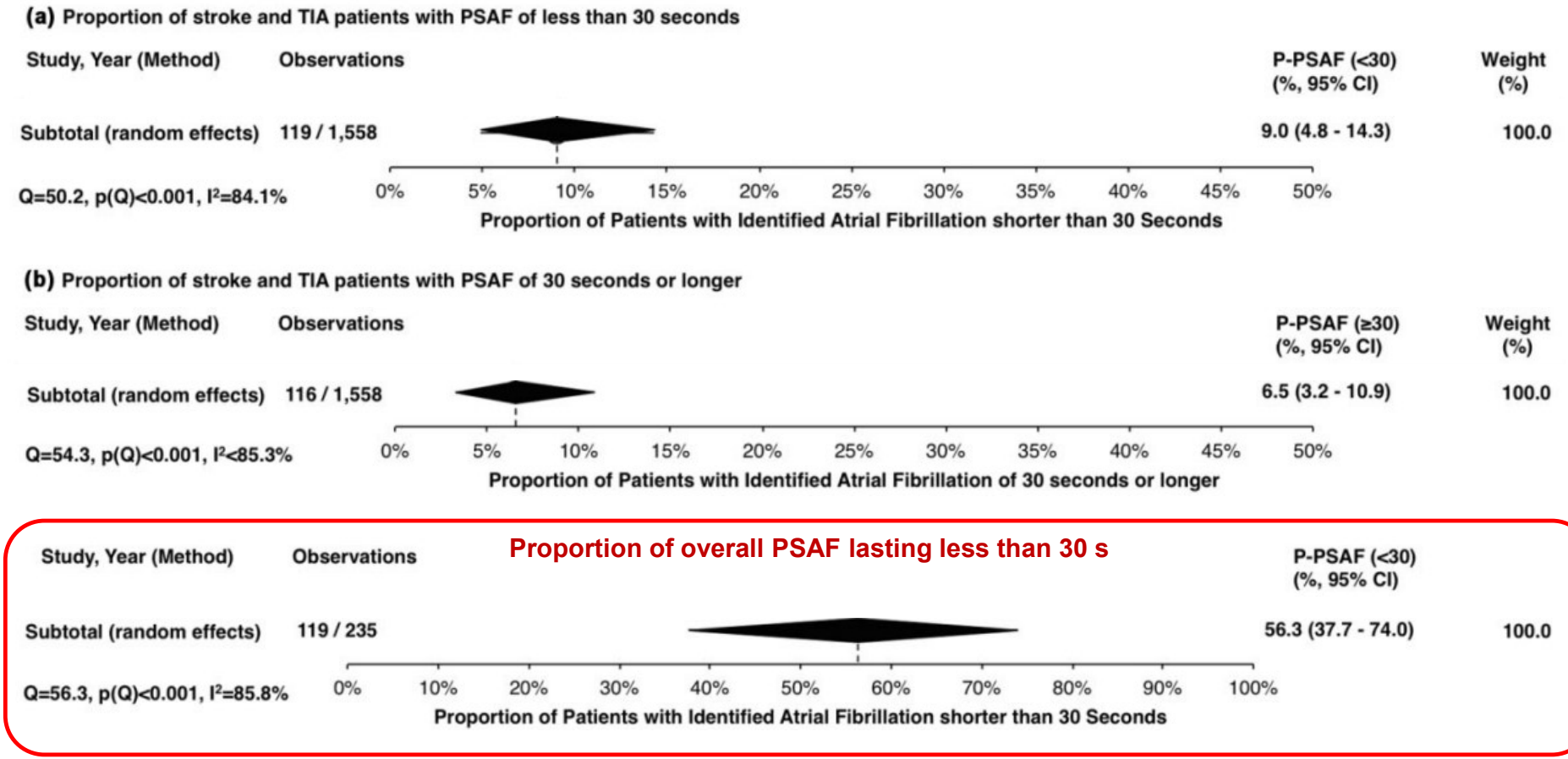


Adjusted risk of recurrent ischemic stroke at 1 year For KAF and AFDAS in Cox regression models



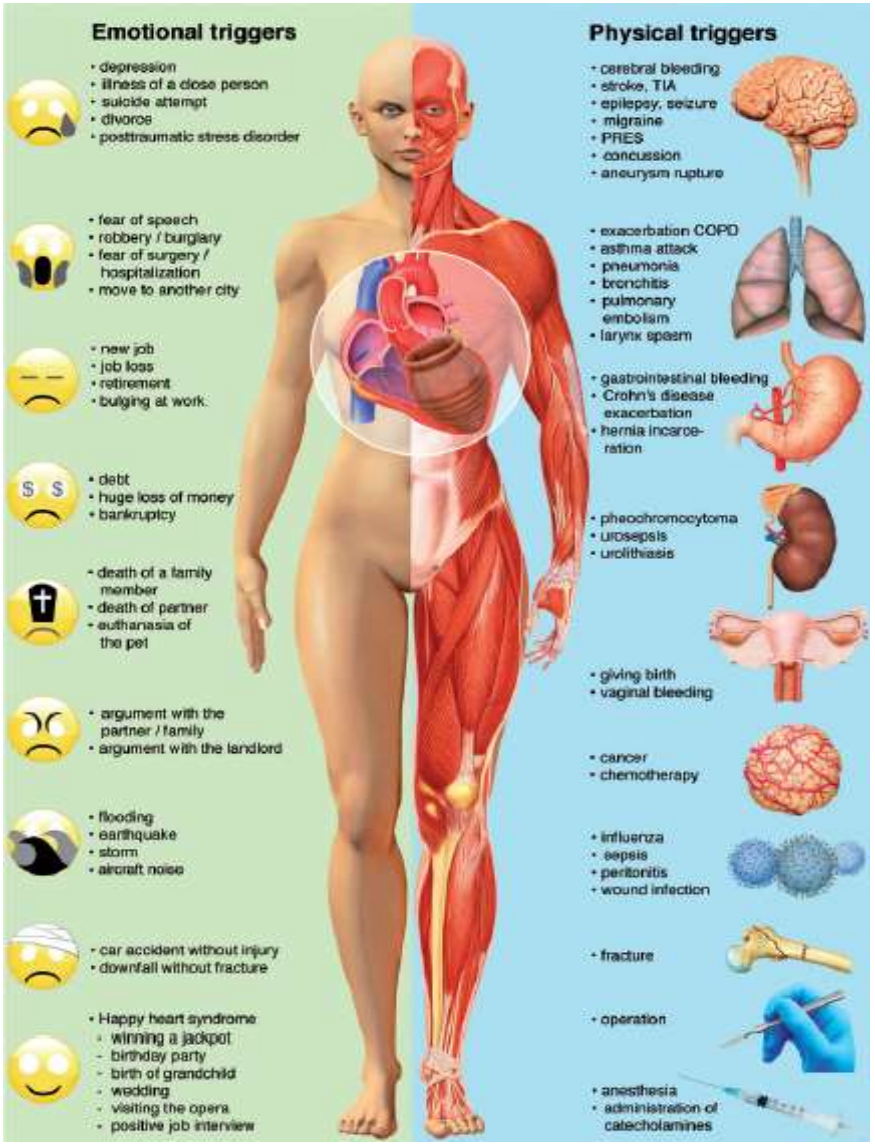
Sposato LA, et al. Neurology 2018;90:e924–31.

Very short AF paroxysms detected after stroke and TIA: a systematic review and meta-analysis



Sposato LA, et al. Int J Stroke 2015;10:801–7

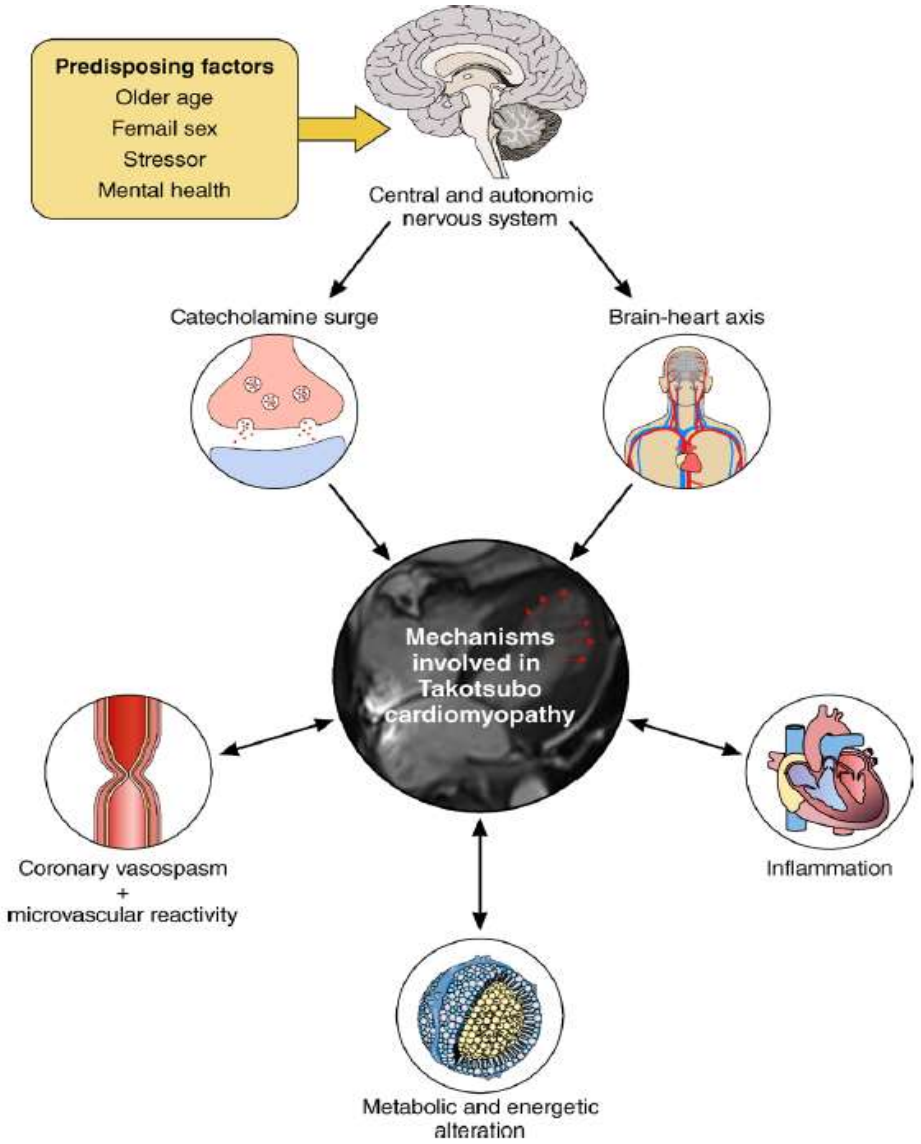
Emotional and physical stress factors precipitating takotsubo syndrome



Ghadri J-R, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I). Eur Heart J 2018, 39, 2032–2046

Schlossbauer SA, et al. Praxis (Bern 1994) 2016;105:1185–1192

Mechanisms involved in takotsubo syndrome



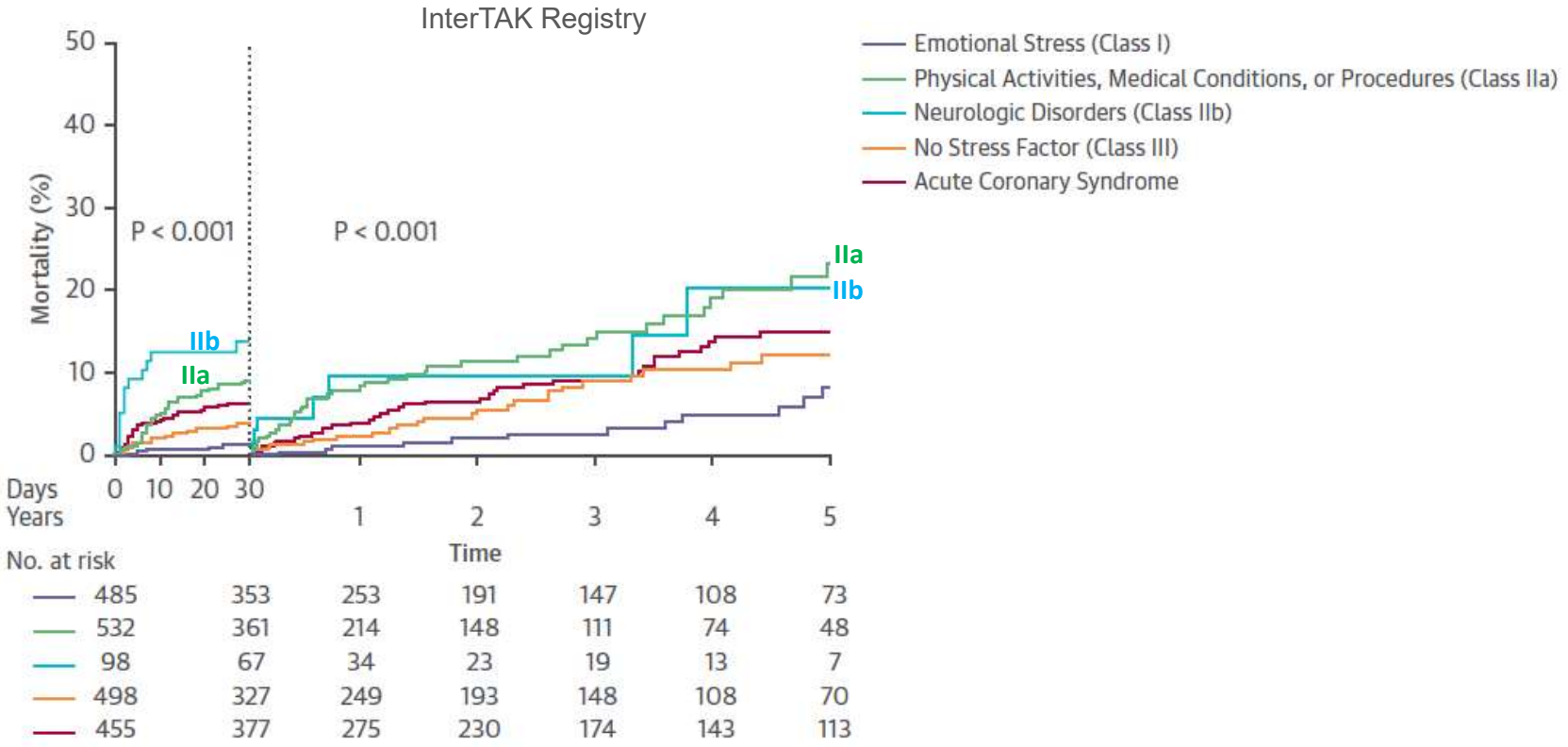
Singh T, et al. *Circulation* 2022;145:1002–1019

Classification of takotsubo syndrome based on the type of triggering event

Class I:	Takotsubo syndrome related to emotional stress
Class II:	Takotsubo syndrome related to physical stress
Class IIa:	Takotsubo syndrome secondary to physical activities, medical conditions, or procedures
Class IIb:	Takotsubo syndrome secondary to neurologic disorders
Class III:	Takotsubo syndrome without an identifiable triggering factor

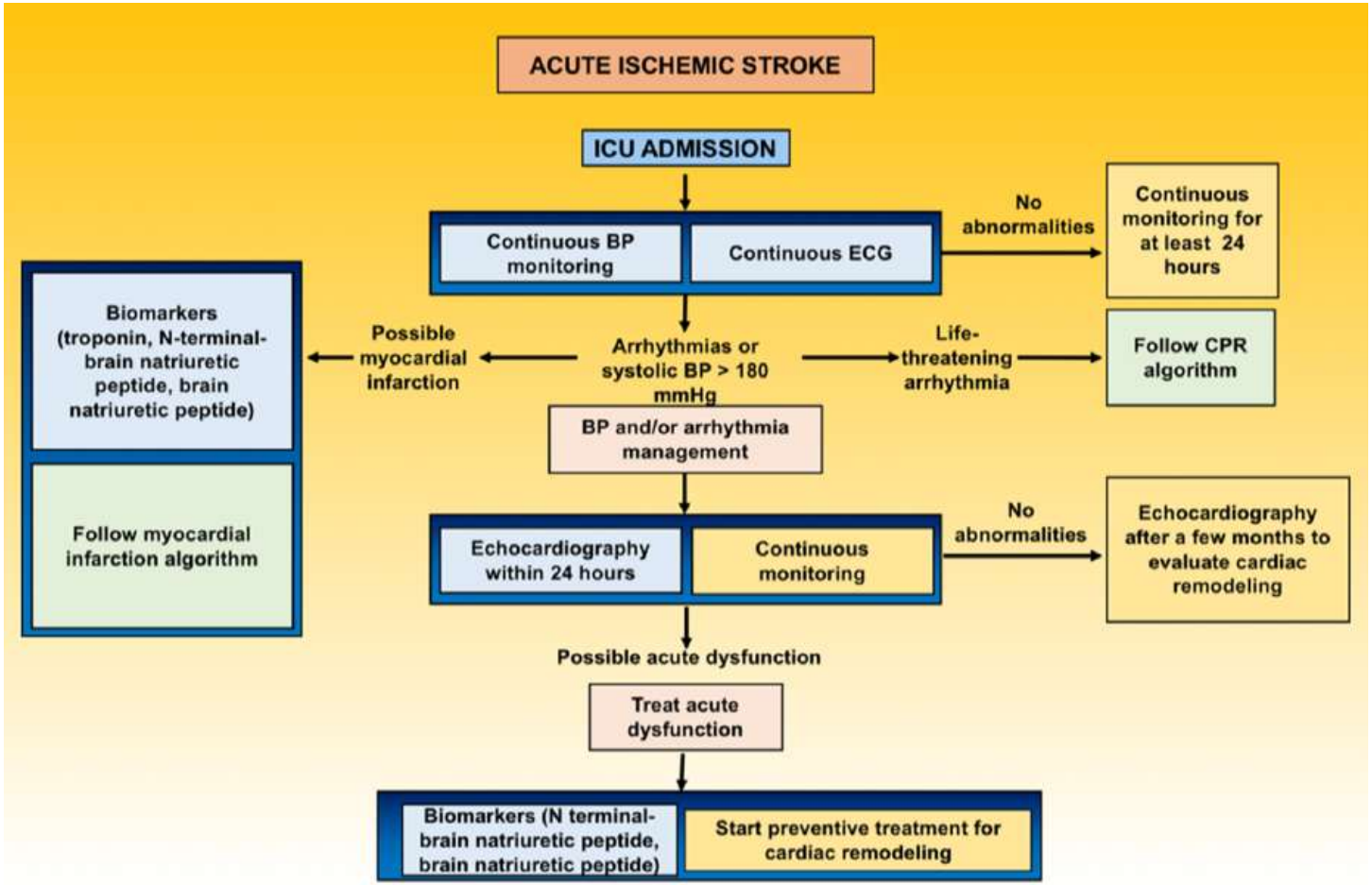
Ghadri JR, et al. J Am Coll Cardiol 2018; 72:874–82

Short- and Long-Term Mortality of Different Triggering Groups of Takotsubo Syndrome Compared With ACS



Ghadri JR, et al. J Am Coll Cardiol 2018; 72:874–82

Flow chart of stroke management after intensive care unit admission



Battaglini D et al. Critical Care 2020; 24:163-175

Ongoing Clinical Studies Exploring the Pathophysiology or Targeting of Long-Term Consequences of Stroke–Heart Syndrome

Study	Title of study (registration)	Design	City, country	Target population	Target no. of patients	Outcomes of interest	Measures	Progress
1	Atrial Cardiomyopathy in Patients With Stroke of Undetected Mechanism[112] (NCT03830983)	Prospective, observational, case–control-study (healthy age- and sex-matched controls)	Copenhagen, Denmark	Ischemic stroke (≤30 d before inclusion) without atrial fibrillation	150 (originally estimated enrolment=225)	Extent of LA fibrosis incidence of silent brain lesions, LA volume, LAEF	Gadolinium-enhanced CMR imaging	Active, recruiting
2	BEHABIS (The Bern Heart and Brain Interaction Study)[67] (NCT03720522)	Prospective, observational, single-center cohort study	Bern, Switzerland	Acute ischemic stroke (<12 h after symptom onset) without severe renal failure (GFR <40)	220	TTS (prevalence of neurogenic stunned myocardium), subacute MI	CMR (gadolinium-enhanced with or without perfusion)	Active, recruiting
3	BeLOVE (Berlin Long-Term Observation of Vascular Events)[113] (DRKS00016852)	Prospective, observational, multicenter cohort study	Berlin, Germany	Hospitalization for: acute ischemic stroke; acute coronary syndrome, acute heart failure, acute kidney injury (4 study arms)	10 000, 2000 each study arm	MACE (cardiovascular mortality, nonfatal stroke, nonfatal myocardial infarction, hospitalization because of heart failure)	Clinical assessment, CMR, MRI (head), ECG, 3-dimensional echocardiography, ocular coherence tomography	Active, recruiting
4	CONVINCE (Colchicine for Prevention of Vascular Inflammation in Non-CardioEmbolic Stroke)[115] (NCT02898610)	Randomized controlled trial (colchicine vs placebo)	Several countries in Europe	Noncardioembolic ischemic stroke without major disability	2623	Recurrence of nonfatal ischemic stroke, nonfatal major cardiac event, vascular death	Clinical assessment	Active recruiting
5	CORONA-IS (Cardiomyocyte Injury Following Acute Ischemic Stroke)[116] (NCT03892226)	Prospective, observational, single-center cohort study	Berlin, Germany	Acute ischemic stroke with hospital admission <48 h after symptom onset	300	Quantify autonomic dysfunction and decipher downstream cardiac mechanisms leading to myocardial injury	Multimodal CMR, echocardiography, autonomic ECG markers, biobanking	Active, recruiting
6	Heart and Brain Study–Substudy of Whitehall II Imaging cohort[117] (NCT03335696)	Prospective, observational, cohort study	Oxford, United Kingdom	Retired British civil servants	775	Brain atrophy, cognitive decline	Vascular ultrasound, MRI (head)	Recruitment completed, extended follow-up

Scheitz JF, et al. J Am Heart Assoc. 2022;11:e026528

enrico natale

Ongoing Clinical Studies Exploring the Pathophysiology or Targeting of Long-Term Consequences of Stroke–Heart Syndrome

Study	Title of study (registration)	Design	City, country	Target population	Target no. of patients	Outcomes of interest	Measures	Progress
7	InsuCor (Insular–Noninsular Stroke Underlying Cardiac Failure (DRKS00012454)	Prospective, observational, case–control study	Würzburg, Germany	Acute ischemic stroke (onset <3 d; with and without involvement of the insular lobe)	180	(New) systolic cardiac dysfunction, stroke, vascular events within 3 mo	Echocardiography, blood biomarker	Active, recruiting
8	MIRACLE (MR Evidence of Cardiac Inflammation Post-Stroke Study)	Prospective, observational, cohort study	London, Ontario, Canada	Acute ischemic embolic stroke of undetermined source	44	NT-proBNP, systemic inflammation, myocardial infarction, LV function, LA fibrosis	NT-proBNP, inflammatory markers, gadolinium enhanced CMR imaging	Active, recruiting
9	Multifactorial Risk Stratification in Patients With Ischemic Stroke or Transient Ischemic Attack and Structural, Inflammatory, or Arrhythmogenic Cardiac Disease[118] (NCT04352790)	Prospective, observational, single-center cohort study	Tübingen, Germany	Ischemic stroke or TIA admitted to hospital	878	Any stroke, mortality, ischemic stroke, TIA, systemic embolism, myocardial infarction, intracranial hemorrhage, major bleeding	Clinical follow-up	Active, not recruiting
10	PRAISE (Prediction of Acute Coronary Syndrome After Acute Ischemic Stroke)[119] (NCT3609385)	Prospective, observational, multicenter cohort study	Multicenter, Germany	Acute ischemic stroke (<72 h) with troponin elevation	251	Presence of acute coronary syndrome, deaths, functional outcome, cardiovascular events	Coronary angiography, echocardiography, ECG	Recruitment completed. Follow-up ongoing
11	Predicting the Development of Myocardial Depression in Acute Neurological Patients (NCT03801694)	Prospective, observational single-center cohort study	Columbus, Ohio, USA	Female patients with acute ischemic stroke or patients with SAH, >50 y, predicted to be on norepinephrine infusion for at least 48 h	10	Stress-induced cardiomyopathy	ST-T changes on ECG, echocardiography and measurement of catecholamines and troponin	Active and recruiting
12	PROSCIS (Prospective Cohort With Incident Stroke)[120] (NCT01363856, NCT01364168)	Prospective, observational, hospital-based cohort study	Berlin (PROSCIS-B); Munich (PROSCIS-M), Germany	First ever acute stroke (including intracerebral hemorrhage in Berlin)	627 with first-ever ischemic stroke (Berlin), 850 (Munich)	Composite of stroke, myocardial infarction, and vascular death (within 3 y)	Clinical follow-up including cerebral MRI, cognitive testing	Recruitment completed (Berlin); active (Munich).
13	RIC-ACS (Protective Effects of Remote Ischemic Conditioning in Elderly With Acute Ischemic Stroke Complicating Acute Coronary Syndrome) (NCT03868007)	Randomized, controlled, double-blind, trial (sham procedure)	Beijing, China	Acute ischemic stroke (onset <24 h) plus acute coronary syndrome (onset <24 h), elderly patients (≤60 y)	80	Any death and recurrence of cardiac and cerebrovascular ischemic events within 3 mo	Remote ischemic conditioning (brief and transient limb ischemia)	Active and recruiting
14	SICFAIL (Stroke-Induced Cardiac Failure in Mice and Men)[40] (DRKS00011615)	Prospective, observational, single-center cohort study	Würzburg, Germany	Acute ischemic stroke with treatment on stroke unit	696	Heart failure, manifestation of cardiovascular disease	Follow-up by mail or telephone, echocardiography and ECG	Recruitment completed. First results published.

enrico natale

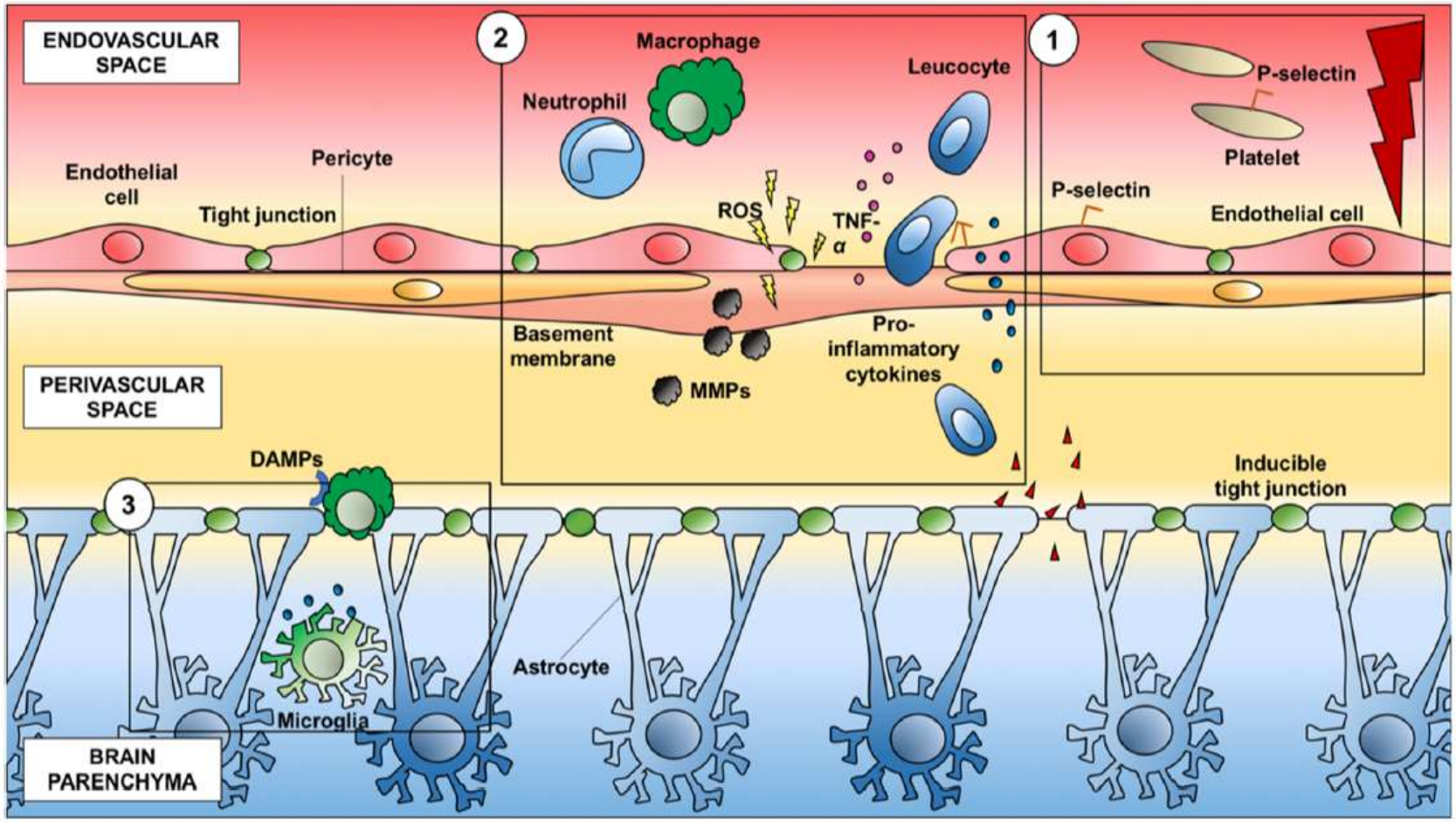
Scheitz JF, et al. J Am Heart Assoc. 2022;11:e026528

Key points

- **La sindrome cuore-cervello dopo stroke ischemico è una realtà clinica.**
  Lo stroke ischemico è indipendentemente associato a un rischio incidente di eventi CV maggiori, più elevato nel primo mese.
  I principali meccanismi fisiopatologici coinvolti nell'alterata regolazione dell'asse cervello-cuore dopo stroke ischemico sono: l'iperattività simpatica, l'asse ipotalamo-ipofisi-surrene, le risposte immunitaria e infiammatoria e l'alterazione del microbiota intestinale.
- **L'AFDAS è un evento fortemente eterogeneo dal punto di vista patogenetico, prognostico e terapeutico, che richiede soprattutto per la variante neurogenica ulteriori studi clinici.**
- **Dopo stroke ischemico è consigliato come standard di cura il ricovero in Terapia Intensiva con monitoraggio continuo del ritmo e dell'emodinamica.**
  Le strategie di terapia costituiscono una sfida e sono necessarie ulteriori ricerche per completare questo complesso puzzle multidisciplinare.


grazie per l'attenzione
By Renzo Rizzo

Local inflammatory response after stroke



Battaglini D et al. Critical Care 2020; 24:163-175