Does Late-onset Epilepsy Predict Stroke?

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Disclosures

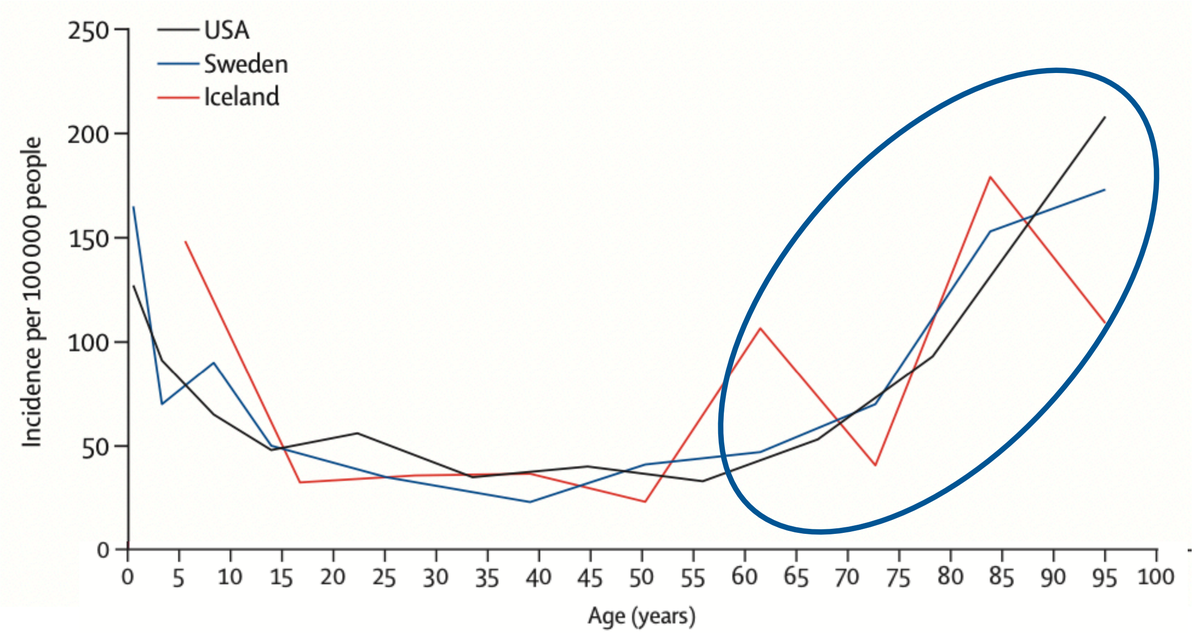
- No financial disclosures relevant to this talk

Outline

- Risk of subsequent stroke after seizure/epilepsy
- Pathophysiology
- Antiseizure medications(ASMs) & risk of subsequent stroke
- Clinical management

The scale of the “problem”

- Epilepsy: ***third most common neurological disorder*** in elderly after stroke, dementia
- Incidence of epilepsy: bimodal distribution, with ***rate being highest in elderly***
- Given shifts in demographics, ***number of late-onset epilepsy(LOE) is set to rise***
- Standardised definition is **NOT** available [50-70 years]

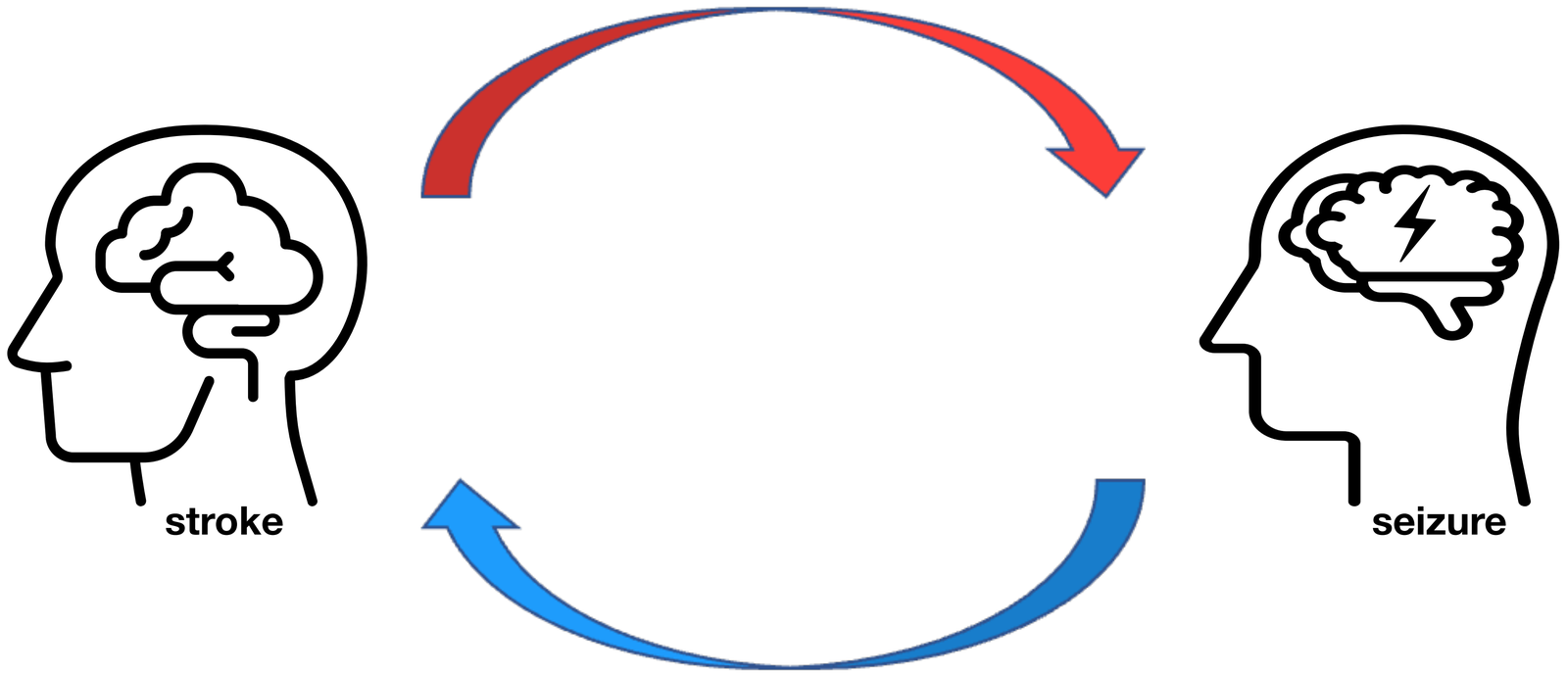


Sen et al. *Lancet* 2020

Bidirectional relationship: Stroke & Epilepsy

acute symptomatic seizure: 3.14%[1]

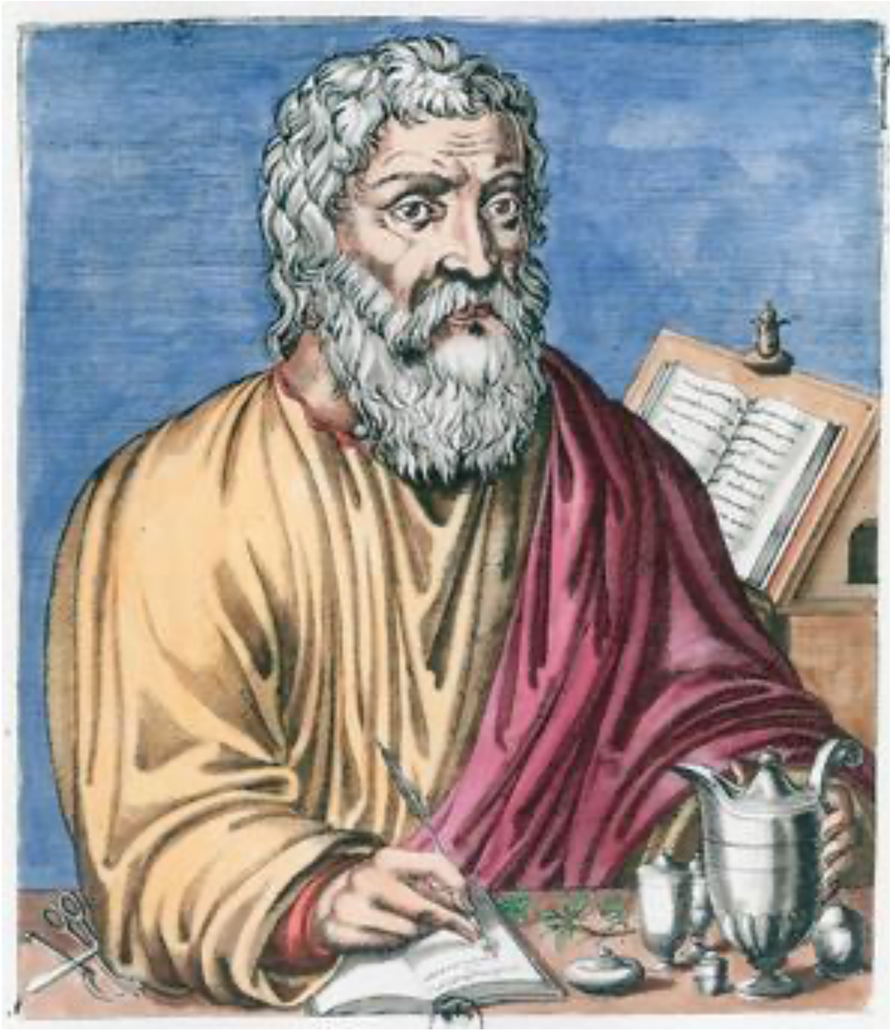
remote symptomatic seizure ~ poststroke epilepsy: 6.7%[1]



Does late-onset epilepsy predict stroke? [pre-stroke seizure, heraldic seizure, vascular precursor epilepsy]

1. Lekoubou et al. *Stroke* 2020

Vascular precursor epilepsy - Old wine in new skins?



“[seizure] in old people lead to death or to paralysis, … because, the vessels are exhausted and the blood diminished or diluted”

Hippocrates,
in Recherches sur les causes de l`epilepsie 1876

Trinka et al. *Epilepsy Behav* 2015

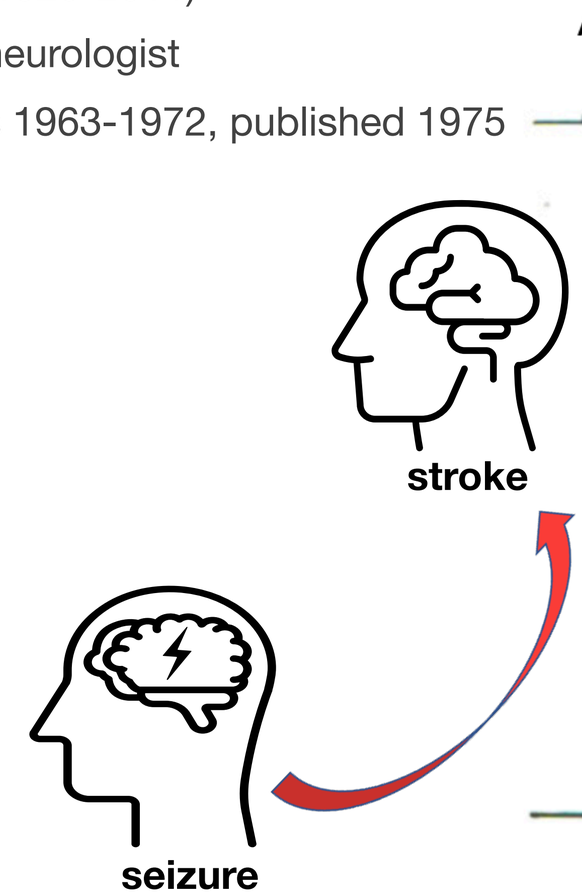
Vascular Precursor Epilepsy

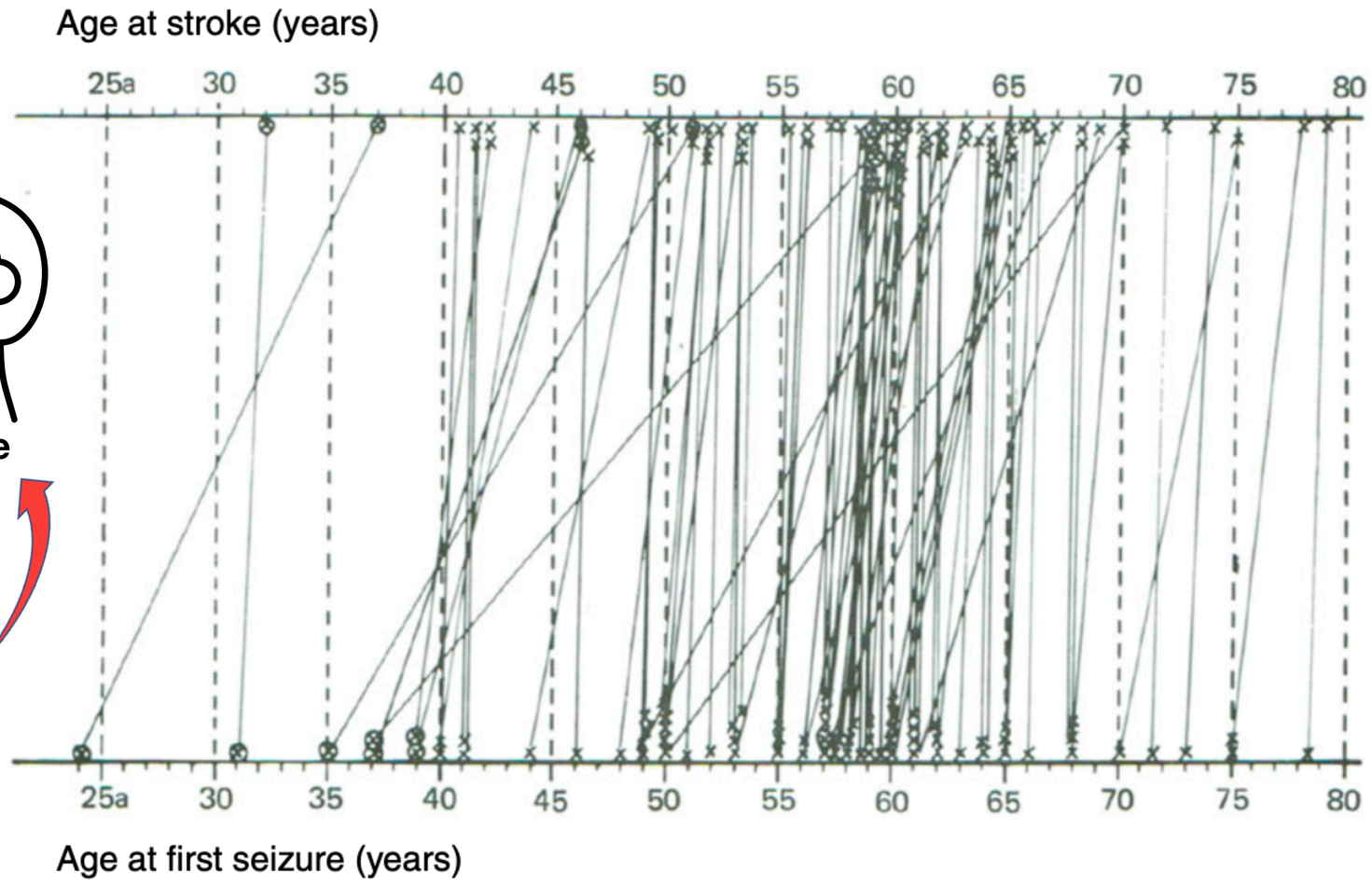
G. Barolin (1929-2011)

Australian neurologist

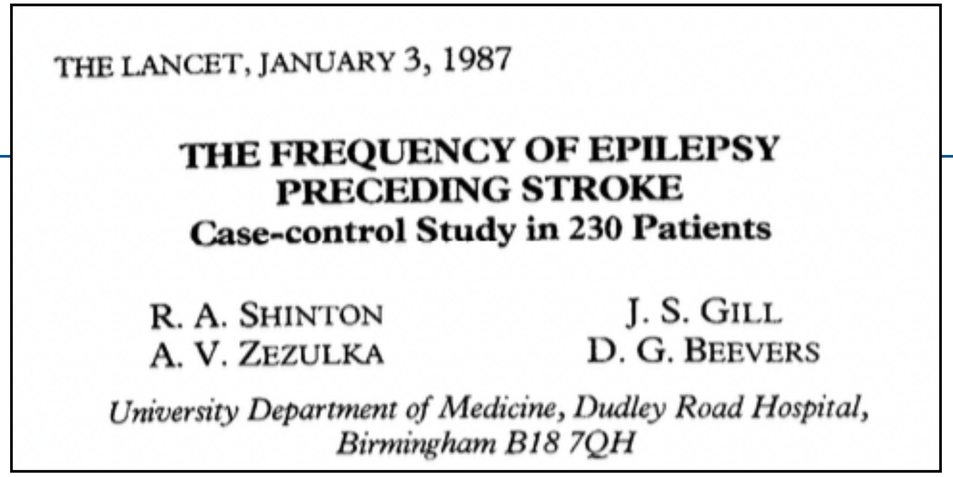
Case series 1963-1972, published 1975

77 patients





Trinka et al. *Epilepsy Behav* 2015



THE LANCET, JANUARY 3, 1987

THE FREQUENCY OF EPILEPSY PRECEDING STROKE
Case-control Study in 230 Patients

R. A. SHINTON J. S. GILL
A. V. ZEZULKA D. G. BEEVERS

University Department of Medicine, Dudley Road Hospital, Birmingham B18 7QH

To investigate patient admitted to hospital with a stroke for prevalence of epilepsy
Case-control study, age of <70 admitted to hospital with stroke
Dudley Road Hospital, Birmingham; 1983-1984
n=230 patients with stroke vs 230 controls

	First stroke (n=176)	Controls (n=230)	p-value
Epileptic	8	1	
Non-epileptic	168	229	
Prevalence of epilepsy	4.5%	0.6%	**<0.05**

Epilepsy can herald a stroke

median duration of epilepsy 9.5y (2wk - 38y); median age at seizure onset 42y (11-62)

Shinton et al. *Lancet 1987*

Review

Increased risk of stroke and myocardial infarction in patients with epilepsy: A systematic review of population-based cohort studies

Francesco Brigo [a,b,*], Piergiorgio Lochner [c], Raffaele Nardone [a,d], Paolo Manganotti [e], Simona Lattanzi [f]

Population-based cohort studies

	Country	Epilepsy patients without prior stroke	Adjusted HR for stroke (95% CI)
Cleary, 2004	UK	4709 (age >60y) (4709 controls)	**Stroke (all types) 2.89 (2.45-3.41)**
Olesen, 2011	Denmark	21,315 (age ≥10y) (4,481,132 controls)	Ischemic stroke 2.22 (2.09-2.36)
Chang, 2014	Taiwan	3812 (age ≥20y) (15,248 controls)	**Stroke (all types) 2.92 (2.58-3.30)** Ischemic stroke 2.85 (2.49-3.26) Hemorrhagic stroke 3.30 (2.46-4.43)
Wannamaker, 2015	South Carolina	21,035 (age ≥35y) (16,638 controls)	Stroke (type not specified) 1.60 (1.42-1.80)
Hsu, 2019	Taiwan	6746 (age ≥20y) (26,984 controls)	**Stroke (all types) 2.24 (2.02-2.49)** Ischemic stroke 1.91 (1.62-2.26) Hemorrhagic stroke 2.27 (1.80-2.85)

PWE are at higher risk of both ischemic & hemorrhagic stroke!

Population-based cohort studies

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Brigo et al. *Epilepsy Behav* 2020

Radiological CVD is more prevalent in LOE

Evidence from radiological studies

	Country	Outcomes	Epilepsy patients	Controls	p-value
Shorvon, 1984	UK	CT scan *Ischemic lesions*	74 (age >40y) 13 (18%)	74 2 (3%)	**0.005**
Roberts, 1988	UK	CT scan *Silent cerebral infarcts*	132 (age >40y) 15 (11%)	132 2 (1%)	**0.003**
Maxwell, 2013	UK	CT or MRI scan *Radiological CVD* *Large vessel disease* *Small vessel disease*	105 (age >60y) 69 (65%) 23 (22%) 52 (49%)	105 35 (33%) 2 (2%) 34 (32%)	 **<0.001** **<0.001** **<0.05**

1. Shorvon et al. *J Neurol Neurosurg Psychiatry* 1984; 2. Roberts et al. *Epilepsia* 1988; 3. Maxwell et al. *Clin Neurol Neurosurg* 2013

Late-onset → Adult-onset Epilepsy

Patients with epilepsy are at an increased risk of subsequent stroke: A population-based cohort study

Chen-Shu Chang [a,b,1], Chun-Hui Liao [c,d,1], Che-Chen Lin [e], Hsien-Yuan Lane [c,d], Fung-Chang Sung [d,e,*], Chia-Huang Kao [d,f,**]

To investigate incidence & risk of stroke in PWE

Taiwan National Health Insurance claims data, 2000-2008

Age ≥18 years having epilepsy

Age group	Controls (n=15,248)	Epilepsy (n=3812)	aHR (95% CI)
	rate (per 1000 person-year)		
20-39	0.98	8.71	**8.88 (5.71-13.82)**
40-59	4.09	20.38	**4.89 (3.83-6.26)**
≥60	22.77	54.99	**2.32 (1.99-2.71)**

↑ stroke risk even from the third or fourth decades of life!

Chang et al. *Seizure* 2014

What could mechanistically explain the relationship between seizures & subsequent stroke?

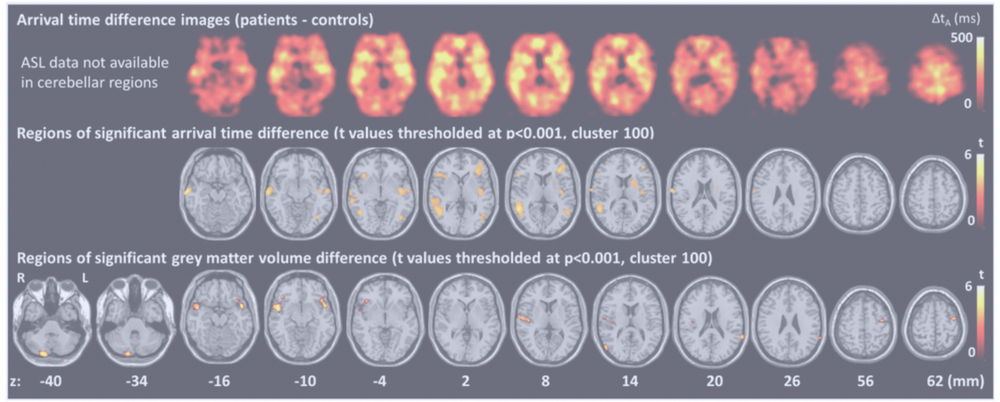
Structural and physiological MRI correlates of occult cerebrovascular disease in late-onset epilepsy

Martha F. Hanby[a,b,*], Sarah Al-Bachari[a], Fadiyah Makin[a], Rishma Vidyasagar[a], Laura M. Parkes[a], Hedley C.A. Emsley[b,c]

To determine whether physiological imaging markers of occult CVD were more common in LOE

Multimodal MRI (arterial spin labeling, FAIR, dynamic contrast enhanced sequence, blood oxygenation level-dependent signal, assessment of cerebrovascular reactivity)

16 late-onset (>50 years) epilepsy, and no clinical CVD vs Controls (n=14)



	LOE (n=16)	Controls (n=15)	p-value
Cortical GM volume (% of ICV)	33.8 ± 3.8	38.0 ± 5.5	**0.02**
WMH volume (mm^3)	1340 ± 1408	514 ± 481	**0.047**
Baseline AAT (ms)	1539 ± 129	1363 ± 167	**0.005**

Cortical atrophy related to small vessel disease

Prolonged arrival time for blood to reach tissue

AAT, arterial arrival time; WMH, white matter hyperintensities; GM, grey matter

Vascular Determinants of Epilepsy: The Rotterdam Study

*Xinhua Li, *†Monique M. B. Breteler, †‡Martine C. de Bruyne, §Harry Meinardi, ‖W. Allen Hauser, and *†Albert Hofman

To investigate relation between vascular determinants and epilepsy in elderly

Cross-sectional, community-based, case-control study

Rotterdam Study, Netherlands

n=4944, age ≥ 55 years, 65 had epilepsy (39 late-onset epilepsy)

Some vascular risk factors are more frequent in late-onset epilepsy

Epilepsy covariates	Lifetime epilepsy OR	Lifetime epilepsy 95% CI	Late-onset OR	Late-onset 95% CI
Total cholesterol (mmol/l)	1.1	0.9–1.3	1.3	1.0–1.6
Left ventricular hypertrophy	1.7	0.6–4.8	2.9	1.0–8.6
Myocardial infarction	1.5	0.6–3.9	1.8	0.6–5.4
Peripheral arterial disease	1.6	0.8–3.2	1.5	0.6–3.6
Any vascular determinant[a]	1.8	1.0–3.2	2.1	1.0–4.7

[a] Defined as total cholesterol >6.5 mmol/l or previous myocardial infarction or peripheral arterial disease or left ventricular hypertrophy.

CI, confidence interval; OR, odds ratio.

adjusted for age/sex
and previous stroke are excluded

Li et al. *Epilepsia* 1997

JAMA Neurology | Original Investigation

Association Between Midlife Risk Factors and Late-Onset Epilepsy
Results From the Atherosclerosis Risk in Communities Study

Emily L. Johnson, MD; Gregory L. Krauss, MD; Alexandra K. Lee, PhD, MSPH; Andrea L. C. Schneider, MD, PhD; Jennifer L. Dearborn, MD, MPH; Anna M. Kucharska-Newton, PhD, MPH; Juebin Huang, MD; Alvaro Alonso, MD, PhD; Rebecca F. Gottesman, MD, PhD

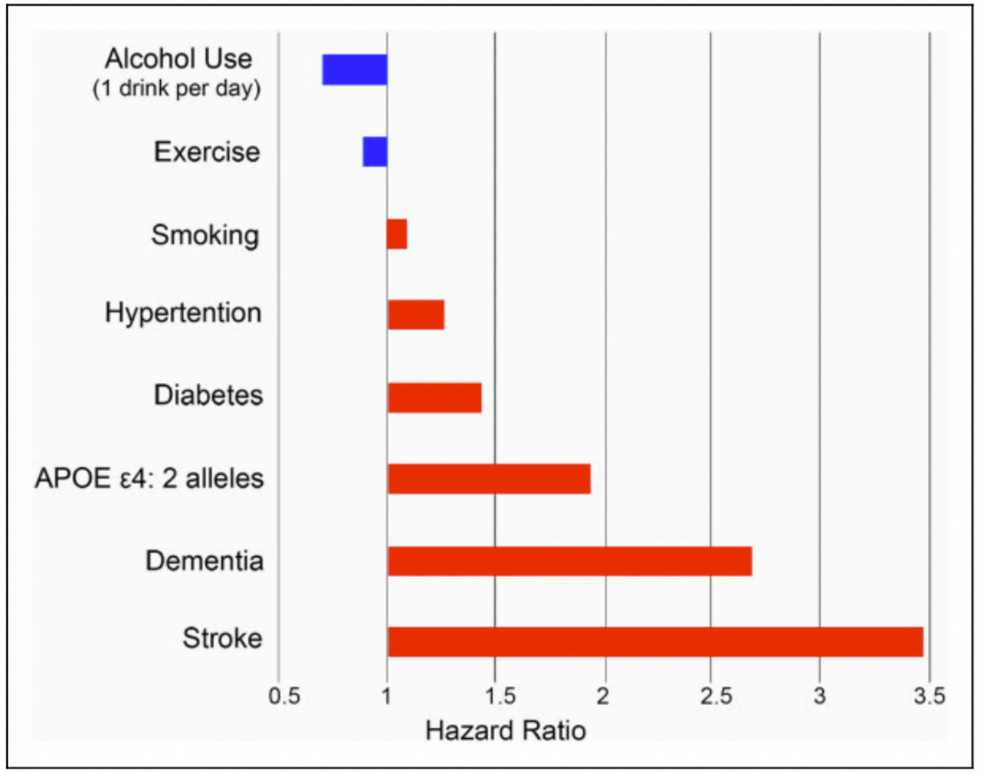
To identify midlife vascular & lifestyle risk factors for LOE (age >60 years)

ARIC, recruited ages 45-64 years between 1987-1989 from 4 US communities

n=10,420 with 596 LOE

Modifiable risk factors in midlife are associated with risk of LOE

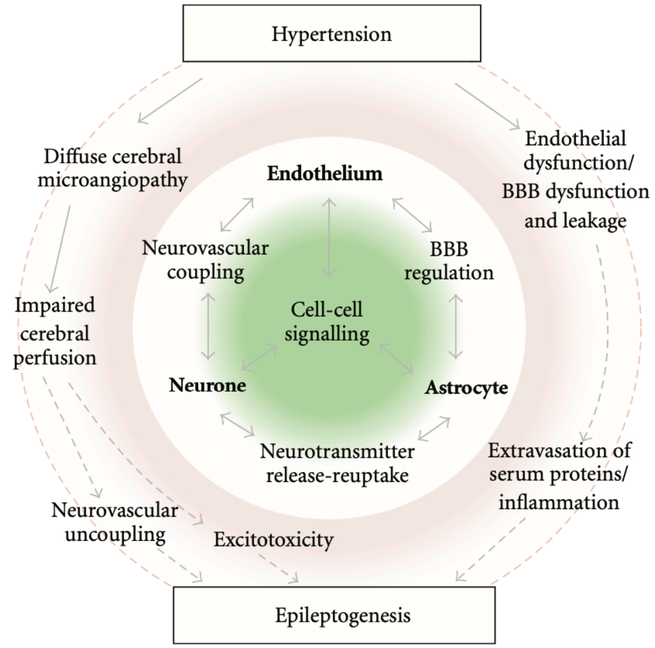
Figure 1. Midlife hazard ratios for developing epilepsy plotted as a distance from 1. None of the plotted risk factors had a 95% confidence interval that traversed 1 (i.e., all are significant).



Johnson et al. *JAMA Neurol* 2018

Pathophysiology

- Small vessel disease (SVO)
  - ➡ Disruption of cortico-subcortical circuits → altered balance between exitability & inhibitory pathways
  - ➡ Neurovascular unit dysfunction → disruption of cerebral metabolism and/or perfusion
- Vascular comorbidity & Epilepsy may share a common basis



Gibson et al. *Cardiovasc Psychiatry Neurol* 2011

Effects of ASMs on vascular risk markers

	Total cholesterol	Lipoprotein(a)	CRP	Homocysteine	cIMT
Enzyme-inducing					
Carbamazepine	↑	↑	↑	↑/⇔	↑
Phenytoin	↑	⇔	↑	↑	↑
Phenobarbital	↑	↑	?	↑	?
Enzyme-inhibiting					
Valproic acid	↓	↑/↓	↑	↑/↓	↑

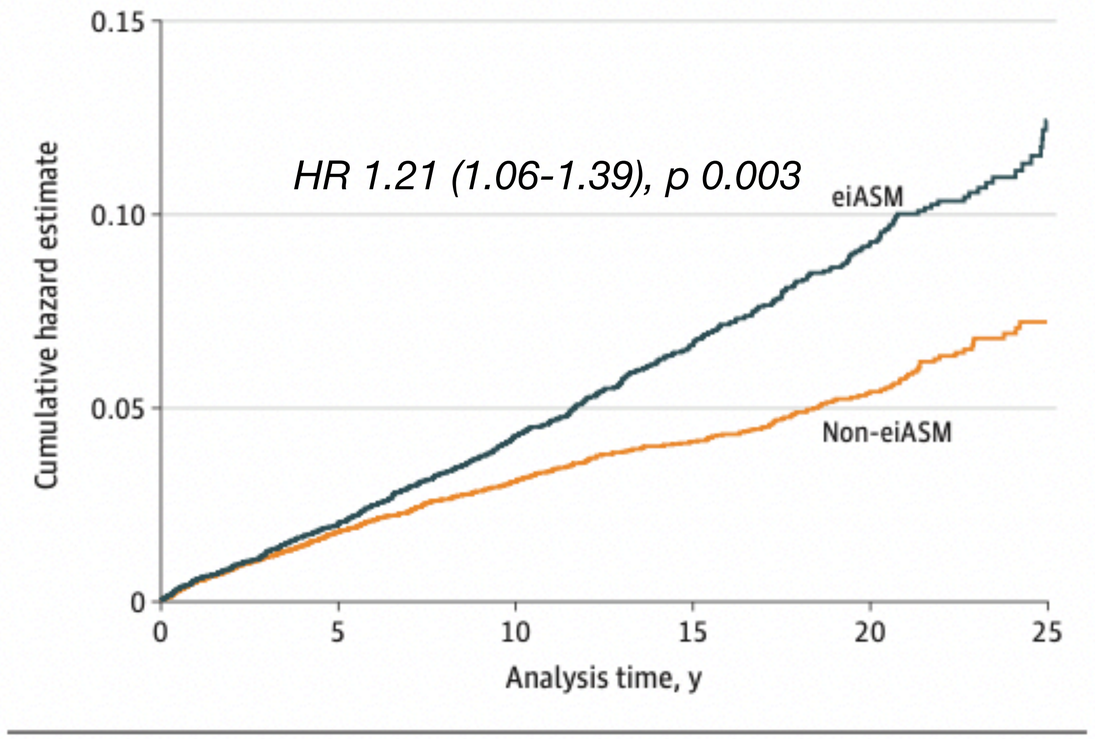
CRP, C-reactive protein; cIMT, carotid intima-media thickness

JAMA Neurology | Original Investigation

Association of Enzyme-Inducing Antiseizure Drug Use With Long-term Cardiovascular Disease

Colin B. Josephson, MD, MSc; Samuel Wiebe, MD, MSc; Guillermo Delgado-Garcia, MD, MSc; Arturo Gonzalez-Izquierdo, PhD; Spiros Denaxas, PhD; Tolulope T. Sajobi, PhD; Mubasiru Lamidi, MSc; Meng Wang, MSc; Mark R. Keezer, MDCM, PhD

Figure. Nelson-Aalen Cumulative Hazard Graph of the Risk of Incident Cardiovascular Disease (Ischemic Heart Disease, Transient Ischemic Attack, or Stroke) Following a Diagnosis of Adult-Onset Epilepsy Stratified by Exposure Status



To quantify hazard of cardiovascular disease secondary to enzyme-inducing ASM use

National Health Service hospitals in England, 1990-2019

Age ≥18 years having epilepsy

31,479 patients

↑ incident cardiovascular disease following repeated enzyme-inducing ASMs

eiASM, enzyme-inducing antiseizure medication

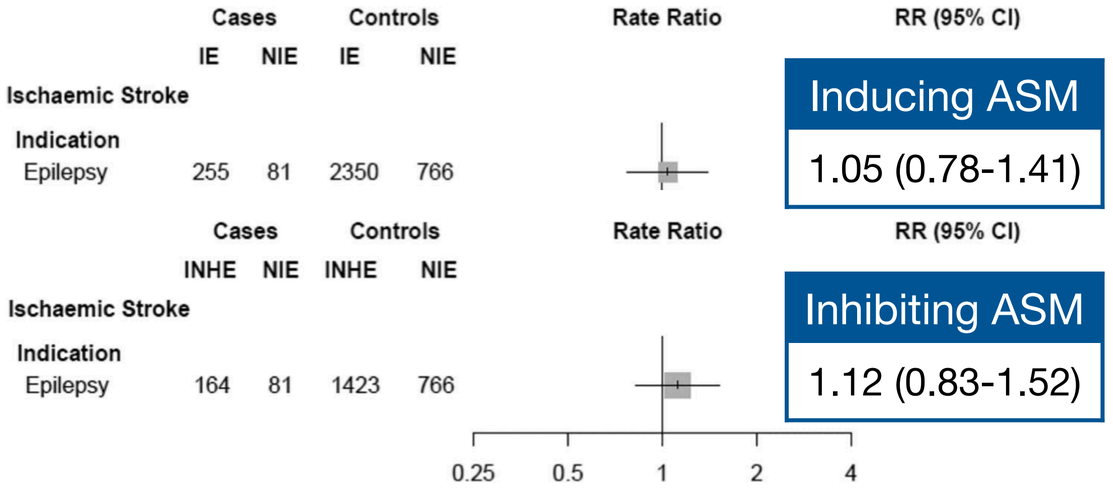
Association between ASM & Risk of Stroke

4,614,807 individuals aged ≥10 years, Danish population
54,693 (1.2%) diagnosed with epilepsy, 46.6% used ASM

	HR for stroke	
Non-ASM treated without previous stroke	1.58 (1.47-1.70)	
ASM treated epilepsy without previous stroke	2.22 (2.09-2.36)	
Individual ASM		
Carbamazepine	reference	
Valproate	**0.86 (0.76-0.96)**	↓
Oxcarbazepine	**1.21 (1.10-1.34)**	↑
Phenobarbital	1.07 (0.97-1.19)	=
Lamotrigine	0.88 (0.76-1.03)	=
Phenytoin	0.96 (0.84-1.10)	=

Insufficient & conflicting evidence

4,614,807 individuals aged ≥18 years,
Population-based cohort
UK Clinical Practice Research Datalink (CPRD)
870 epilepsy vs 8115 controls developed stroke



1. Olesen et al. *Pharmacoepidemiol Drug Saf* 2011; 2. Renoux et al. *BMJ Open* 2015

Patients with epilepsy are at an increased risk of subsequent stroke: A population-based cohort study

Chen-Shu Chang [a,b,1], Chun-Hui Liao [c,d,1], Che-Chen Lin [e], Hsien-Yuan Lane [c,d], Fung-Chang Sung [d,e,*], Chia-Huang Kao [d,f,**]

To investigate incidence & risk of stroke in PWE

Taiwan National Health Insurance claims data, 2000-2008

Age ≥18 years having epilepsy

3812 newly diagnosed epilepsy vs Controls 15,248

Taking high doses of ASMs exhibited a high risk of stroke

	All stroke			Ischemic			Hemorrhagic		
	Event	Rate	aHR	Event	Rate	aHR	Event	Rate	aHR
Comparison	653	7.96	Ref	547	6.67	Ref	106	1.29	Ref
Epilepsy	427	24.08	2.92(2.58–3.30)	349	19.68	2.85(2.49–3.26)	78	4.40	3.30(2.46–4.43)
Anti-epilepsy drug used[a]									
<5 DDD	78	10.44	1.30(1.03–1.64)	61	8.16	1.21(0.93–1.58)	17	2.27	1.75(1.05–2.92)
5–69 DDD	121	21.31	2.58(2.13–3.14)	102	17.96	2.60(2.10–3.21)	19	3.35	2.51(1.54–4.10)
≧70 DDD	228	49.77	5.84(5.02–6.80)	186	40.60	5.68(4.81–6.72)	42	9.17	6.69(4.67–9.58)
P for trend			<0.0001			<0.0001			<0.0001

lower

higher dose

lodel adjusted for AF.

HR: adjusted hazard ratio; rate: incidence rate, per 1000 person-year.

[a] Average DDD, per year.

Chang et al. *Seizure* 2014

Relationships between pre-, clinical stroke, and post-stroke seizures

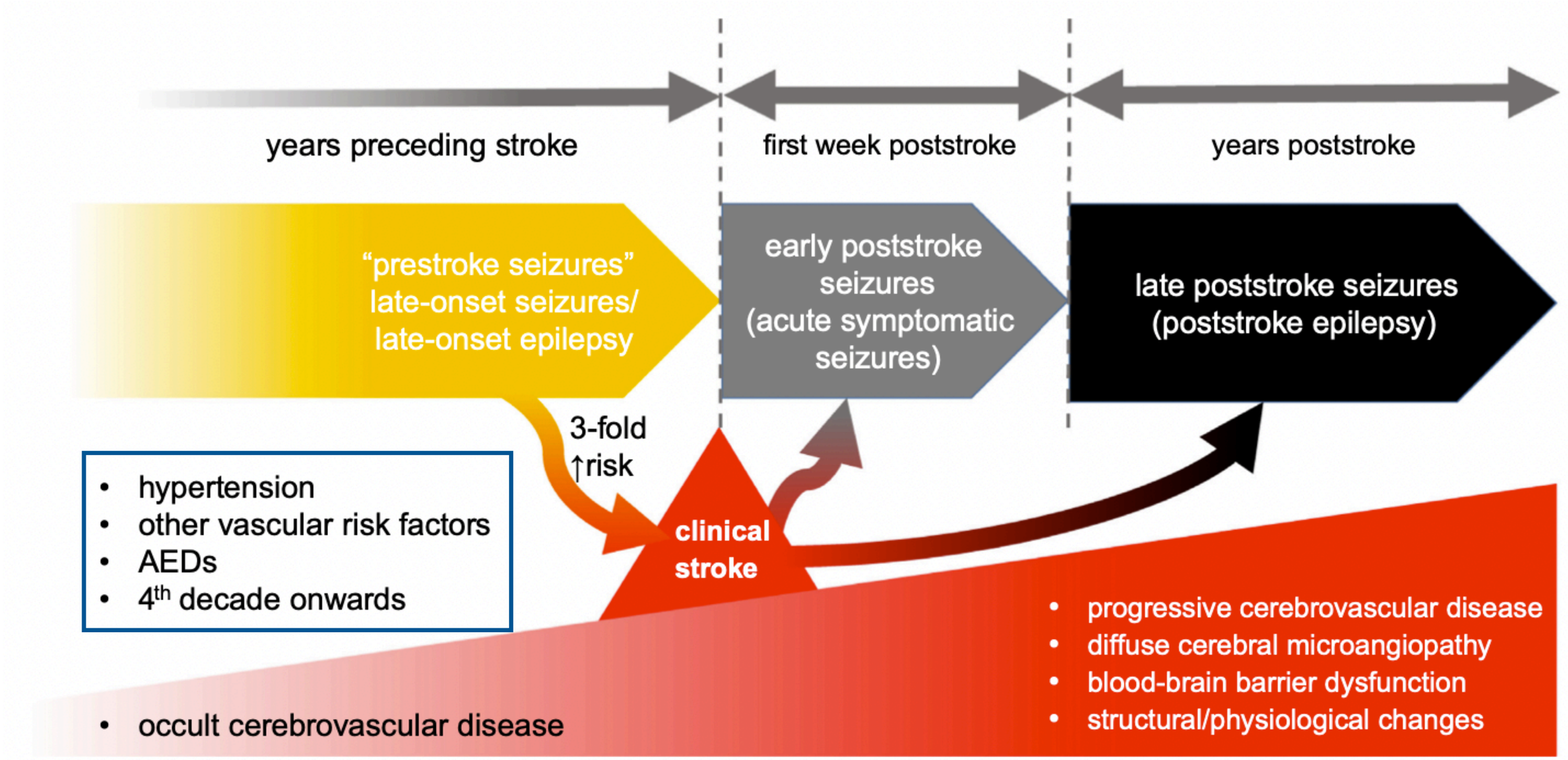


Fig. 1. This schematic depicts the temporal relationships between 'prestroke seizures', clinical stroke, and 'poststroke seizures' and the underlying growing burden of cerebrovascular disease over time.

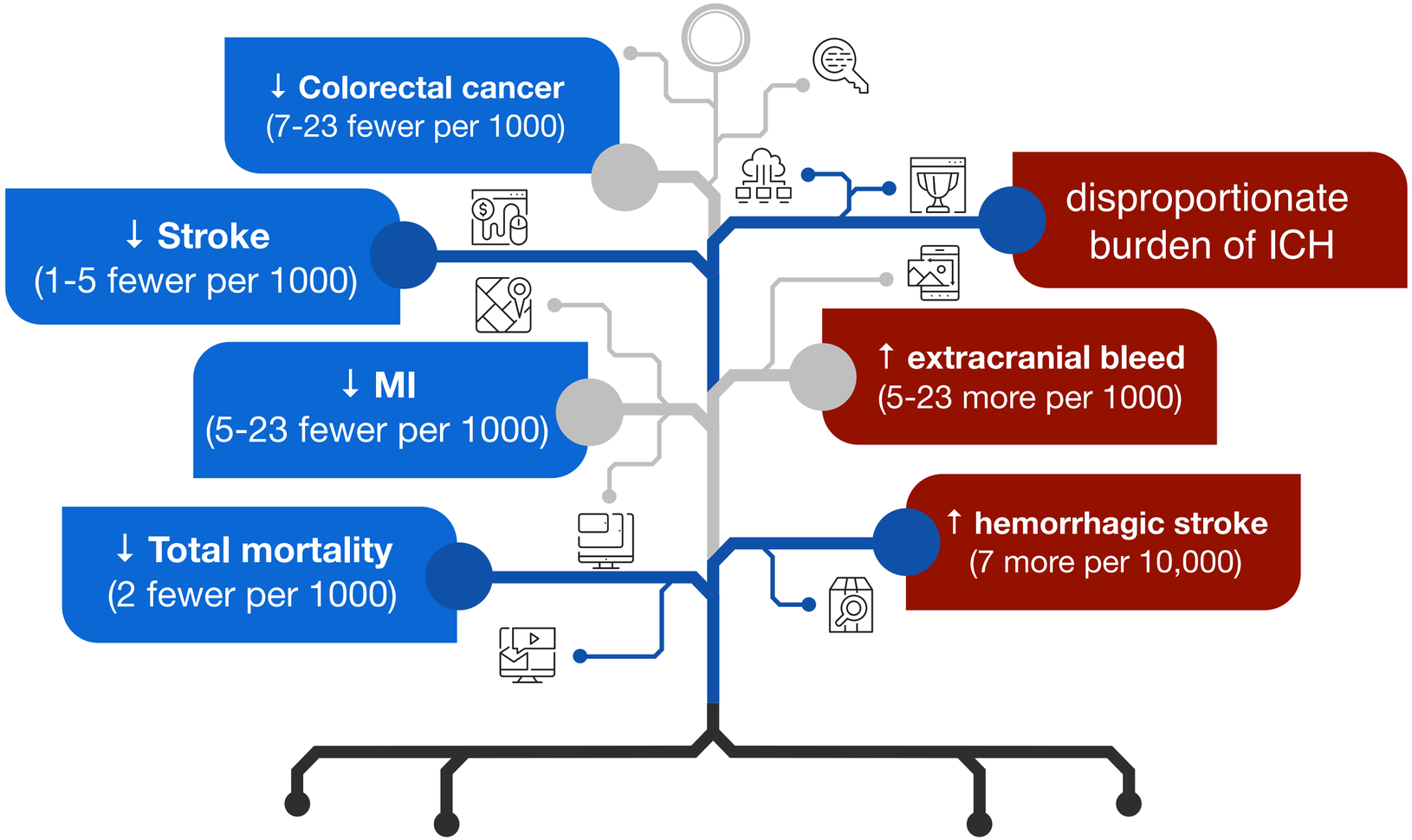
Emsley & Parkes. *Epilepsy Behav* 2020

Clinical Management

- Occult CVD often underlies LOE, relationship between vascular risks & risk of LOE
  - Older with new-onset seizures: “assessment for the presence of cerebrovascular risk factors with an appropriate treatment thereafter”[1]
  - Further studies are needed to elucidate risk-benefit ratio of vascular prevention
- Aspirin for primary prevention of stroke in LOE???
  - AHA/ASA 2014, *reasonable if 10-year cardiovascular(including but not specific to stroke) risk >10%* (Class IIa, level of evidence A), is **NOT** useful in low-risk individuals (Class III, level of evidence A)
  - Cleary 2004, risk of stroke in LOE is 10% in 6 years

1. Scottish Intercollegiate Guidelines Network (SIGN) 2019

Is aspirin for primary prevention justified?



1. Vandvik et al.*Chest* 2012; 2. Whitlock et al. *Ann Intern Med* 2016

Conclusions

- Occult CVD often underlies unexplained late-onset seizure/epilepsy(LOE)
- LOE represent population with high risk of stroke [OR 3.88 (2.76-5.46)[1]]
- *LOE: effective identification & management of modifiable vascular risks*
- Pathophysiology: subcortical small vessel disease & neurovascular unit dysfunction
- ASMs exert different effects on vascular risk markers

1. Wall et al. *Epilepsy behav* 2021

สมัครเป็นสมาชิกครอบครัว Neuro CMU
สแกน qr code

ขอบคุณครับ

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