GÖTEBORGS UNIVERSITET

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

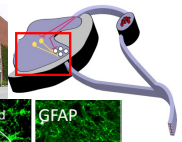
Wallenberg Centre for Molecular and Translational Medicine

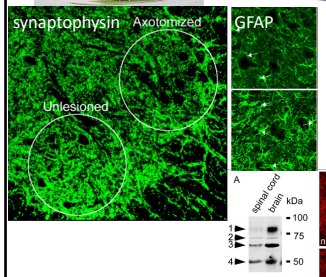
Poststroke epilepsy; epileptogenesis and biomarkers

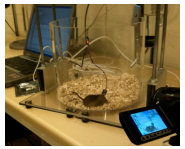
Johan Zelano
MD PhD

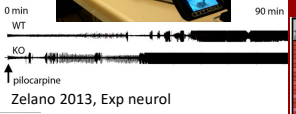
1

From neural networks to epilepsy

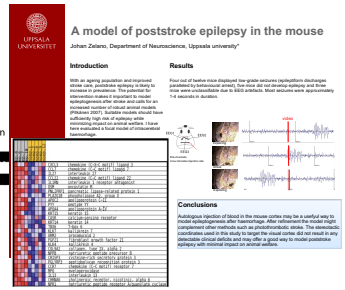








Zelano 2013, Exp neurol



2

Epilepsy after stroke is common

- Cerebrovaskular disease is the most common identifiable cause of epilepsy (14-21%).
- Risk after stroke varies with method. Infarction 6.4% (UK), ICH 13.5% (Finland)
- Risk factors are young age, large stroke, cortikal lokalisation, acute symptomatic sz and bleeding.

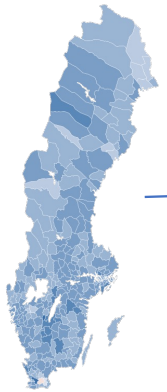
1015 first seiures in Stockholm 2001-2004:

Etiology	%
Stroke	11
Brain tumor, primary	8
Trauma/metastasis/dementia	<3%
Unknown	65%

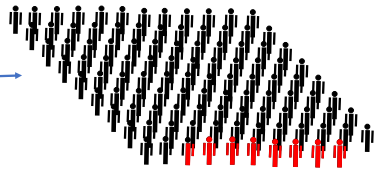
Lahti 2017, Graham 2013, Forsgren 2005, Adelöw 2008

3

Epilepsy after stroke



Riksstroke
Stroke 2005-2010
n = 106 000



Patient register
Epilepsy
n = 7740

Total 7.3%
Infarction 6.4%
ICH 12.4%

Risk factors
Ung ålder
Stor stroke
Blödning
Förmaksflimmer

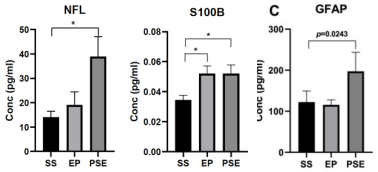
Zelano 2016, Eur stroke journal
Hansen 2017, Plos ONE
Larsson 2019, Seizure

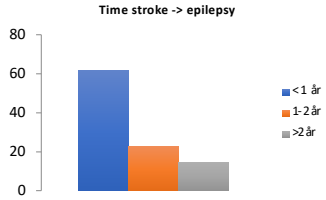
4

Lesion and vulnerability

Acute symptomatic sz: TNF-R1↓ och NCAM↑

PSE: S100B↓ och HSC70↓ in acute phase, but ↑ later.



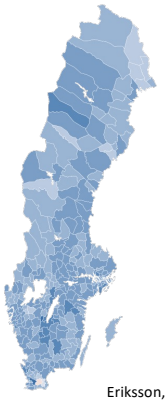


Latency (y)	Alla	ICH	Infarkt
Median (min-max)	1.11 (0.02-9.80)	0.90 (0.02-9.80)	1.16 (0.02-9.41)

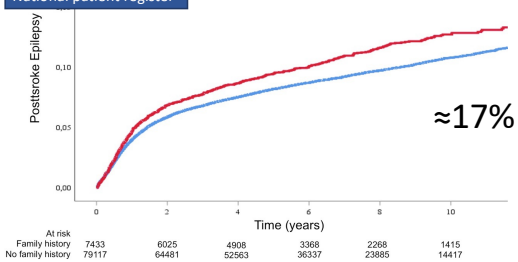
Gui, Zelano 2016, Abraira 2020a,b, Eriksson 2019, Zelano mfl *unpubl*

5

Family history?



Multi generation register
Riksstroke
National patient register



≈17%

Eriksson, Neurology, 2020

VGR/GU PhD-student
Hanna Eriksson

6

Can the risk be reduced?

- Valproate 1 mo after ICH reduces sz risk, but not 1-y risk of PSE (Gilad 2011).
- Statins lower risk PSE? (Etminan 2010, Guo 2015).

Statins	Crude RR	ARR	95%CI
No use	1.00	1.00	1.00
Current use	0.65	0.65	0.46–0.92
Past use	0.67	0.72	0.39–1.30

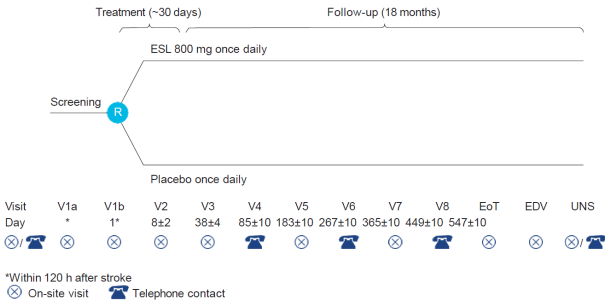
RR of epilepsy, Etminan 2010

In patients w acute symptomatic sz
OR 0.34, 95% CI 0.13–0.88

OR of epilepsy, Guo 2015

7

The quest goes on…



Koepp et al, Epilepsia Open, accepted

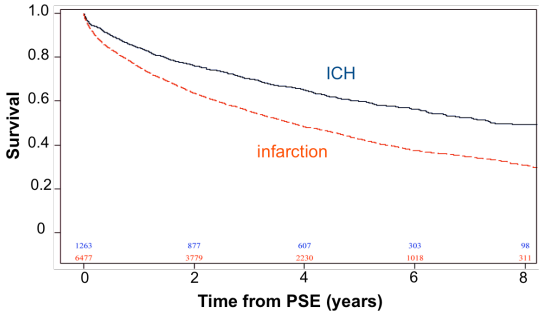
8

Prognosis

106 455 at risk
(9.6%ICH)

HR death:

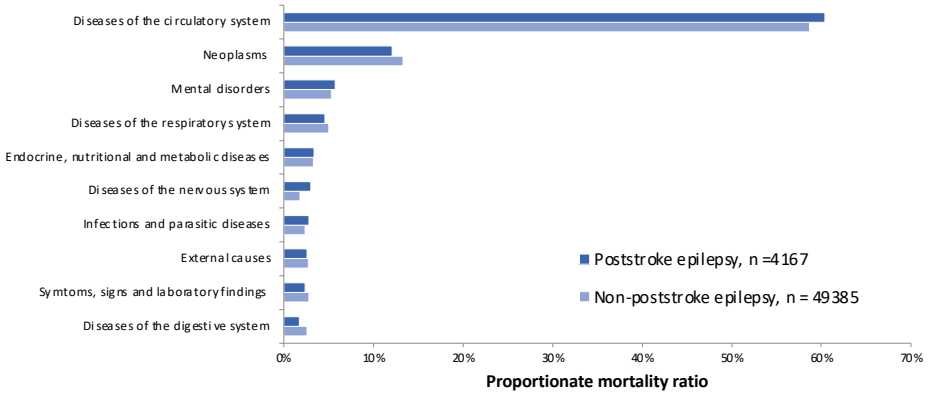
1.69 (1.64-1.74)



Zelano et al ESJ 2016

9

Causes of death

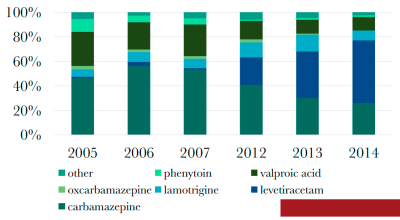


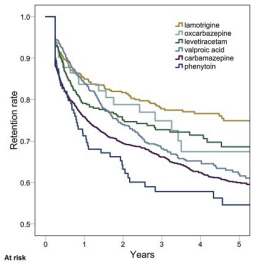
Hansen Zelano 2017

10

ASM and death

Patients w PSE 2005-2014





Larsson 2019

Research

JAMA Neurology | Original Investigation

Association Between Antiseizure Drug Monotherapy and Mortality for Patients With Poststroke Epilepsy

David Larsson, MD; Arton Baftiu, PhD; Cecilie Johannessen Landmark, PhD; Mia von Euler, MD, PhD; Eva Kumlien, MD, PhD; Signild Åsberg, MD, PhD; Johan Zelano, MD, PhD

Larsson 2022

11

Pre stroke seizures

Results

Seizures preceding stroke

Nineteen of the 675 patients (3%) registered with the Oxfordshire community stroke project gave a history of one or more seizures before their first stroke or had documentation of past seizures in their medical record.

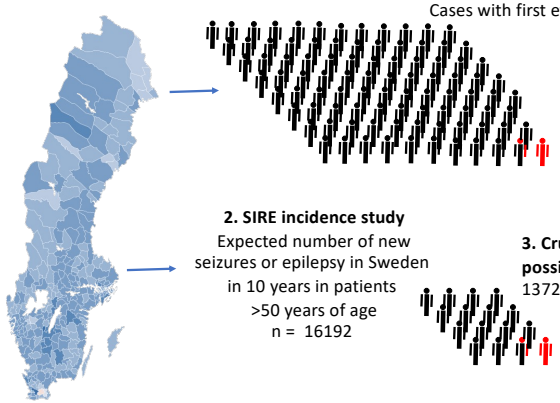
= 1.6%

Eleven of the 19 patients had had a seizure in the year before the stroke: in seven this was a first seizure, and four of these seven patients had partial motor seizures in the same limb as was subsequently affected by the stroke.

Burn 1997

12

Pre-stroke seizures



1. National stroke register
Cases with first efter stroke >60 år 2005-2010
n = 92596

Strokes preceeded by a first seizure or epilepsy diagnosis <10 years, n = 1372 (1.5%)

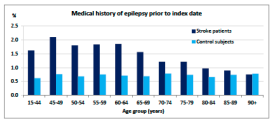
2. SIRE incidence study
Expected number of new seizures or epilepsy in Sweden in 10 years in patients >50 years of age
n = 16192

3. Crude estimate of proportion of possibly heraldic seizures:
1372 / 16192 = 8.5 %

Zelano, Seizure, 2017

13

Prevention?



Late-onset seizure in 123 005 patients with first-ever stroke and 250 506 controls (Larsson, Zelano 2021)

Late-Onset Seizures Trial of vascular risk Investigation and Treatment (LOSTIT)

Late-onset seizure → **-workup**
Blood pressure
Fasting glucose and lipids
Urine analysis
Physical activity/smoking
Smoking, physical activity
SCORE/SCORE-OP
→ **Risk category**
Very high
High → Primary prevention
Moderate
Low

Clinical study
Informed consent → V1 → V2 EOS → Prevalence of modifiable CVD risk factors? **Paper I**
n = 420
Short-term *ΔCVD risk?* ***Paper II***

Late-onset seizure 2024-25 → Neurologist -screen (standard of care) → Primary vascular prevention according to guidelines

Register study
Historic controls: Late-onset seizure 2020-23 (4 years)
Cluster intervention: Late-onset seizure 2024-25 (2 years)
n > 420
n > 840
Providers start with -screen as standard of care
Included: All patients at participating providers and ICD-code for seizure (no exclusion criteria.)
Baseline data: existing CVD, drug prescription for CVD/diabetes, co-morbidities

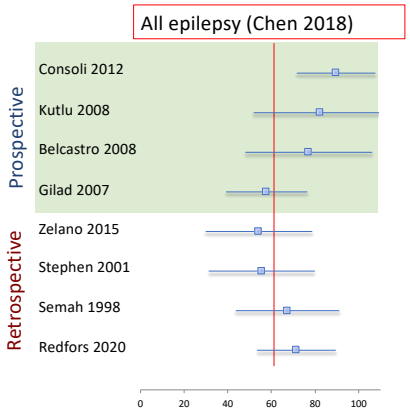
Events
Death? Cardiovascular event?
Epilepsy? **Paper III-IV**

Time-to-event analysis
First late-onset seizure
10 years (if necessary)

14

Seizure prognosis?

- Easy to treat?.
- Some studies 80-90% on first ASM.
- Short latency stroke-epilepsy indicates worse treatment response.[1]



1. Lattanzi et al, Eur J Neurol, 2022

15

Summary

- PSE is an indicator of high vascular risk.
- Interesting questions:
  - can vascular primary prevention after a late first seizure prevent stroke or epilepsy?
  - can better ASM treatment reduce mortality?
  - can PSE be prevented?

16

PREDICT

en biobanksstudie av epilepsi i VGR

Vill du delta i forskning om epilepsi?

Vi rekryterar nu vuxna personer i hela Västra Götalandsregionen som vill delta i en studie av epilepsi.

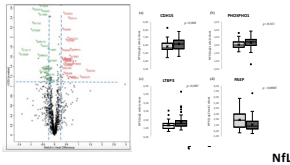
Patient — Blood •whole •serum •plasma — CSF (if LP) — Survey (yearly)

Study center — Medical records: Visits, clinical data, Investigations (lab, imaging, EEG) — National registers: Socioeconomic data, Diagnoses, Prescribed drugs, Cause of Death

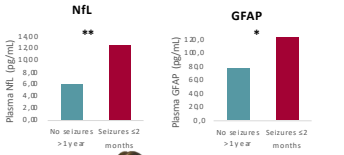
→ Database — Biobank — Biobank Väst

Proteomics — SciLifeLab Proteomics and Olink — Brain injury markers

Proteomics



Brain injury markers



Eriksson 2020, Epilepsy and behav
Banote 2021, Epilepsy Research

WCMTM PhD-student
Sarah Akel

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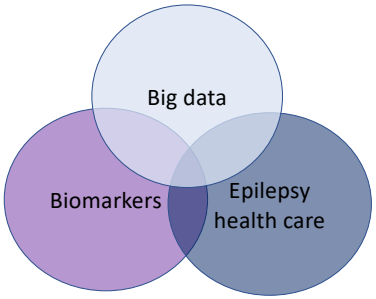
17

Advance neurobiological understanding, diagnosis, and treatment of epilepsy through big data, precision medicine, biomarkers, and clinical trials.



POST DOC WANTED!

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18

Ongoing or planned projects PSE

- Biochemical markers of seizures and side effects in PSE (PREDICT)
- Seizure prognosis (PREDICT)
- (fMRI study)
- Register study of long term outcomes (ASM, side effects - planned)
- LOSTIT (planned)

19

20

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21