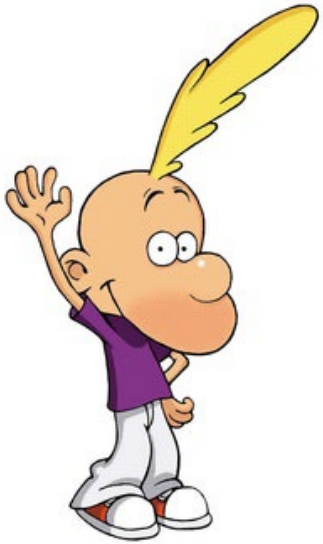


Symposium d'au revoir du Pr L. Hirt, 12.11.2026



Stroke treatment : Learning from patients

Prof. Patrik Michel, MD

Adjoint au Chef du Service de neurologie
Médecin chef, Centre Cérébrovasculaire
Département des Neurosciences Cliniques

canton de vaud
LIBERTÉ ET PATRIE

CHUV Centre Cérébrovasculaire

SIWF ISFM FMH
établissement de formation postgraduée certifié
2026

Unil.



What is a stroke ?

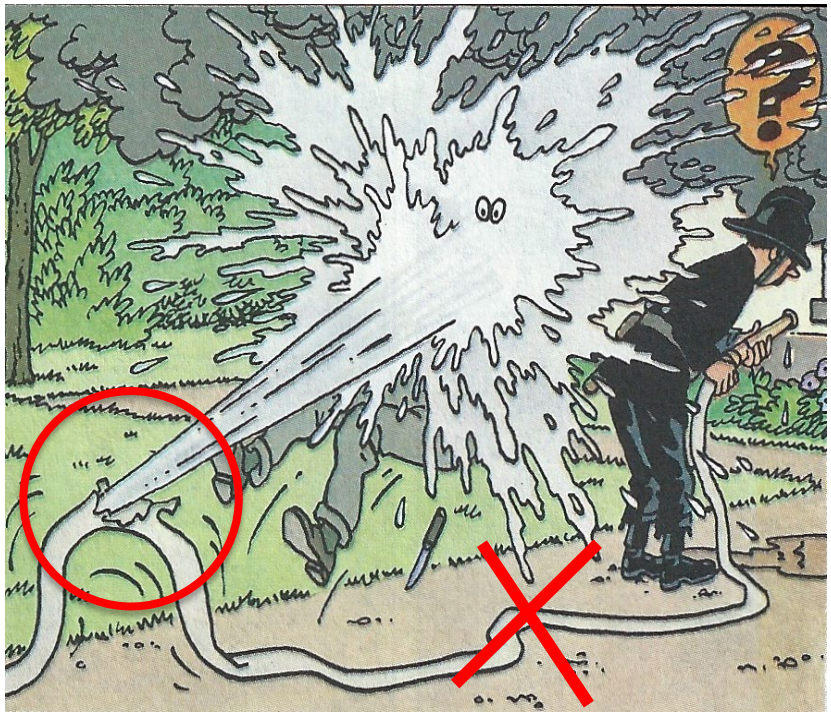
- Ischaemic 85 %
- Haemorrhagic 15 %

→ Acute cerebral dysfunction of a vascular cause, causing cell death





Radiologie, CHUV



HERGE « l'île noire », 1946

Acknowledgement: L. Hirt



Stroke treatment: Learning from ...



- Cells & biological tissue
- Animals
- Patients

1) Observation of individuals or groups *
   → Understand pathophysiology
2) Observation of interventions
   → Potential benefits & errors
3) Randomized controlled interventions
   → Real benefits & side effects

~~Treatment based on myths, believes, and hopes~~

→ Know what really works and what doesn't in humans



* Clinical observation, radiology/exams, laboratory values, tissue ...



Stroke treatment: Learning from ...



- Cells & biological tissue
- Animals
- Patients

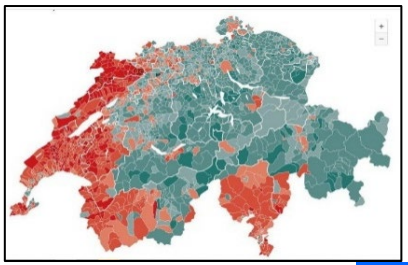
1) Observation of individuals or groups *

2) Observation of interventions

3) Randomized controlled interventions





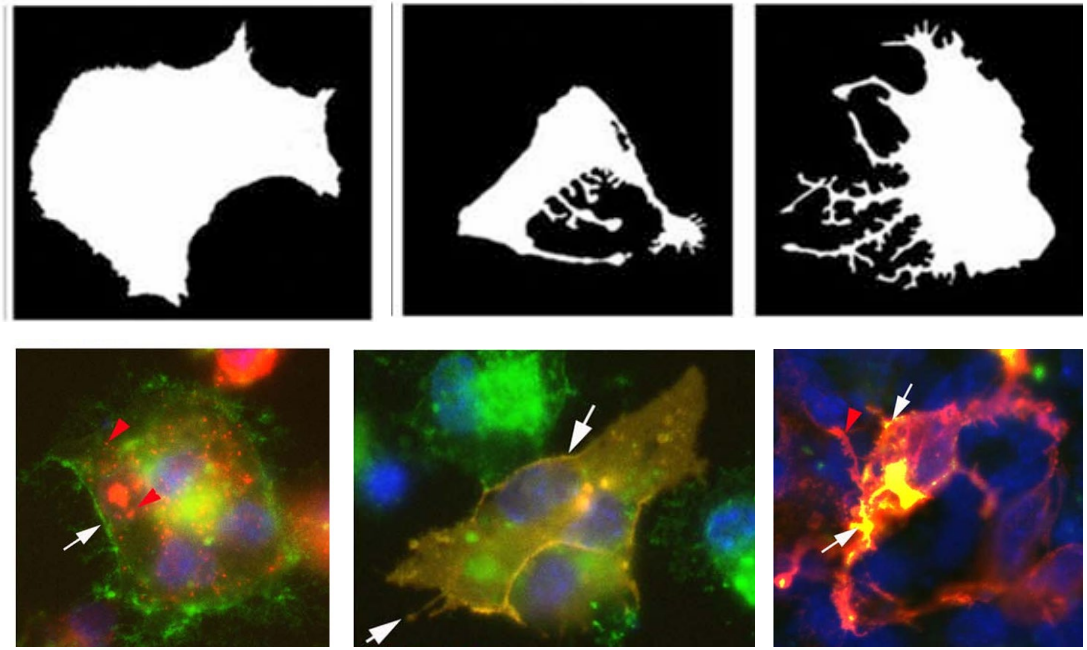


* Clinical observation, radiology/exams, laboratory values, tissue ...

Observation of individual cells in the brain

of mice with in ischemic stroke





AQP9 expression in astrocytes in stroke

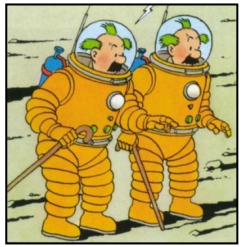
Hirt et al, J Neurosci Res 2018

Observation of patients with unusual strokes

→ to better understand mechanisms and prognosis



Stroke chameleons
(Richoz; Rebordao)



Stroke mimics
(Papavasileiou, Zinstock)



Isolated amnesia
(Michel)



Isolated vertigo
(Sueur, in prep.)



NIHSS zero
(Eskioglou)



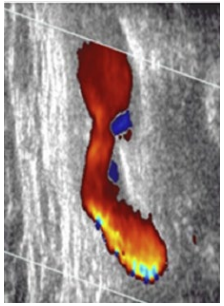
Consciousness
(Palazzo)



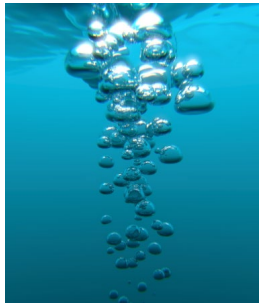
Skiing-strokes
(Strambo)



Hairdresser
(Correia)



Doppler-induced
(Papavasileiou)



Gaz emboli
(Tsetsou)

Observation of groups → « Soft » stroke risk factors

↑ Increase stroke risk



◆ Passive smoking	+25%	Oone JPubHealth 2011
◆ Air pollution (particulate matter)	linear	Verhoeuven, Lancet Planet Health 2021
◆ Active cancer	++	Costamagna SeminThrombHemos 2023
◆ Depression	+45%	Pan JAMA 2011
◆ Contraceptives (estrogenes)	+65%	Marto Stroke 2021 – supplement
◆ Red meat	+11%	Kaluza Stroke 2012
◆ Soda beverages	+29%	WHI/Mossavar, Stroke 2019
◆ Artificial sweetener	+18%	Debras/NutriSanté BMJ 2022

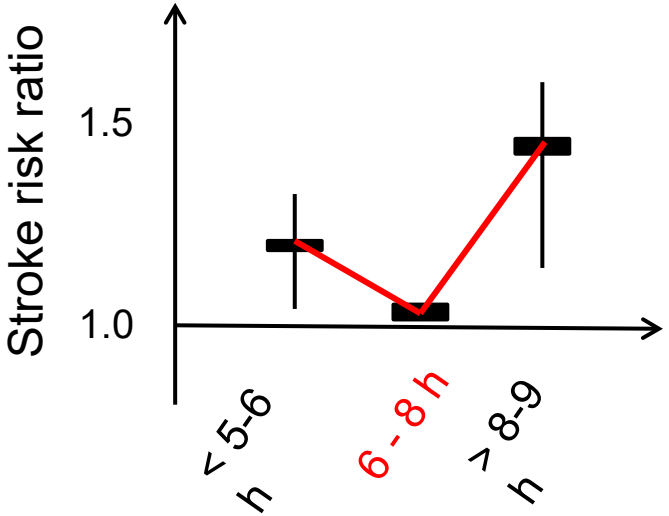
↓ Decrease stroke risk



◆ Physical activity	- 27%	Lee Stroke 2003
◆ Mediterranean diet	- 39%	Estruch NEJM 2016
◆ Chocolate	- 27%	WHI/Greenberg AmJNutr 2018
◆ Influenza vaccination	- 22%	Holodinsky Lancet Publ Health 2022

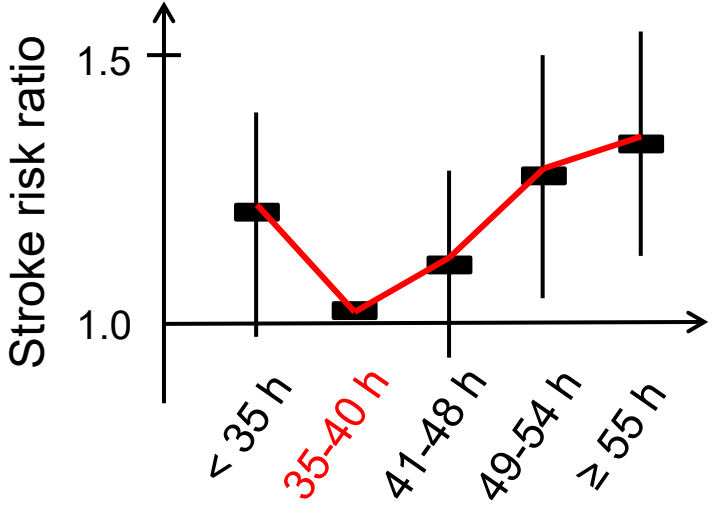
Observation of groups → « Soft » stroke risk factors

Hours of sleep



Meta-analysis
Leng Neurology 2015

Work hours



Meta-analysis (N=603'838)
Kivimäki Lancet 2015

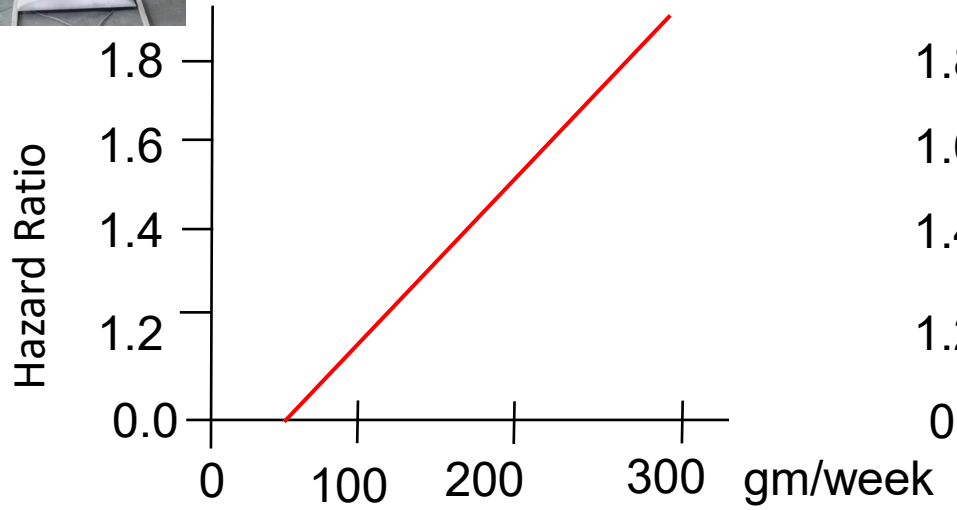


Observation of groups of persons

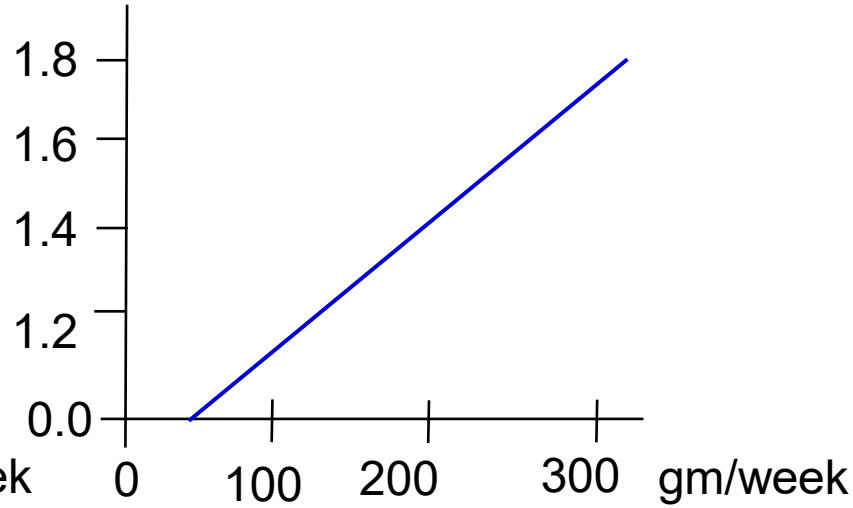
How much alcohol is too much ?



Haemorrhagic strokes



Ischaemic strokes



Wood Lancet 2018; similar in Millwood Lancet 2019



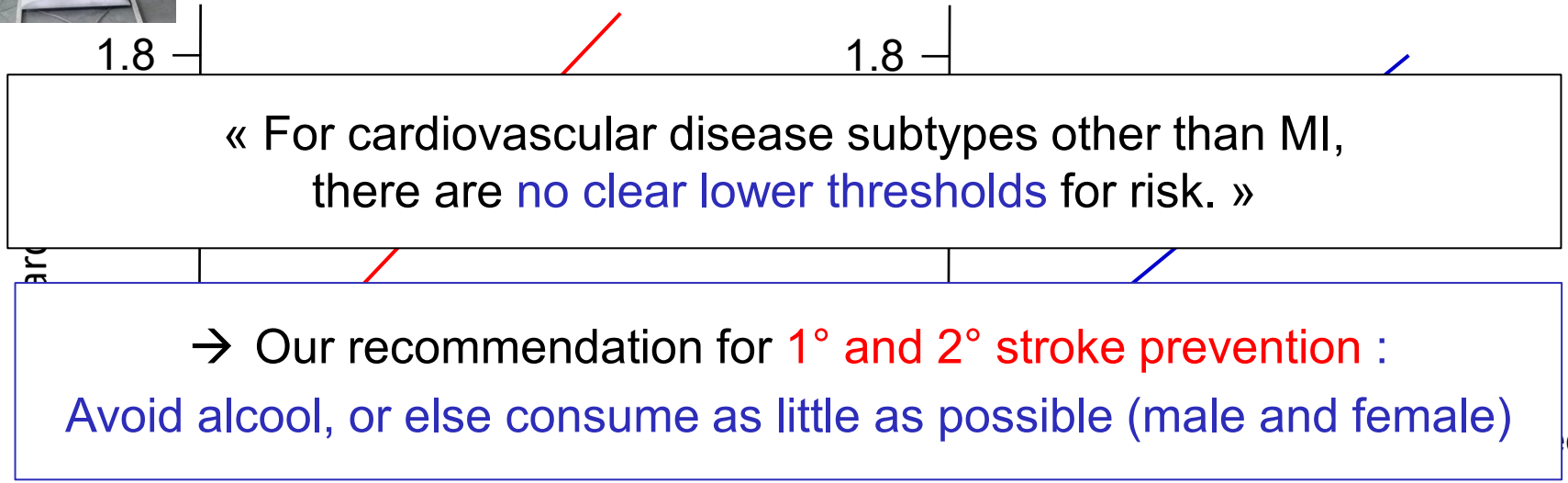
Observation of groups of persons

How much alcohol is too much ?



Haemorrhagic strokes

Ischaemic strokes



« For cardiovascular disease subtypes other than MI, there are no clear lower thresholds for risk. »

→ Our recommendation for 1° and 2° stroke prevention :

Avoid alcool, or else consume as little as possible (male and female)

Wood Lancet 2018; similar in Millwood Lancet 2019



Stroke treatment: Learning from ...



- Cells & biological tissue
- Animals
- Patients

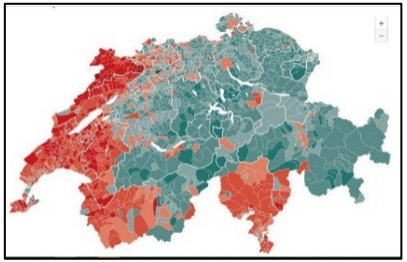
1) Observation of individuals or groups *

2) Observation of interventions

3) Randomized controlled interventions







* Clinical observation, radiology/exams, laboratory values, tissue ...

The 3 most effective interventions to date
for acute ischemic stroke treatment

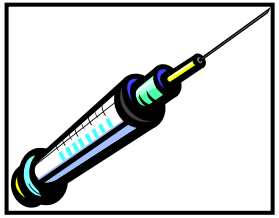
- Admission to a specialized stroke unit



Applicable in

100%

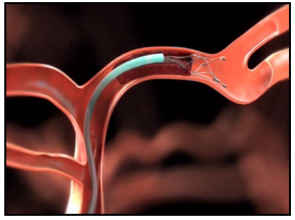
- Thrombolysis

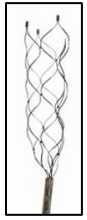




~ 20%

- Thrombectomy

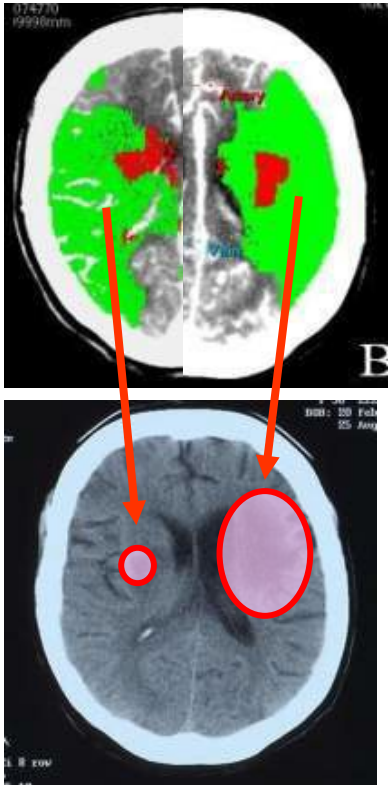




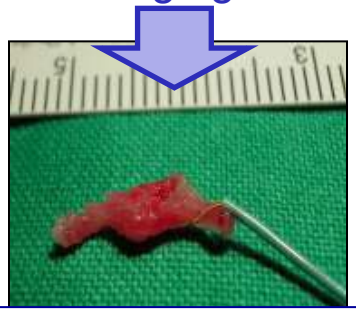
~ 10%

Individuals: the world's smallest controlled trial (N=1)

38 year old woman, mechanical heart valve, Sintrom®



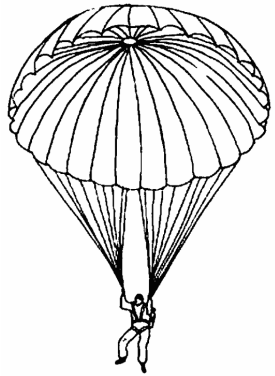
1. Left stroke:
   - Imaging at 9h
   - Penumbra=green
   - Not treated
2. Right stroke 6 months later
   - Imaging at 12h



Conclusion: endovascular recanalisation is very effective

→ For clearly effective treatments, do we still need controlled randomized trials (RCT) ?

= The parachute question: « If you had to jump out of an airplane, would you use a parachute ? »



→ Clinical trials may not be feasible for this question ... , but even parachutes may be futile :





Treatments may fail, or have unexpected side effects.

Observing treatments in individuals and groups

mostly help to improve safety of interventions

Flying an airplane → Ø RCT



but learn from individual mistakes

- 76 y.o. hypertensive man
- Acute onset of
  - Aphasia & dysarthia
  - Some confusion
  - Right sensory symptoms

→ NIHSS 6

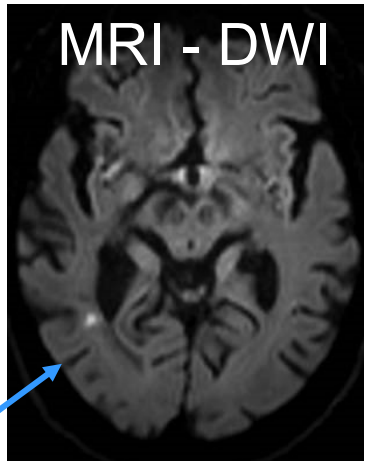
→ Clinically: Left brain stroke

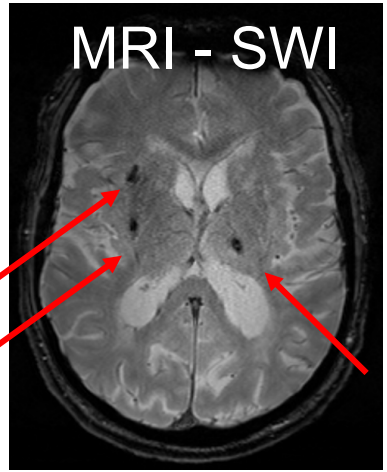
→ Acute MRI

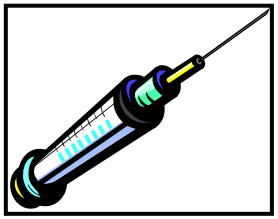


Observing treatments in individuals

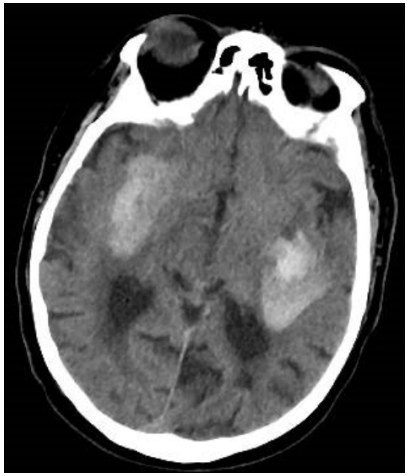
76 y.o. man, aphasia, right sensory problems







Thrombolysis

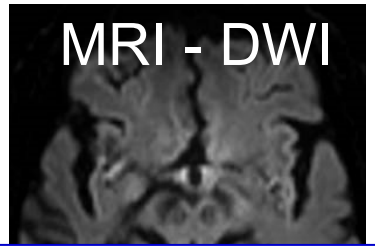


→ Radiologist: « Right brain acute ischemic stroke, some old haemorrhagic scars »

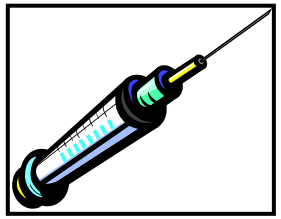


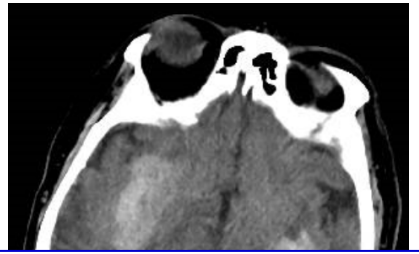
Observing treatments in individuals

76 y.o. man, aphasia, right sensory problems







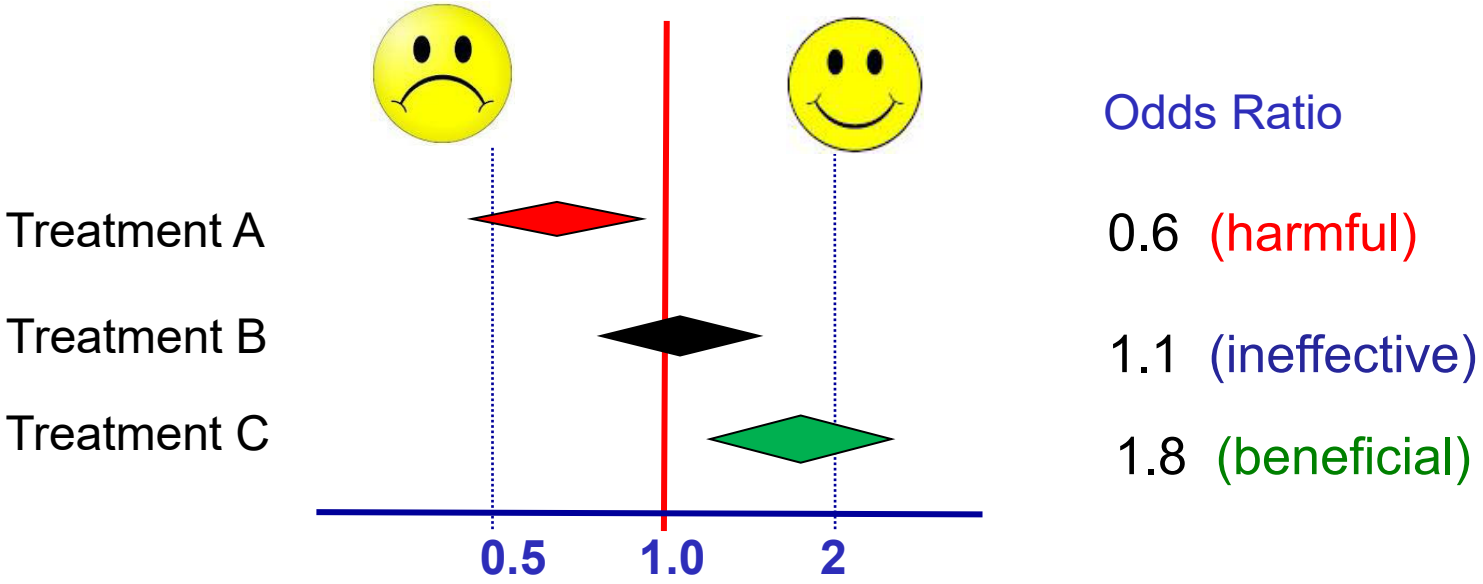


→ Action points:

1) Additional MRI training,
2) Verbal double-checks,
3) Joint reading of images (neurologist & radiologist), and
4) Explicit radiology reports: « No contra-indication to thrombolysis »

How do we present effectiveness of treatments ?

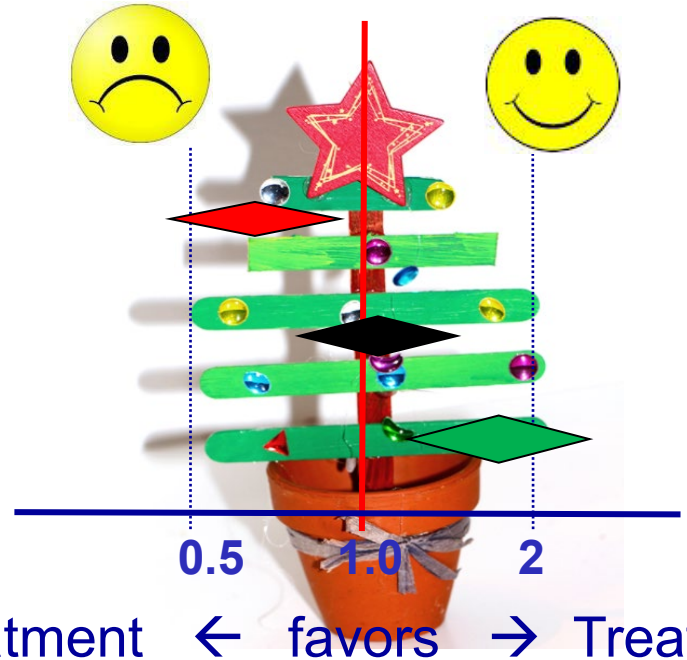
→ Presentation of results as “forest plots”



First use of «modern» forest plots:
Antiplatelet Trialists' Collaboration on 2nd prevention, BMJ 1988

How do we present effectiveness of treatments ?

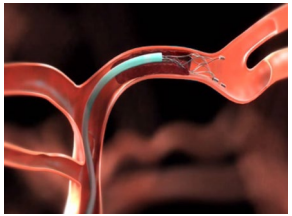
→ Presentation of results as “forest plots”



	Odds Ratio
Treatment A	0.6 (harmful)
Treatment B	1.1 (ineffective)
Treatment C	1.8 (beneficial)

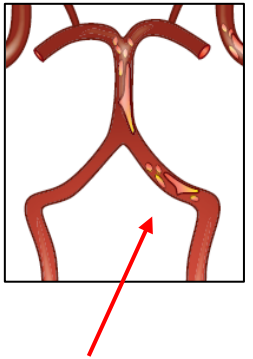
No treatment ← favors → Treatment/Placebo

First use of «modern» forest plots:
Antiplatelet Trialists' Collaboration on 2nd prevention, BMJ 1988



Observation of groups of patients

Thrombectomy for isolated occlusion of the vertebral artery occlusion (N= 494)



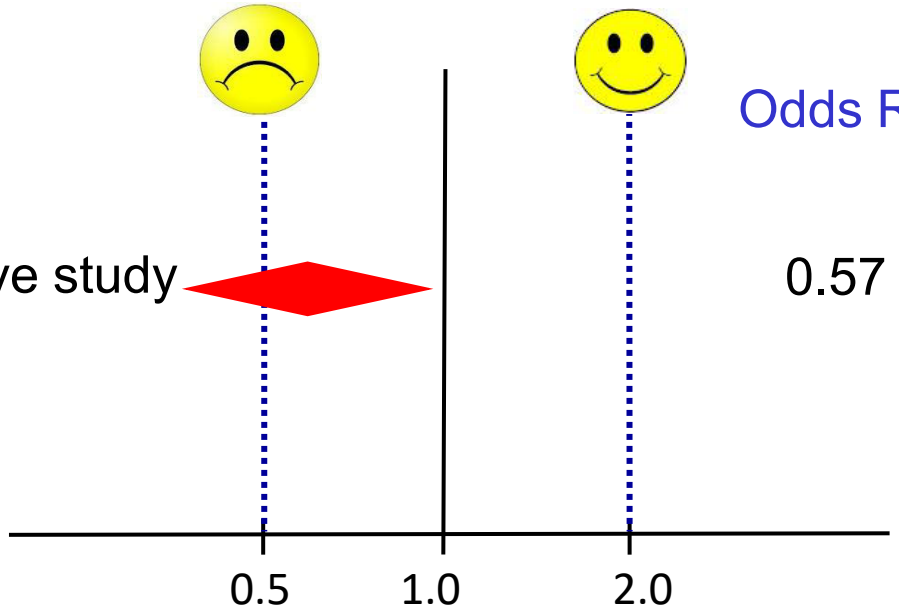
Study (mRS 0-2)

Odds Ratio

BRAVO retrospective study

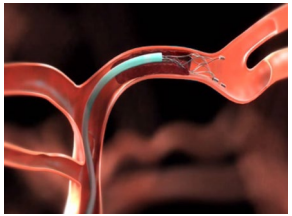
pw-mRS-shift

0.57 (0.36-0.90)



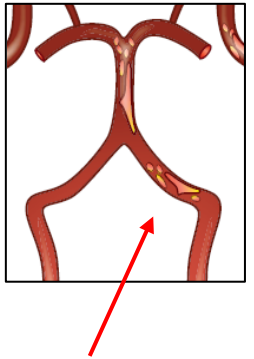
No endovascular ← Favoring → Endovascular

BRAVO: Salerno: Stroke 2026



Observation of groups of patients

Thrombectomy for isolated occlusion of the vertebral artery occlusion (N= 494)



Study (mRS 0-2)

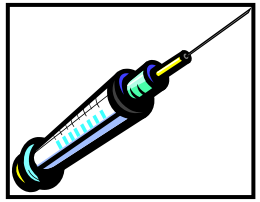
Odds Ratio

BRAVO retrospective study
pw-mRS-shift

0.57 (0.36-0.90)

→ Thrombectomy seems dangerous in isolated vertebral artery occlusion

BRAVO: Salerno: Stroke 2026



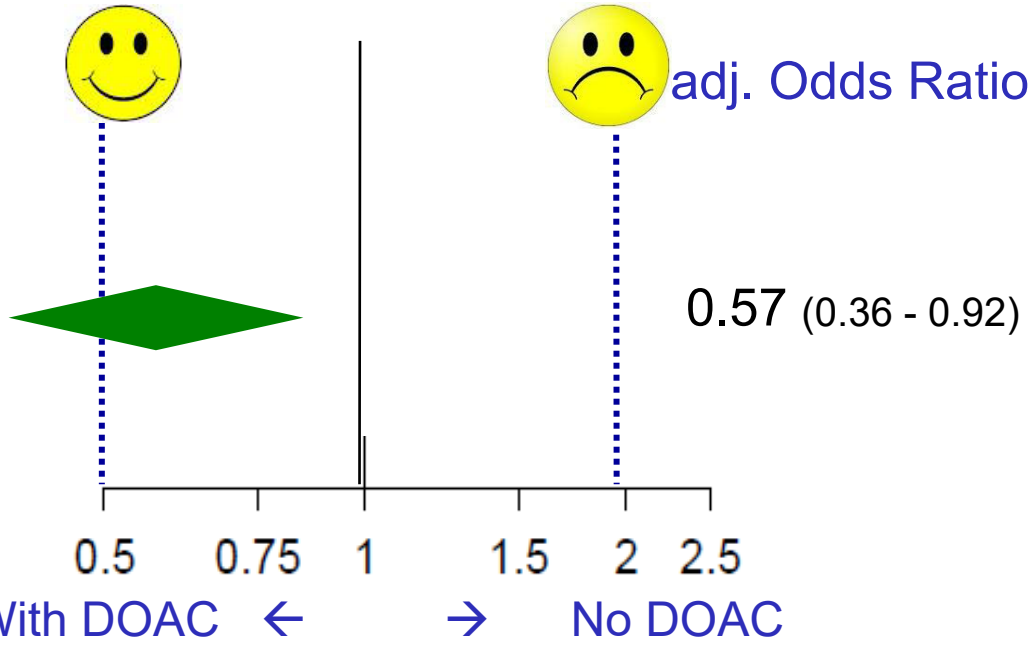
Observation of groups of patients

Thrombolysis in DOAC-anticoagulated patients (N=33’207)

Outcome :

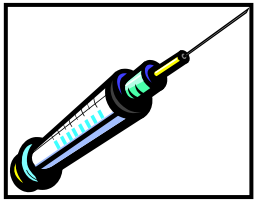
Symptomatic intracranial bleeds





Meta: Meinel & Duncan & Seiffge JAMA Neurol 2022

similar in : Seiffge Circulation 2015; Xian Circulation 2017, Shahjouei Stroke 2020



Observation of groups of patients

Thrombolysis in DOAC-anticoagulated patients (N=33’207)

Outcome :

Symptomatic intracranial bleeds







adj. Odds Ratio

0.57 (0.36 - 0.92)

→ Thrombolysis in patients on (modern) anticoagulants seems very safe ... ☺

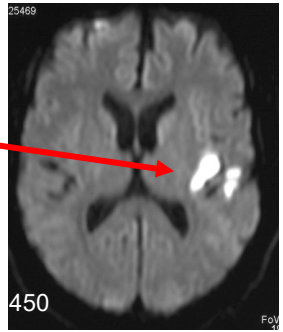
Meta: Meinel & Duncan & Seiffge JAMA Neurol 2022
similar in : Seiffge Circulation 2015; Xian Circulation 2017, Shahjouei Stroke 2020

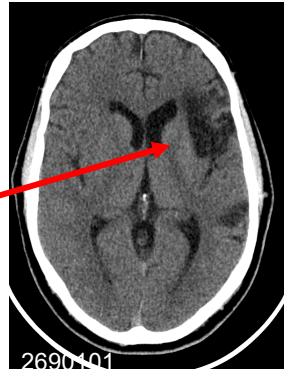
Observing individuals: stroke is always bad (?)



→ In fact, stroke can occasionally treat medical problems

- Disappearance of chronic tinnitus
  - Heschl gyrus stroke
- Disappearance of pain
  - of severe migraines
  - of excerice headaches
  - of chronic sciatica pain
  - of phantom pain (amputated finger)
- Improved social integration
  - Abandons smoking/alcoholism/homelessness
  - Helps with household & family, sociable







Stroke treatment: Learning from ...



- Cells & biological tissue
- Animals
- Patients

1) Observation of individuals or groups *

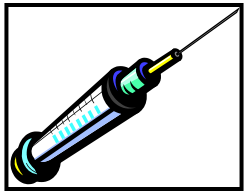
2) Observation of interventions

3) Randomized controlled interventions



Rolex ®

* Clinical observation, radiology/exams, laboratory values, tissue ...



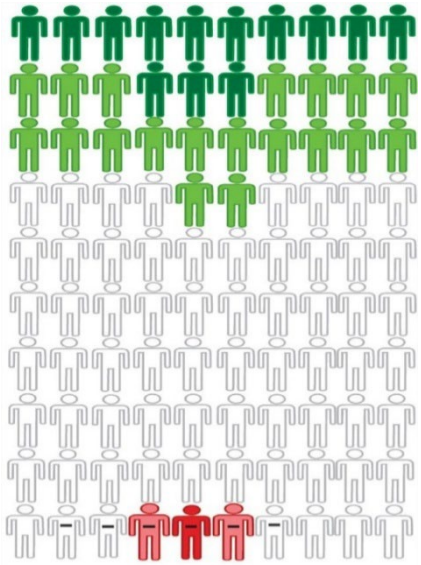
The power of randomized controlled trials

in therapeutic clinical medicine



Rolex ®

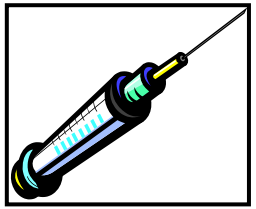
Effects and danger
of IV thrombolysis



- Identify effective treatments
- Identify the danger of treatments
- Identify useless (futile) treatments
- Know the magnitude of the benefit
- Know the magnitude of side effects
- Hint to which subgroups benefit more/less

CHUV

Unil.



The power of randomized controlled trials

Thrombolysis seems effective for .....

- All ethnic groups (Mishra Int J Stroke 2014)
- Dissections (Zinkstok Stroke 2011)
- Posterior circulation stroke (Sarikaya, Stroke2011)
- Recurrent stroke > 6 weeks, rethrombolysis (Kahles Stroke 2016 etc.)
- Severe hypertension (IST-3, Wardlaw JW et al, Lancet 2012)
- Glucose ↑↓ (IST-3, Wardlaw JW et al, Lancet 2012)
- INR up to 1.7 (Mazya/VISTA Ann Neurol 2013)
- Asymptomatic aneurysms (Edwards Stroke 2012; Sheth NeurocritCare 2012)
- Moderate leukoaraiosis (Neumann-Haefelin Stroke 2005)
- Moderate microbleeds (Fiehler Stroke 2007; Shoamanesh Int J Stroke 2013)

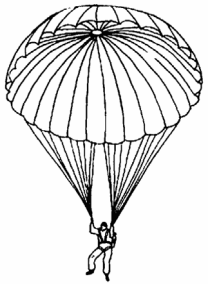
→ There seems generalized effectiveness of thrombolysis if given early. Really ? Even minor strokes ?

CHUV

Unil.

Evident success? The parachute question

→ RCT of volunteers jumping from plane ± parachute



Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

Robert W Yeh,[1] Linda R Valsdottir,[1] Michael W Yeh,[2] Changyu Shen,[1] Daniel B Kramer,[1] Jordan B Strom,[1] Eric A Secemsky,[1] Joanne L Healy,[1] Robert M Domeier,[3] Dhruv S Kazi,[1] Brahmajee K Nallamothu[4] On behalf of the PARACHUTE Investigators

thebmj

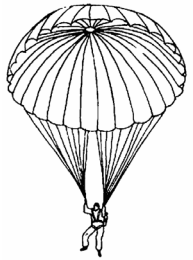
Christmas edition 2018

→ Conclusions: " Parachute use did not reduce death or major traumatic injury in the first randomized evaluation of this intervention. "

Yeh et al: PARACHUTE - RCT, BMJ 2018

Evident success? The parachute que

→ RCT of volunteers jumping from plane ± par



Methods: jump from mean altitude of 0.5 m from an immobile airplane

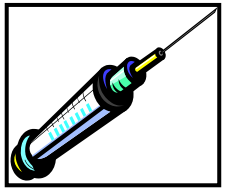
Parachute use to prevent death and major trauma wh from aircraft: randomized controlled trial

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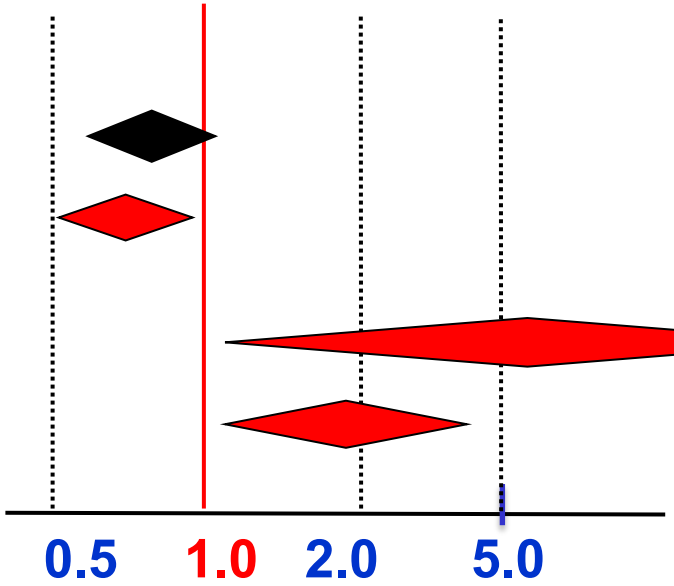


Minor strokes and thrombolysis

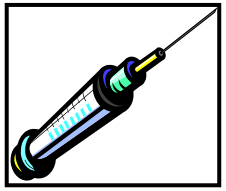
NIHSS ≤ 5: meta-analysis 4 RCTs (N=3'364)

MYTH

Outcome	Odds ratio
Benefit: Rankin 0-1	0.85 (0.70–1.03)
Benefit: Rankin 0-2	0.71 (0.55–0.91)
Sympt. IC-haemorrhage	5.22 (1.76–15.48)
Death 90 days	2.40 (0.23–4.67)



Without IVT ← more frequent → with IVT

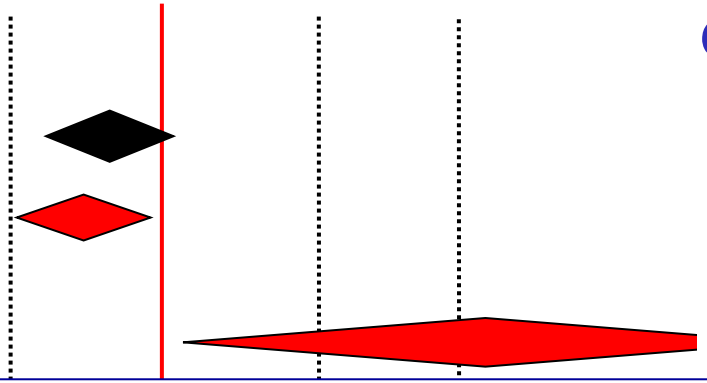


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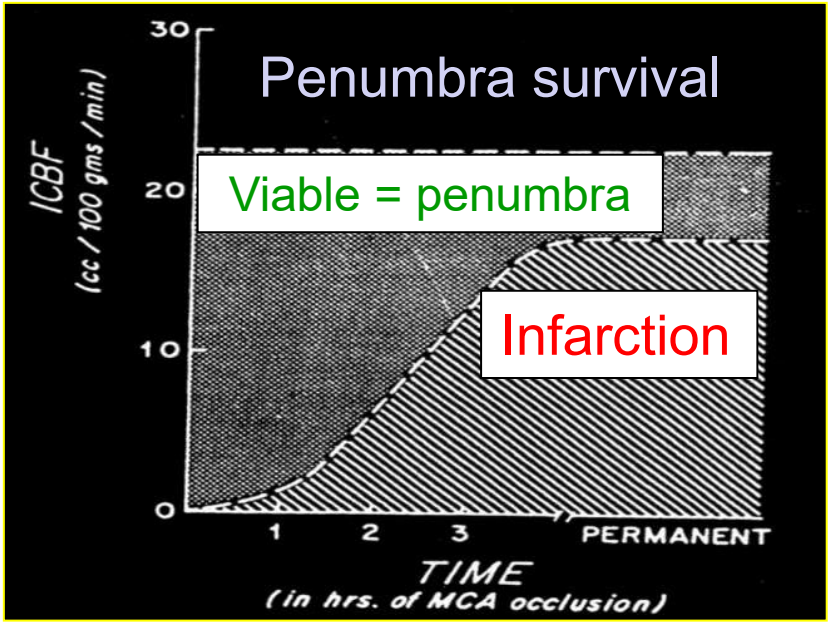
Unexpectedly, thrombolysis of minor stroke not only ineffective but even dangours ....

→ Keep doing randomized trials till you trust your evidence

Late arriving stroke patients : Do they benefit from thrombolysis and thrombectomy?

Correlation blood flow – neurol. deficit in Macaca monkeys





Penumbra survival depends on :

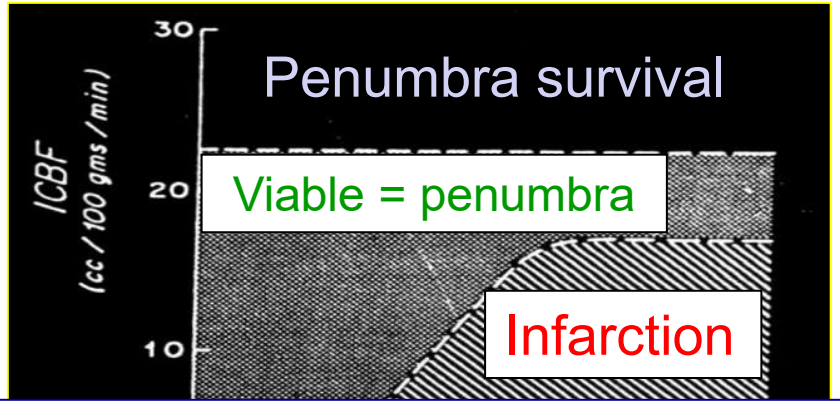
- Duration of ischemia
- Cortex vs. white matter
- Local tissue susceptibility
- Temperature, metabolics
- Genetics
- And more

Image: Jones J Neurosurg, 1981; Edito Astrup Stroke 1977

Late arriving stroke patients : Do they benefit from thrombolysis and thrombectomy?



Correlation blood flow – neurol. deficit in Macaca monkeys



Penumbra survival depends on :

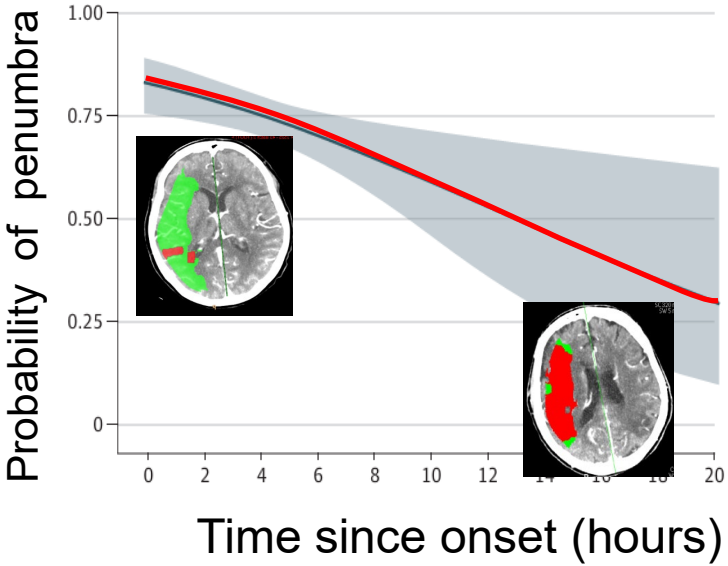
- Duration of ischemia
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- Local tissue susceptibility
- Temperature, metabolics

« Penumbra salvage is a multifactorial survival game » :
Time, and many other factors

Sirimarco et al, J Clin Med 2023

Acute stroke : « Time is brain »

Time is penumbra



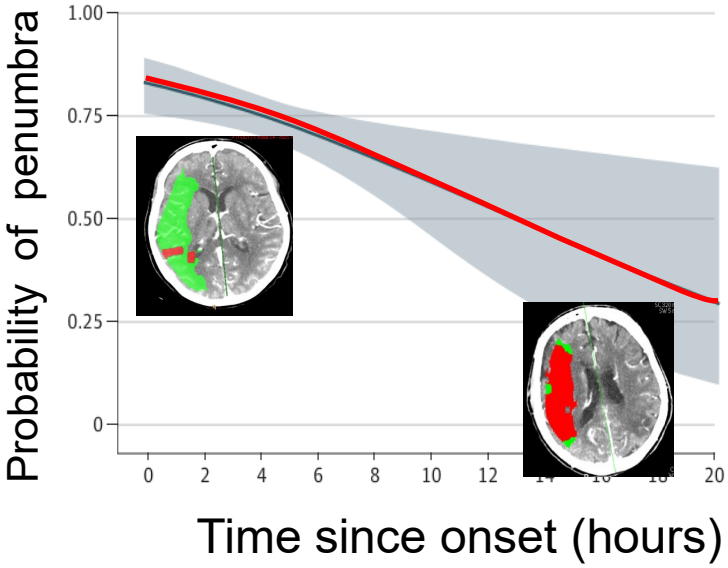


Seners JAMA Neurol 2023

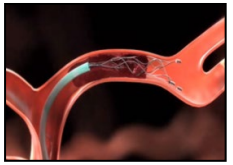
Acute stroke : ~~« Time is brain »~~

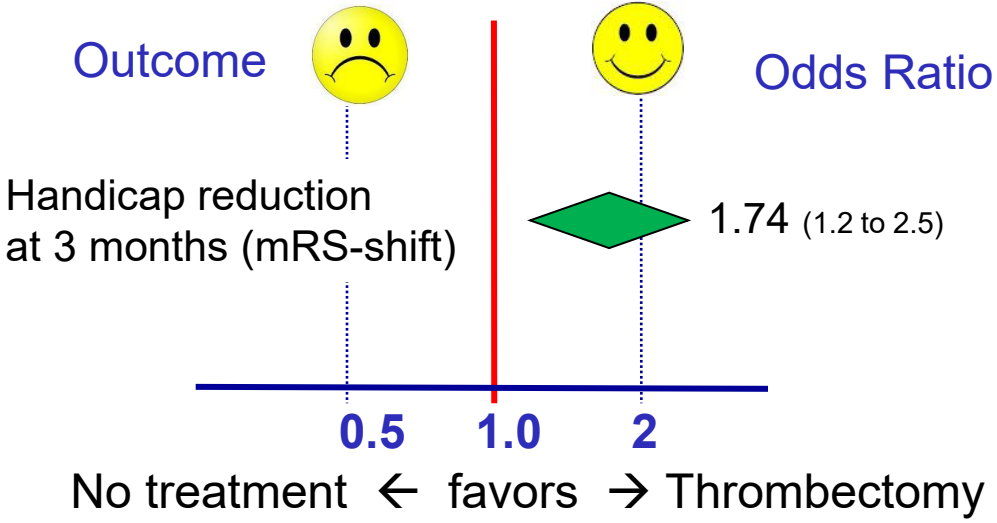


Time is penumbra



RCT: very-very late thrombectomy
24-72 hours after stroke onset
if significant penumbra





Seners JAMA Neurol 2023

LATE-MT/Yang NEJM 2026

Acute stroke : ~~« Time is brain »~~

Time is penumbra, which is brain



EDITORIALS

2019

Image-Guided Intravenous Alteplase for Stroke — Shattering a Time Window

Randolph S. Marshall, M.D.

EDITORIALS

Annals of NEUROLOGY

An Official Journal of the American Neurological Association and The Child Neurology Society

2005

Penumbra Is Brain: No Excuse Not to Perfuse

Patrik Michel, MD, and [redacted] *MD*

EDITORIAL

Neurology® 2026

Treat the Brain, Not the Clock

Penina Krieger, Rose Healy, and Thanh N. Nguyen

And neuroprotection in acute stroke

Does it work ?

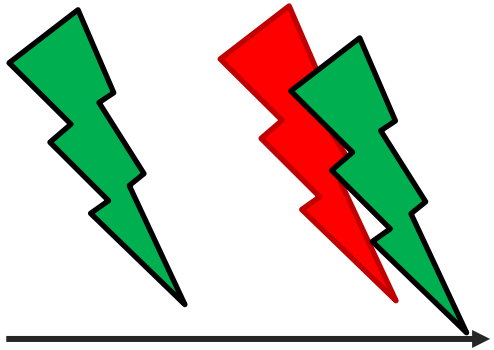




Exemple:

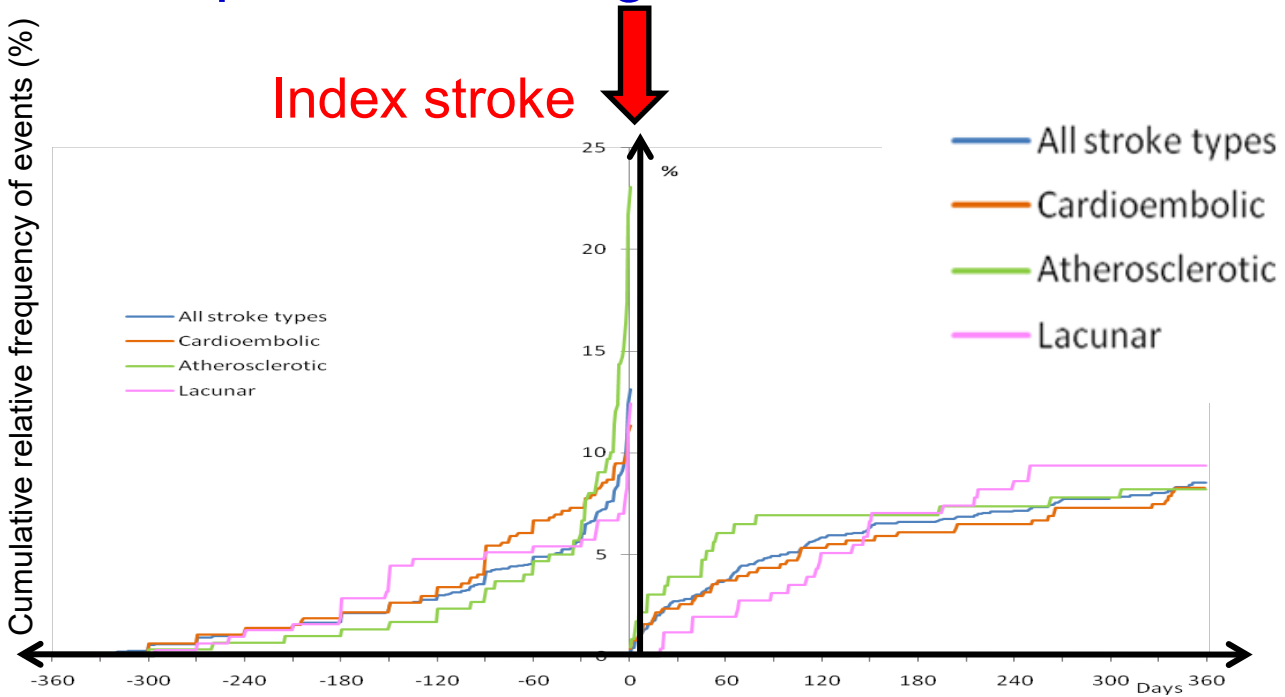
« Ischaemic conditioning »

- Of the brain
- Of remote organ



Observation in a large patient group

Ischemic preconditioning of the **brain before** stroke



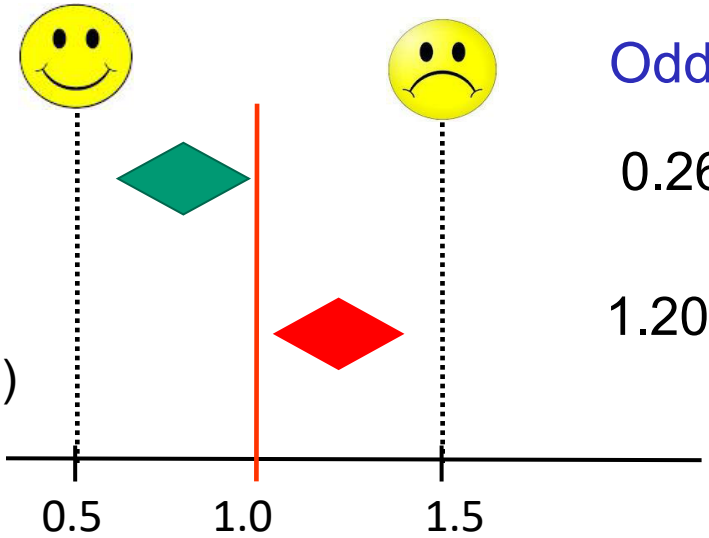
Ntaios, Cerebrovasc Dis 2011

Observation in a large patient group

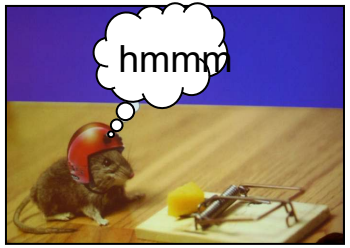
Ischemic preconditioning of the **brain before** stroke

→ 1001 patients with TIA/Stroke before index stroke

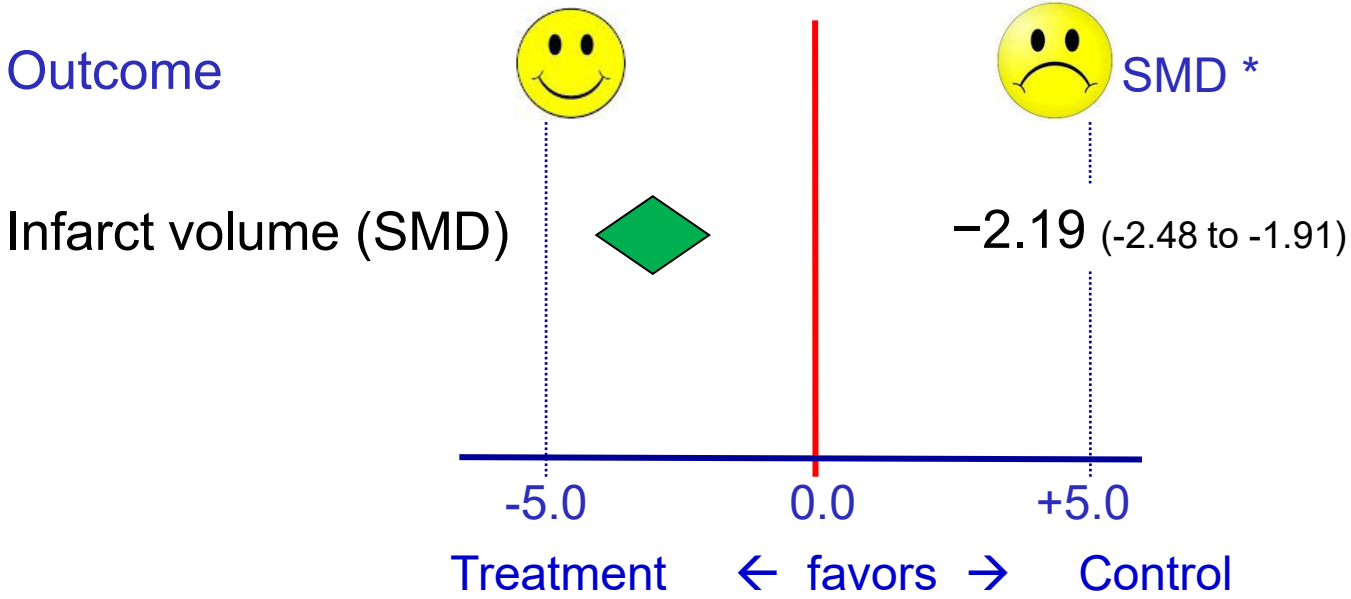
Outcome	Odds Ratio
Acute stroke severity (NIHSS)	0.26 (0.10–0.51)
Handicap at 3 months (mRS-shift towards worse)	1.20 (1.04-1.39)



Correia J Am Heart Assoc 2021

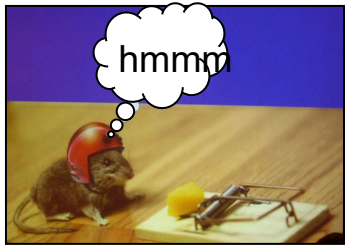


Does remote ischemic conditioning work
in animals with acute stroke ?



* Standardized mean difference

Ripley Transl Stroke Res 2021

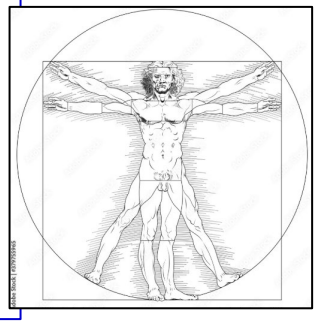


Does remote ischemic conditioning work
in animals with acute stroke ?

Outcome	SMD *
Infarct volume (SMD)	−2.19 (-2.48 to -1.91)

And in humans ? Meta-analysis of RCTs in acute stroke:
« ... appear to improve functional outcomes ... », but
results remain inconsistent across individual large trials

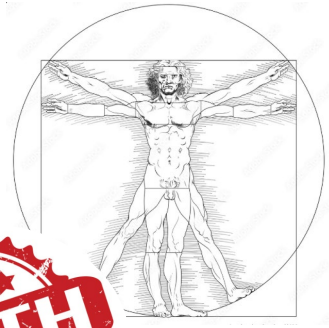
Lam Int J Stroke 2026, meta-analysis (N=6304)



* Standardized mean difference

Ripley Transl Stroke Res 2021

« Neuroprotection doesn't work in patients with acute stroke »



JAMA Neurology | Original Investigation

Sublingual Edaravone Dexborneol

JAMA Neurology

JAMA Network Open

Original Investigation | Pharmacy and Clinical Pharmacology

Tongxinluo and Functional Outcomes Among Patients With Acute Ischemic Stroke

Efficacy and safety of intravenous nerinetide initiated by paramedics in the field for acute cerebral ischaemia within 3 h of symptom onset (FRONTIER): a phase 2, multicentre,

" .... but given the repeated failures of the past, caution is warranted »

Saver JAMA 2026

Prevention: « If a treatment doesn't have side effects, it probably doesn't have any effects at all ».



Risks

Benefits





Rolex ®

→ RCTs clarify magnitude of benefits and side effects

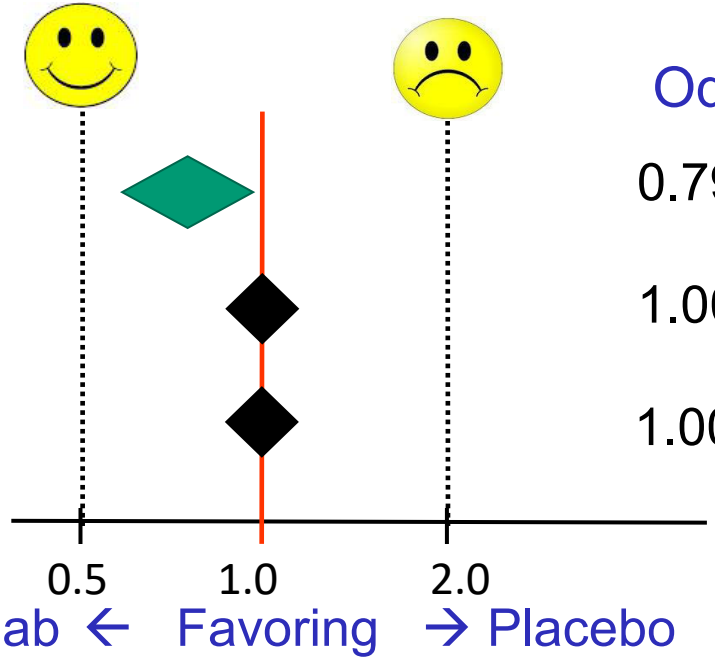
→ Recent results indicate effective drugs without side effects (!)



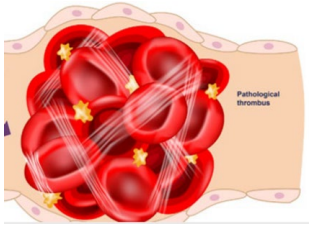
Effects and side effects in randomized trials

for cardiovascular prevention with lipid lowering (evolocumab)

Outcome	Odds Ratio
Any strokes	0.79 (0.66–0.95)
Any side effects	1.00 (0.95 to 1.06)
Serious side effects	1.00 (0.95 to 1.06)

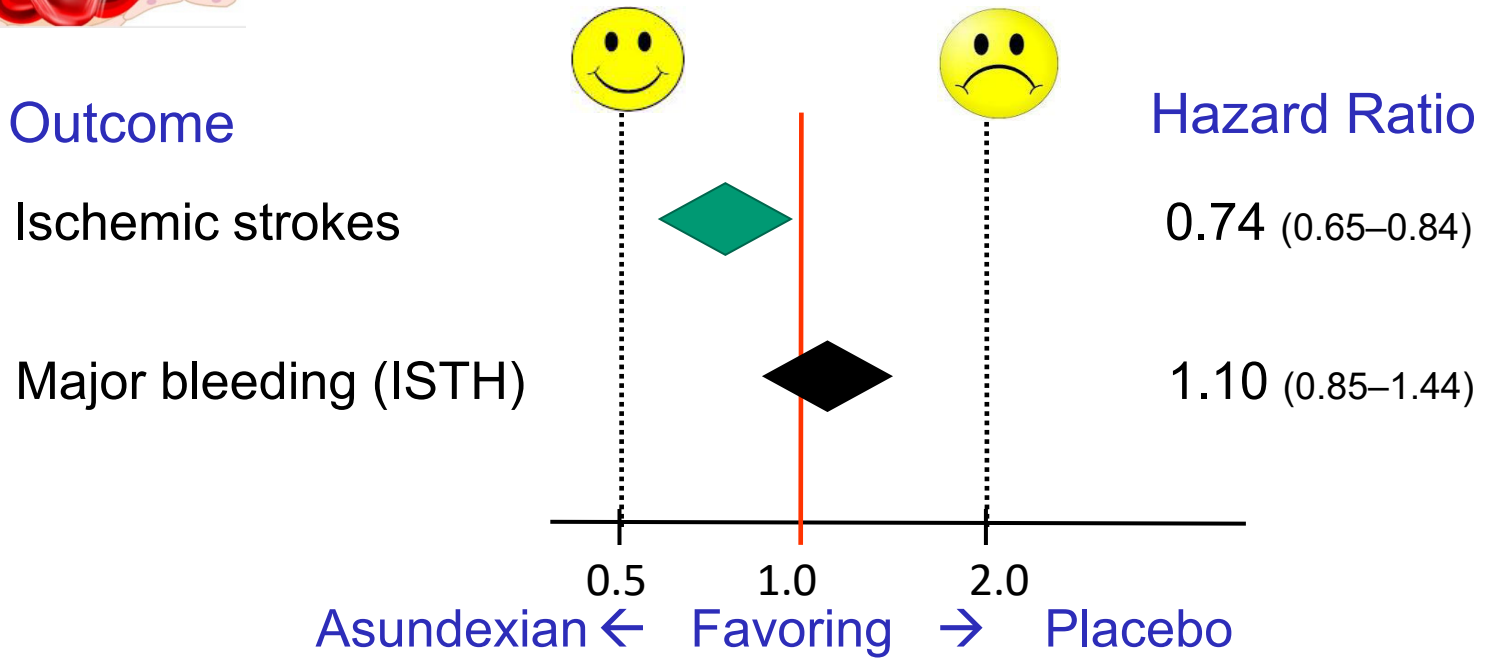


FOURIER/Sabatine NEJM 2017



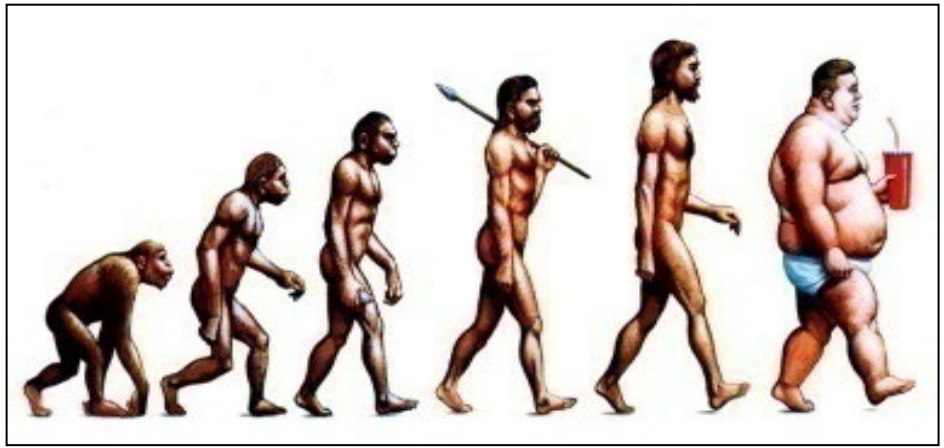
Effects and side effects in randomized trials

for 2° stroke prevention with an anticoagulant (asundexian)



OCEANIC-STROKE/Sharma NEJM 2026; Wegener & Michel Stroke 2026

Prevention: Lifestyle change is difficult





Patient education after stroke

Lifestyle change and patient education

New proof from RCTs

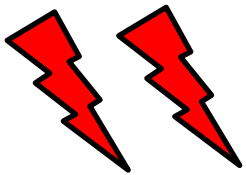


Rolex ®









- ↑ Risk factor control (HTN, lipids, smoking...)
  - INSPiRE-TMS (Ahmadi, Lancet Neurol 2019)
  - ICARUSS (Joubert, Int J Stroke 2019)
  - SINEMA (Tan JAMA Network Open 2024)
- ↑ Quality of life / patient satisfaction
  - STROKE-CARD (Willeit, EClinicalMedicine 2020)
  - TACAS (Fu, Int J Stroke 2020)
- ↓ Long-term handicap
  - STROKE-CARD (Willeit, EClinicalMedicine 2020)
  - TACAS (Fu, Int J Stroke 2020)
  - StroCare (ESOC 2025)
- ↓ Recurrent cardio-cerebrovascular events
  - STROKE-CARD (Willeit, EClinicalMedicine 2020)
  - SINEMA (Tan JAMA Network Open 2024)
  - FINGER cerebrovascular (Lehtisalo Eur Heart J 2022)



6 Swiss secrets how to prevent strokes
by lifestyle change





6 Vaudois secrets how to prevent strokes



Vegetables & fruits

He Lancet 2006



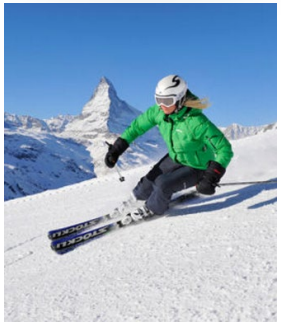
3-5 cups/day

Ding Circulation 2013



Low-fat milk products

Larsson Stroke 2012/ Dehghan Lancet 2018



Lots of sport

Lee Stroke 2003



Relax family & friends

Henderson Stroke 2013



Dark chocolate

Buitrago-Lopez BMJ 2011

Merci, Lorenz !

