Mahidol University
Faculty of Medicine Siriraj Hospital

Comprehensive Management of Post Stroke Seizure and Epilepsy

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DEFINITION

- Acute symptomatic seizures
- Late poststroke seizure
- Poststroke epilepsy

Epilepsia, 51(4):671–675, 2010
doi: 10.1111/j.1528-1167.2009.02285.x

SPECIAL REPORT

Recommendation for a definition of acute symptomatic seizure

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Summary

Purpos seizure teria u seizure **Metho** demiol **Results** ical sei close insult. seizure stroke, intracr hematoma; at the presence of an active central nervous system (CNS) infection; or during an active phase of multiple sclerosis or other autoimmune diseases. In additi a diagnosis of acute symptomatic seizure should be ments l or ation genic be ately com- t the nder- with which tom- neta- bolic dysfunction still require a clear identification.

KEY WORDS: Epidemiology, Definition, Acute, symp-

"Acute symptomatic seizure is defined as a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult. Suggestions are made to define acute symptomatic seizures as those events occurring within 1 week of stroke, traumatic brain injury, anoxic encephalopathy, or intracranial surgery"

Beghi E, et al. Epilepsia, 51(4):671–675, 2010

- Acute symptomatic seizures

: seizures occur within one week after acute stroke

- Late poststroke seizure

: unprovoked seizure that occurs > 1 week after acute stroke

- Poststroke epilepsy

ILAE OFFICIAL REPORT

A practical clinical definition of epilepsy

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Epilepsia, 55(4):475–482, 2014
doi: 10.1111/epi.12550

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Summary

Epilepsy was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. The International League Against Epilepsy (ILAE) accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years. "Resolved" is not necessarily identical to the conventional view of "remission or "cure." Different practical definitions may be formed and used for various specific purposes. This revised definition of epilepsy brings the term in concordance with common use.

KEY WORDS: **Epilepsy, Seizure, Definition, Unprovoked, Recurrence.**

Table 2. Operational (practical) clinical definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be *resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Its intent is to encompass circumstances for which some practitioners and expert epileptologists manage patients as if epilepsy is present after a single unprovoked seizure, because of a very high risk of recurrence.

Such examples may include patients with a single seizure occurring at least a month after a stroke or a child with a single seizure conjoined with a structural or remote symptomatic etiology and an epileptiform electroencephalography(EEG) study

Epilepsia, 50(5):1102–1108, 2009
doi: 10.1111/j.1528-1167.2008.01945.x

FULL-LENGTH ORIGINAL RESEARCH

Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure

***Dale C. Hesdorffer, †Emma K. T. Benn, ‡Gregory D. Cascino, and §¶W. Allen Hauser**

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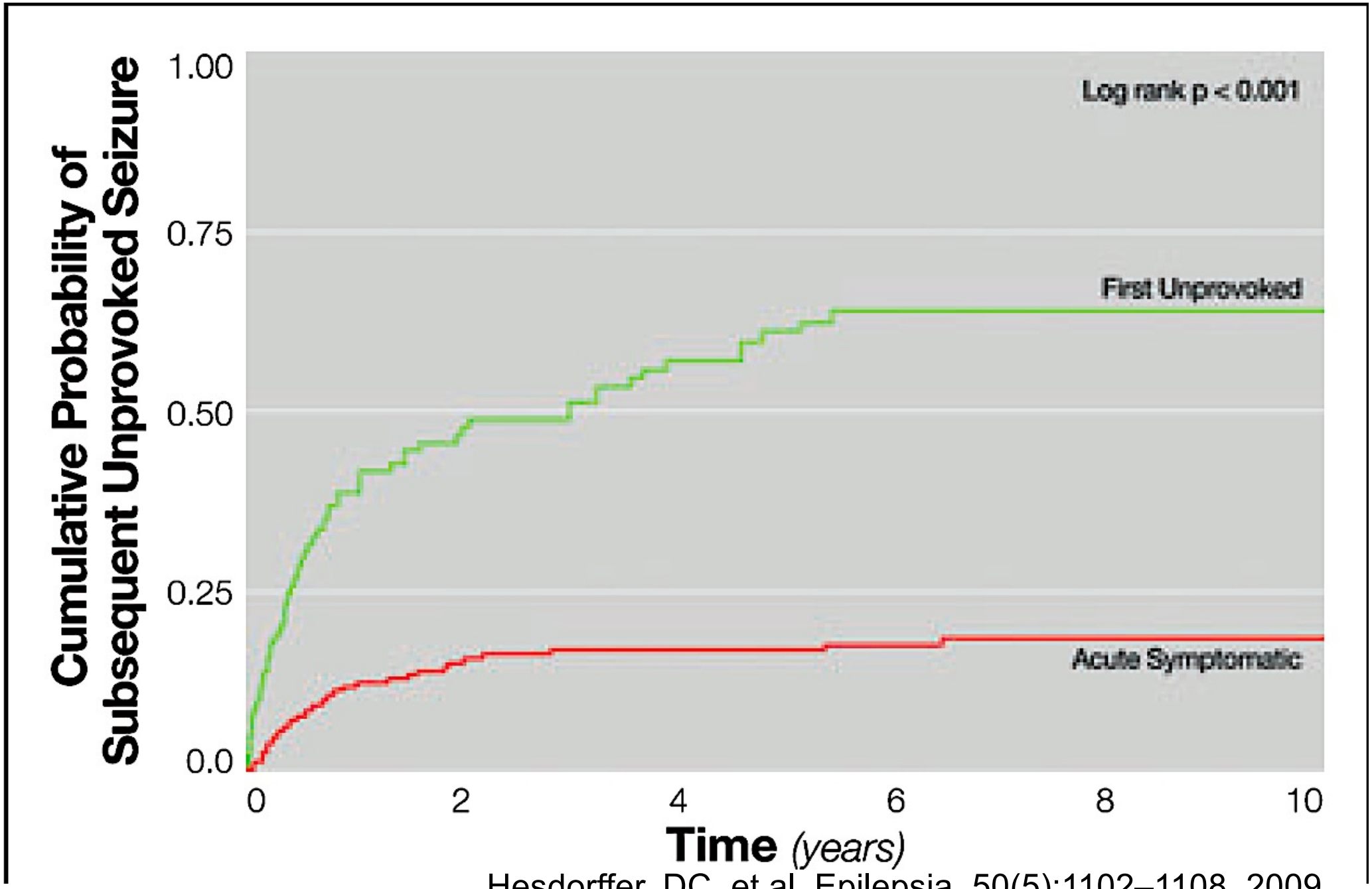
- To compare mortality and subsequent unprovoked seizure risk in a population-based study of acute symptomatic seizure and first unprovoked seizure due to static brain lesions
- Subjects were residents of Rochester, Minnesota, identified through the Rochester Epidemiology Project's records-linkage system between 1/1/55 and 12/31/84.
- Information was collected on age, gender, seizure type, etiology, status epilepticus (SE), 30-day and 10-year mortality, and subsequent episodes of unprovoked seizure.

Hesdorffer, DC, et al. Epilepsia, 50(5):1102–1108, 2009

- 262 individuals experienced a first acute symptomatic seizure and 148 individuals experienced a first unprovoked seizure, all due to static brain lesions.



Hesdorffer, DC, et al. Epilepsia, 50(5):1102–1108, 2009

Risk of subsequent unprovoked seizure

	Acute symptomatic seizure	First unprovoked seizure	p
Stroke	33.0% (95% CI = 20.7–49.9%)	71.5% (95% CI = 59.7–81.9%)	p = 0.001
Traumatic brain injury	13.4% (95% CI = 7.0–24.8%)	46.6% (95% CI = 30.4–66.3%)	p < 0.001
CNS infection	16.6% (95% CI = 9.5–28.0%)	63.5% (95% CI = 21.2–98.6%)	p = 0.010

Hesdorffer, DC, et al. Epilepsia, 50(5):1102–1108, 2009

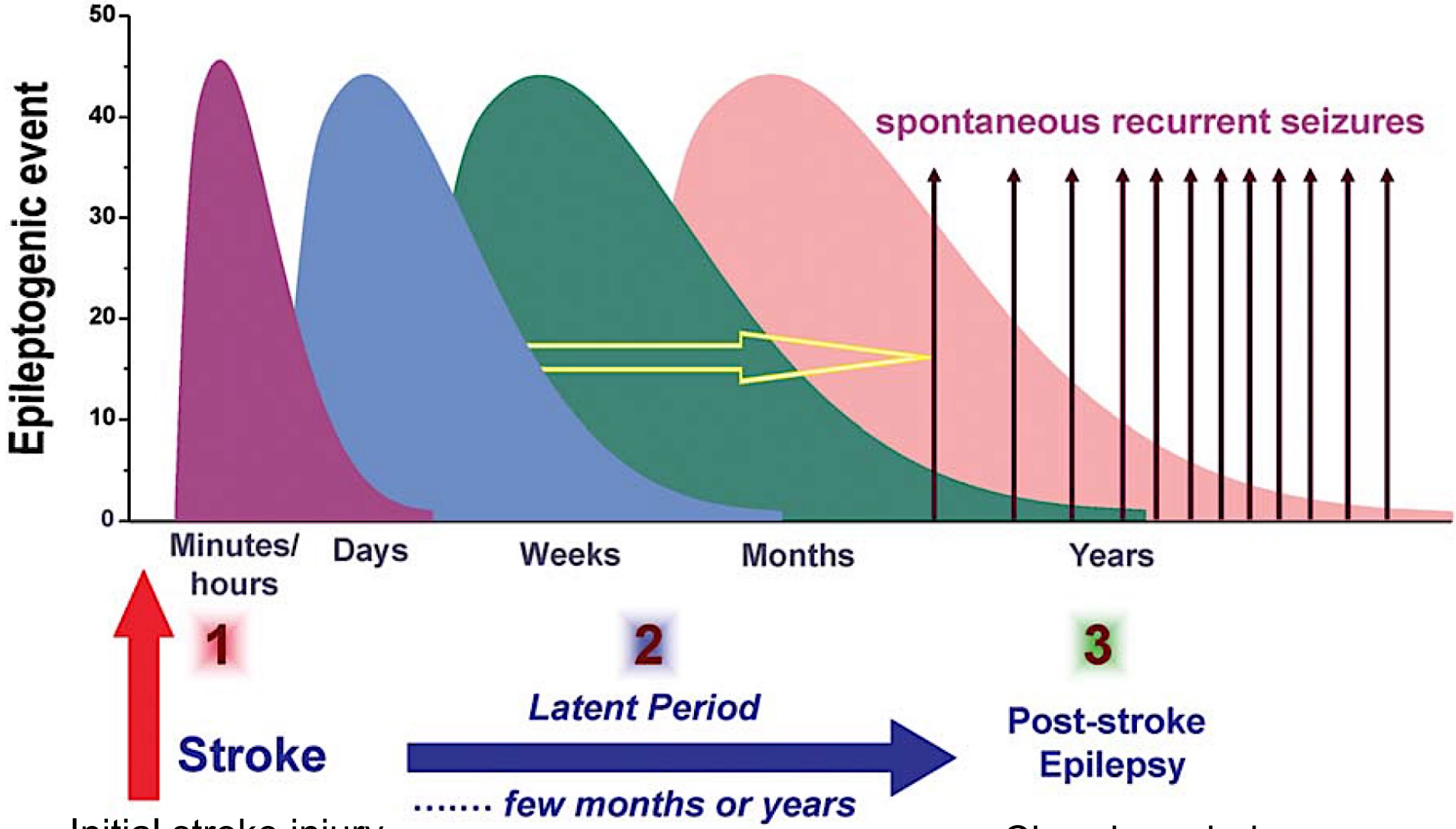
- Acute symptomatic seizures
- Late poststroke seizure

=?

- Poststroke epilepsy

“ The new definition is not uncontroversial, mostly due to conflicting data on the actual recurrence risk of seizures after a first late-poststroke seizure and whether a diagnosis benefits patients”

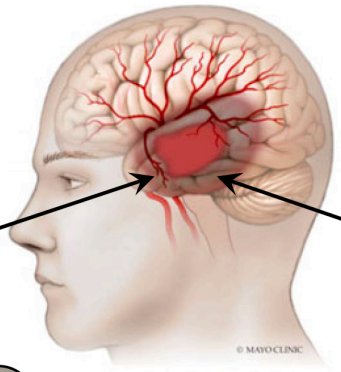
POSTSTROKE EPILEPTOGENESIS



Initial stroke injury
Epileptogenic event

Chronic period

Reddy DS, et al. J or Neurosci Res 2017;95:1000-16



- Hypoperfusion/reperfusion
  - Hypoxia
    - Glutamate-induced excitotoxicity
    - Reduced GABAergic inhibition
  - Ischemic encephalopathy
- Blood–brain barrier disruption
  - Activation of astrocytes
    - TGFβ, TNFα, IL-6 (neuroinflammation)
    - Protease activated receptor-1
  - K^+ inc
  - Glutamate-induced excitotoxicity
  - Thrombin-induced depolarization
- Ion channel dysfunction
  - Intracellular Na^+ and Ca^{++} inc
  - Extracellular K^+ inc

  } Depolarization
- Altered gene expression
  - Upregulation of inflammation and cell death
  - Alteration of neuronal plasticity
- Hemosiderin deposition

- Chronic inflammation
- Gliotic scarring
  - Leukoaraiosis
  - Angiogenesis
  - Neurogenesis
  - Selective neuronal loss
- Altered synaptic plasticity
- Deafferentation
- Collateral sprouting
- Selective neuronal loss

} Hyperexcitablity + neuronal synchrony

- Siderosis
- Comorbidities with stroke
  - Hyperglycemia (DM)
  - Dementia
  - Hypertension
  - Depression and use of antidepressants
  - Alcoholism

Early seizures

Late seizures

Stroke-related epilepsy

Feyissa AM, et al. Eur J Neurol 2019, 26: 18–26, e1–e3

EPIDEMIOLOGY OF POSTSTROKE EPILEPSY

- Major cause of epilepsy after middle age
- long-term overall cumulative risk of PSE after a cerebrovascular event varies between 3% and 13%

Cumulative risk of poststroke epilepsy from different series

	Cumulative risk at the end of the study (3-10 yrs)	Remarks
Overall risk	3.2 (7 yrs) 12.4% (10 yrs)	Include series with follow up>3 yrs
Ischemic stroke	2.3% (3 yrs) 4.4% (10 yrs) 8% (9 yrs)	Include prospective series with follow up > 3 yrs
ICH	18.2%(10 yrs) 23% (9 yrs)	Include only series with adequate no. of ICH with follow up > 3 yrs
SAH	12.5% (5 yrs) 21.7% (10 yrs)	Include only series with adequate no. of SAH with follow up > 3 yrs

Zelano J. Ther Adv Neurol Disord 2016; 9:424–35

- Predictors include
  - Stroke severity
  - Cortical locations
  - Hemorrhage
  - Total anterior circulation infarcts
  - Young age at stroke
  - Early seizures

Prediction model	Stroke type	Cohort size (*n*)	Follow-up (years)	Risk factors scored (values)	STRE predictions
SeLECT score (maximum score 9) [28]	Ischaemic	1200	5	Severity of stroke (0–2) Large-artery atherosclerosis (0–1) ESs (0–3) Cortical involvement (0–2) Territory of MCA involvement (0–1)	Total score ≥ 6 Sensitivity 18.2% Specificity 96.7% PPV 27.2% NPV 94.6%
Post-Stroke Epilepsy Risk Scale (PoSERS) (maximum score 8) [89]	Ischaemic and hemorrhagic	264	1	Supratentorial stroke (0–1) Cortical ICH (0–1) Cortical or subcortical ischaemic stroke (0–1) Ischaemia + ongoing neurological deficit (0–1) Stroke-related neurological deficit, mRS>3 (0–1) Vascular encephalopathy (0–1) ESs (0–1) LSs (0–1)	Total score ≥7 Sensitivity 70% Specificity 99.6% PPV 87.5% NPV 98.8%
CAVE score (maximum score 4) [90]	ICH	993	2.7	Cortical involvement (0–1) Age <65 years (0–1) Volume >10 mm (0–1) ESs (0–1)	Score ≥2 Sensitivity 81% Specificity 89% PPV 18% NPV 97%

CAVE, Cortical involvement-Age-Volume-Early seizures; ES, early seizure; ICH, intracerebral hemorrhage; LS, late seizure; MCA, middle cerebral artery; mRS, Modified Rankin Scale; NPV, negative predictive value; PPV, positive predictive value; SeLECT, severity of stroke-large-artery atherosclerotic aetiology-early seizures-cortical involvement- territory of middle cerebral artery involvement.

Galovic M, et al. Lancet Neurol 2018; 17: 143–52
Strzelczyk A, et al. J Neurol 2010; 257: 1322–6
Haapaniemi E, et al. Stroke 2014; 45: 1971–6

TREATMENT DECISION IN POSTSTROKE EPILEPSY

Acute symptomatic seizures

- There is no evidence to date that treatment with AEDs prevents the development of PSE and the risk of seizure after stroke is relatively low, so primary prevention is usually not appropriate
- Short-term treatment is often initiated if multiple early seizures occur or after a single seizure in cases of ICH or hemorrhagic transformation

AEDS SELECTION IN POST STROKE EPILEPSY

Consideration for using AEDs in post stroke epilepsy

- Efficacy
- Side effects
- Drug interaction

AEDs in the elderly

Study	Type of epilepsy	Discontinuation rates	Efficacy
KOMET (Pohlmann-Eden, 2016)	> 60 yo	LEV<VPA<CBZ	similar
Rowan, 2005	New onset epilepsy >60 yo VA population	LTG<GBP<CBZ	similar
Werhahn, 2015 (RCT)	New onset epilepsy >60 yo	LEV<LTG<CBZ	similar

FULL-LENGTH ORIGINAL RESEARCH

A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy

*[1]Konrad J. Werhahn, †‡Eugen Trinka, †‡Judith Dobesberger, ‡Iris Unterberger, §Petra Baum, ¶Maria Deckert-Schmitz, #Tobias Kniess, **Bettina Schmitz, *Viviane Bernedo, ††Christian Ruckes, ††Anne Ehrlich, and ‡‡[2]Günter Krämer

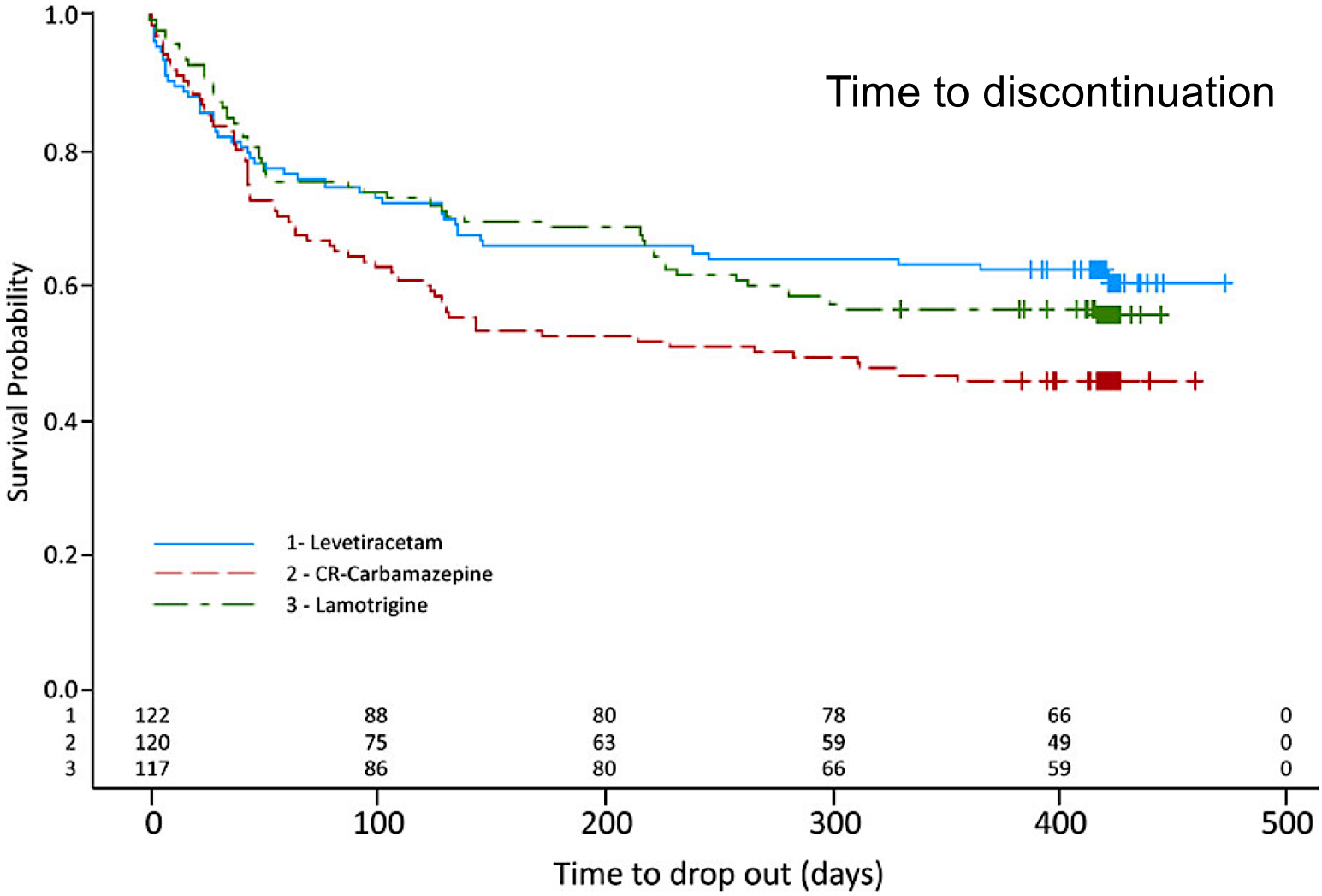
Objective: To compare the effectiveness of controlled-released carbamazepine (CRCBZ) to levetiracetam (LEV) and to lamotrigine (LTG) in elderly patients with newly diagnosed focal epilepsy

Methods: Randomized, double-blind, parallel-group trial conducted between January 2007 and August 2011, in 47 ambulatory or hospital sites in Germany, Austria, or Switzerland. Eligible participants were aged ≥60, had new-onset epilepsy, had no acute illness as the cause of their seizures, and had no contraindication to the drugs in the trial

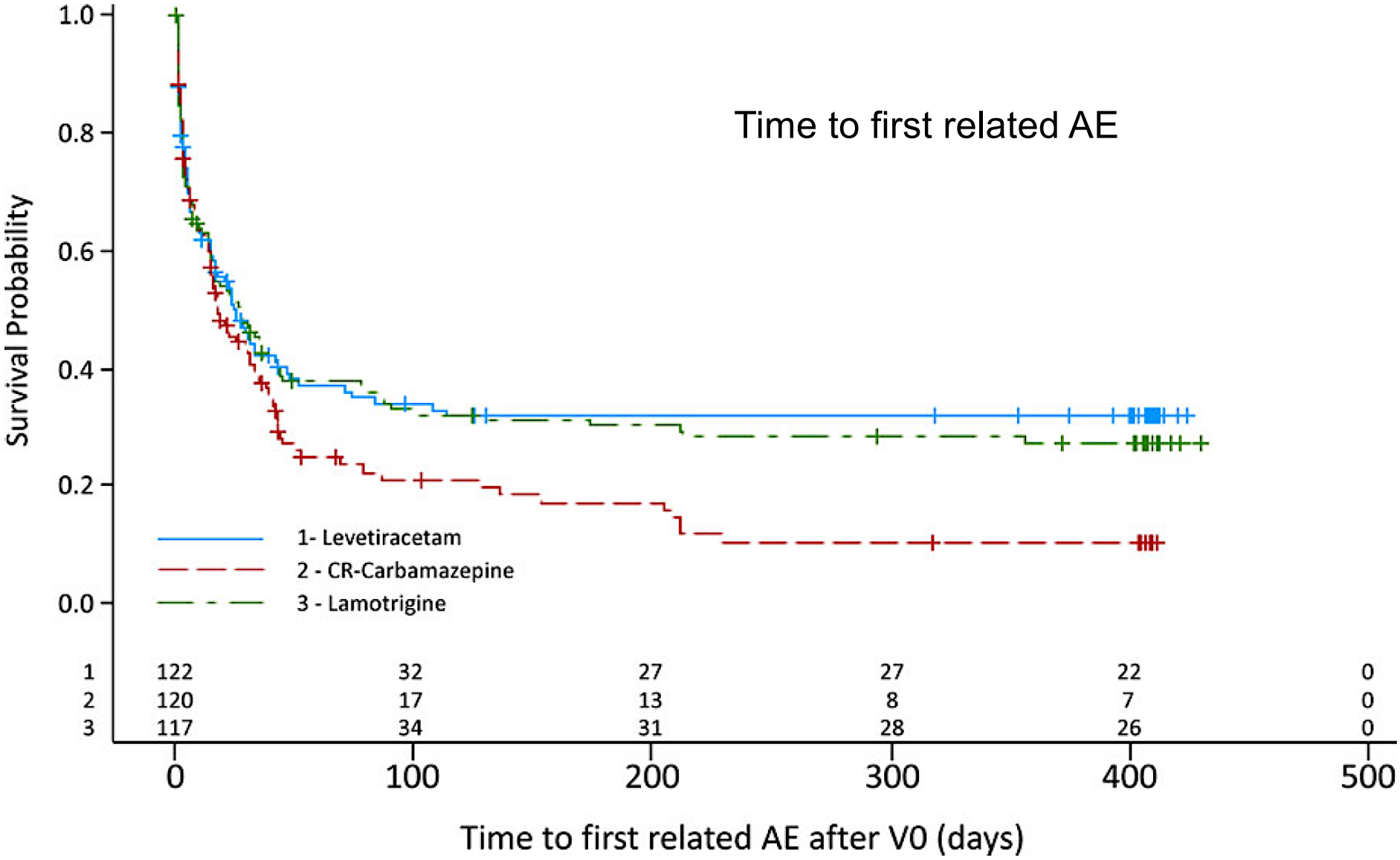
361 randomized patients, 359 were included (CR-CBZ n = 121, LTG n = 117, LEV n = 122) in the modified intent-to-treat population (mean age [range] 71.4 [60–95] years).

Epilepsia 2015, 56:450–459

At week 58, the retention rate for LEV was significantly higher than for CR-CBZ (61.5% vs. 45.8%, p = 0.02), and similar to LTG (55.6%). Seizure freedom rates at weeks 30 and 58 were not different across the groups.



Epilepsia 2015, 56:450–459



Epilepsia 2015, 56:450–459

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Randomized controlled trials of antiepileptic drugs for the treatment of post-stroke seizures: A systematic review with network meta-analysis

F. Brigo[a,b,*], S. Lattanzi[c], J. Zelano[d,e], N.L. Bragazzi[f], V. Belcastro[g], R. Nardone[b,h], E. Trinka[h,i,j]

Results:
Only 2 RCTs were included, one comparing levetiracetam (LEV) with CR-CBZ and the other comparing lamotrigine (LTG) with CR-CBZ.

- No significant difference was found in seizure freedom between either LEV or LTG and CR-CBZ.
- Occurrence of AEs were lower for LEV and LTG than for CR-CBZ.
- Indirect comparisons showed:
  - No difference between LEV and LTG for seizure freedom (OR 0.86; 95%CI: 0.15–4.89).
  - Occurrence of AEs was higher for LEV than for LTG (OR 6.87; 95%CI: 1.15–41.1).

Brigo F, et al. Seizure 2018;61: 57–62

Study	Comparisons	Study design	Study phases
Gilad et al., 2007	LTG versus CR-CBZ	Monocentric, randomised, open-label trial	1. Titration: LTG dose increase by 25 mg/week up to 200 mg/day (possible further increase of 50 mg/week until suitable response); CR-CBZ: dose increase by 100 mg/week up to 600 mg/day (possible further increase of 100 mg/day until suitable response);
Consoli et al., 2012	LEV versus CR-CBZ	Multicentre, randomised, open-label trial	1. Titration: 2 weeks; LEV starting dose 500 mg/day (250 mg twice daily); CR-CBZ starting dose 200 mg/day (100 mg twice daily) 3. Maintenance: 52 weeks; LEV 1000 mg/day (500 mg twice daily; possible up-titration to maximum of 3000 mg/day); CR-CBZ 600 m/day (300 mg twice daily; possible up-titration to maximum of 1600 mg/day)

Conclusions:

- Direct and indirect comparisons did not find a difference in seizure freedom between the various AEDs, probably because of the small number of patients included.
- LEV and LTG appears better tolerated than CR-CBZ
- LEV seems associated with more AEs than LTG.
- Further studies are required to provide robust evidence on efficacy and tolerability of AEDs for treating poststroke epilepsy

Brigo F, et al. Seizure 2018;61: 57–62

Consideration for using AEDs in post stroke epilepsy

- Efficacy
- Side effects
- Drug interaction

IV AEDs for established SE

	Route of administration	Adult dose
Phenytoin	IV (<50 mg/min)	15-20 mg/kg
Fosphenytoin	IV (<100 mg PE/min)	15-20 mg PE/kg
Phenobarbital	IV (<100 mg/min)	10-20 mg/kg
Valproate	IV (50-100 mg/min)	20-30 mg/kg
Levetiracetam	IV (100 mg/min)	2000-4000 mg
Lacosamide	IV (30-60 min/ up to 15 min)	200-400 mg

Shorvon S. Curr Opin Neurol 2011;24:165–170

Caution of SE of AEDs in elderly

AEDs	Special precautions
Phenobarbital	Drowsiness, cognitive dysfunction May reduce effects of other drugs (enzyme inducer)
Phenytoin	Reduced metabolism and clearance Reduced protein binding → increased free fraction Increase incidence of adverse effects PHT level may be increased by amiodarone, cimetidine, isoniazid, trazodone May reduce effects of other drugs (enzyme inducer)
Carbamazepine	Increase incidence of adverse effects May reduce effects of other drugs (enzyme inducer) Hyponatremia
Sodium valproate	Drowsiness, parkinsonism Thrombocytopenia
Oxcarbazepine	Increase incidence of adverse effects Hyponatremia
Topiramate	Cognitive side effects at higher dosage (can be avoided by slow titration)

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Hyperlipidemia in patients newly treated with anticonvulsants: A population study

Scott Mintzer[1] | Misung Yi[2] | Sarah Hegarty[2] | Vittorio Maio[3] | Scott Keith[2]

Objective: To determine the incidence of hyperlipidemia after first anticonvulsant treatment for seizures, using a large US administrative claims database.
Results: Of 11,374 subjects, 8778 (77%) were prescribed noninducers and 2596 (23%) were prescribed inducers.

New hyperlipidemia diagnoses were seen in 14.6% of the patients started on EIAEDs and 10.7% of the patients started on NEIAEDs (P < .001).
After accounting for covariates, EIAED was still associated with 23% higher odds of a subsequent diagnosis of hyperlipidemia (OR = 1.225, 95% confidence interval = 1.066-1.408, P 0.004).

Mintzer S, et al. Epilepsia. 2020;61:259–66.

Unadjusted results among patients treated with inducing or noninducing AEDs

	All subjects		Inducers		Noninducers		
	n	%	n	%	n	%	*P*
Hyperlipidemia	1316	11.57%	379	14.60%	937	10.67%	<.0001
Cardiovascular diseases	682	6.00%	221	8.51%	461	5.25%	<.0001
Hyperlipidemia or cardiovascular diseases	1841	16.19%	546	21.03%	1295	14.75%	<.0001

Fully adjusted analysis results for association of incident hyperlipidemia diagnoses in patients newly prescribed AEDs

Effect	Odds ratio	95% CI, low-high	*P*
Inducing vs noninducing drug	1.225	1.066-1.408	.004[a]
Age, per 10-y increase	1.072	1.035-1.110	<.001[a]
Male sex	1.211	1.070-1.370	.002[a]
Year of diagnosis	0.824	0.777-0.873	<.001[a]

Consideration for using AEDs in post stroke epilepsy

- Efficacy
- Side effects
- Drug interaction

Interaction with cardiac drugs

- Phenytoin → ⬇ amiodarone level (CYP induction)
  ⬇ digoxin level (upreg. P-gp)
- Enzyme inducers
  → ⬇ calcium channel blocker level
  ⬇ beta blocker level
- Verapamil and diltiazem inhibits carbamazepine metabolism

- Potential interaction of EIAEDs with drug used in secondary prophylaxis

Drug interaction with warfarin

- Metabolites through CYP3A4, 2C9
- Phenytoin, phenobarbital and carbamazepine reduce the concentration of warfarin by up to 50-65%
- Phenobarbital and carbamazepine also reduce the anticoagulation effects of warfarin metabolites
- Newer AEDs do not have significant interaction with anticoagulant

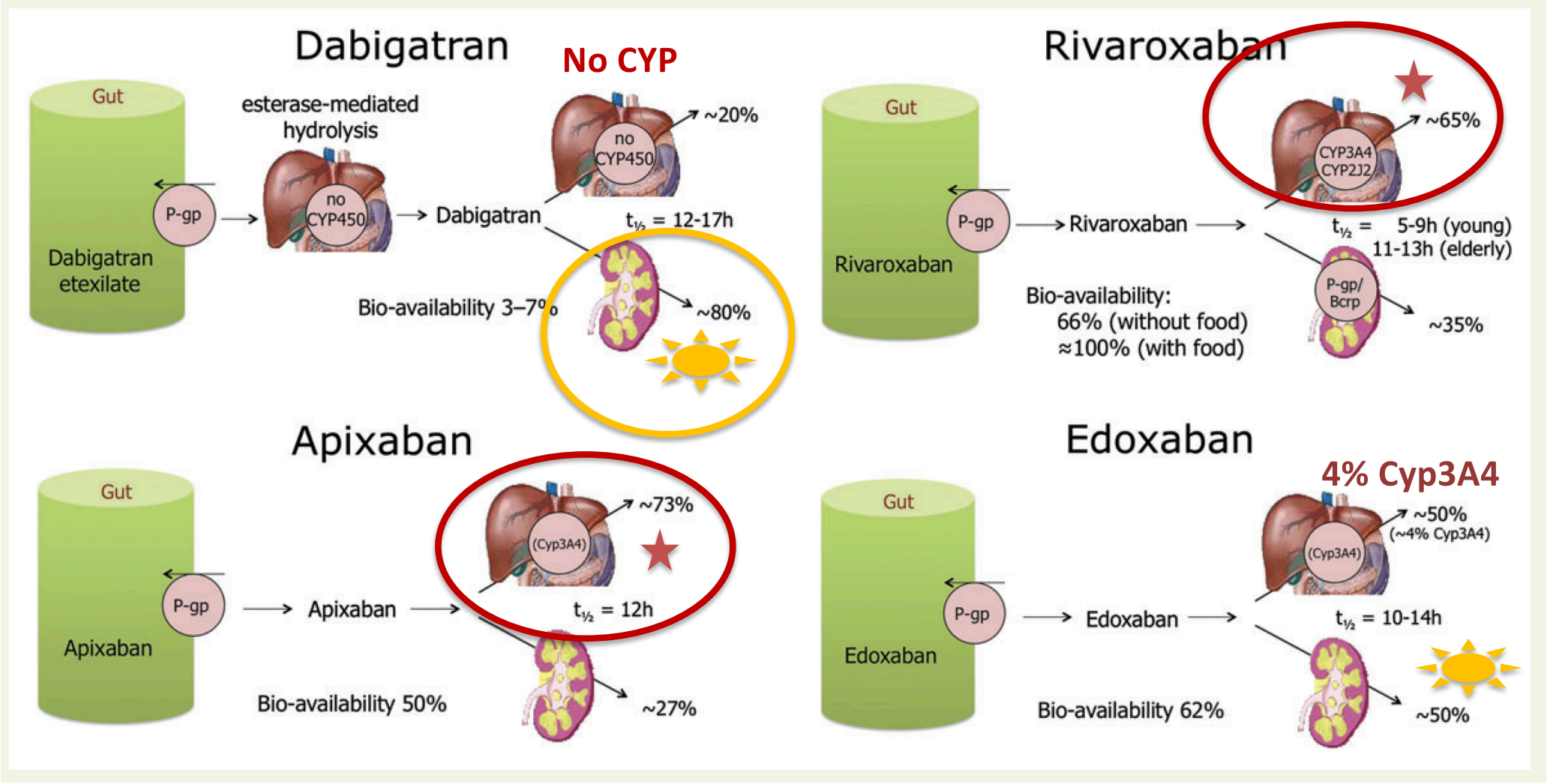
Interaction between AEDs and NOACs

Table 2 **Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF**

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

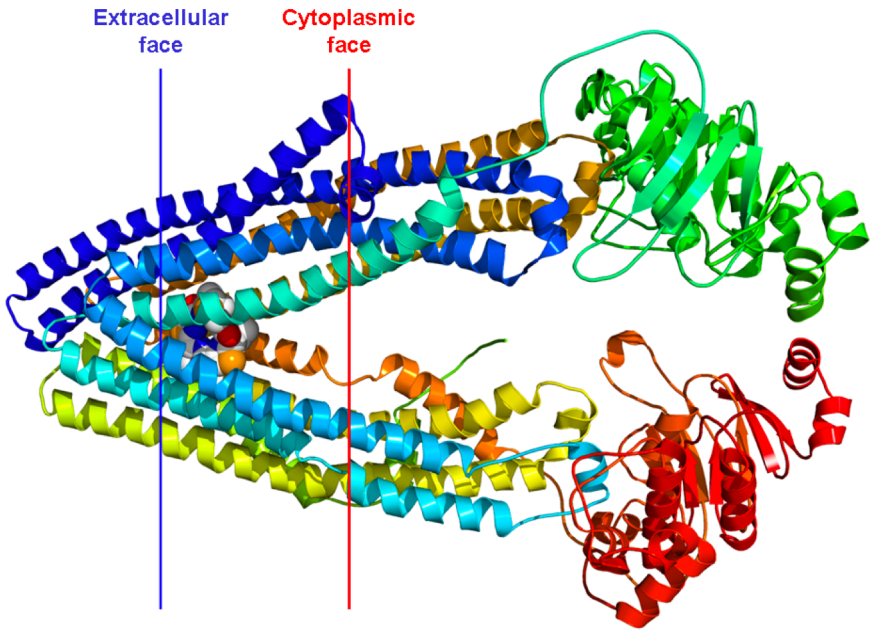
- Intestinal absorption and renal elimination of NOACs are dependent on the intestinal and renal permeability glycoprotein (P-gp) efflux transporter protein system
- Some NOACs are substrates of the hepatic CYP3A4 enzymes
- Induction of P-gp or CYP3A4 might decrease serum NOAC levels, reduce anticoagulant effects and lead to an increase in embolic risk.

Absorption and metabolism of the different new anticoagulant drugs



DE-RA

P-glycoprotein



- Permeability glycoprotein
- Also known as **multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1) or cluster of differentiation 243 (CD 243)**
- Important protein of the cell membrane that pumps foreign substances out of cells
- ATP-dependent efflux pump with broad substrate specificity
- Encoded by the *ABCB1* gene

P glycoprotein expression

- Intestinal epithelium: pumps xenobiotics (eg. toxins or drugs) back into the intestinal lumen
- Liver cells: pumps xenobiotics into bile ducts
- Cells of the proximal tubules of the kidney: pumps xenobiotics into urinary filtrate (in the proximal tubule)
- Capillary endothelial cells composing the blood brain barrier and blood testis barrier: pumps back into the capillaries

P-gp transports various substrates across the cell membrane

- Drugs such as colchicine, desloratadine, tacrolimus and quinidine.
- Chemotherapeutic agents such as topoisomerase inhibitors (i.e. etoposide, doxorubicin), microtubule-targeted drugs (i.e. vinblastine), and tyrosine kinase inhibitors (i.e. gefitinib, sunitinib)
- Lipids
- Steroids
- Peptides
- Bilirubin
- Cardiac glycosides like digoxin
- Immunosuppressive agents
- Glucocorticoids like dexamethasone
- HIV-type 1 antiretroviral therapy agents like protease inhibitors and nonnucleoside reverse transcriptase inhibitors

Europace (2015) **17**, 1467–1507
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

Europace (2015) 17, 1467–1507

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

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	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[SmPC]	minus 35%	Up to minus 50%

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 1330–1393
doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

European Heart Journal 2018;39:1330–1393

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Jan Steffel[1]*, Peter Verhamme[2], Tatjana S. Potpara[3], Pierre Albaladejo[4], Matthias Antz[5], Lien Desteghe[6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[2], Ronan Collins[12], A. John Camm[13], and Hein Heidbüchel[6,14]

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SmPC= Summary of product characteristics

	Via[142,145,146]	Dabigatran etexilate	Apixaban[130]	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	SmPC	−50% SmPC	−35% SmPC	SmPC, Ref.[147]
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	No relevant interaction known/assumed				
Lamotrigine	P-gp competition; No relevant interaction known/assumed				
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC, Ref.[148]	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				Ref.[149]
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

SmPC= Summary of product characteristics

	Via[142,145,146]	Dabigatran etexilate	Apixaban[130]	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
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Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	No relevant interaction known/assumed				
Lamotrigine	P-gp competition; No relevant interaction known/assumed				
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC, Ref.[148]	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				Ref.[149]
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

Epilepsy Research (2011) **94**, 18—25

journal homepage: www.elsevier.com/locate/epilepsyres

Antiepileptic drugs modulate P-glycoproteins in the brain: A mice study with ^{11}C-desmethylloperamide

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Short communication

Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs

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ABSTRACT

Atrial fibrillation (AF) is a frequent cause of stroke. Secondary prophylaxis by oral anticoagulants (OAC) is recommended after stroke in AF-patients. OAC can be achieved by vitamin-K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) like dabigatran, rivaroxaban, apixaban or edoxaban. Seizures are frequent after stroke, and antiepileptic drugs (AEDs) are indicated. The review, based on a literature research, aims to give an overview about pharmacokinetic knowledge and clinical data about drug–drug interactions (DDIs) between NOACs and AED.

Carbamazepine, levetiracetam, phenobarbital, phenytoin and valproic acid might decrease the effect of NOACs by inducing P-glycoprotein (P-gp) activity. Carbamazepine, oxcarbazepine, phenytoin, phenobarbital and topiramate might decrease the effect of NOACs by inducing CYP3A4 activity. Controversial data – inhibition as well as induction of CYP3A4 – were found about valproic acid.

The relevance of these DDIs is largely unknown since there are only sporadic case reports available. To increase the knowledge about DDIs between NOACs and AEDs we suggest subgroup analyses addressing effects and safety of VKAs versus NOACs in patients with AF on AEDs, in case they have been included in previously completed or still ongoing trials or registries. This could be easily feasible and would be desirable in view of the large data already accumulated.

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Antiepileptic drugs and evidence of their effects on the activity of P-glycoprotein and CYP 3A4

Antiepileptic drug	P-GP	Evidence	CYP 3A4	Evidence
Carbamazepine	↑ (Giessmann et al., 2004)	Humans	↑ (Puranik et al., 2013)	Humans
Ethosuximide	NR		NR	
Gabapentin	NR		NR	
Lamotrigine	No effect (Wang-Tilz et al., 2006)	Animals	NR	
Levetiracetam	↑ (Moerman et al., 2011)	Animals	No effect (Nicolas et al., 1999)	In vitro
Oxcarbazepine	NR		↑(Andreasen et al., 2007)	Humans
Phenobarbital	↑ (Jing et al., 2010)	Animals	↑ (Ohno et al., 2009)	In vitro
Phenytoin	↑ (Alvariza et al., 2014)	Animals	↑ (Lim et al., 2004)	Humans
Pregabalin	NR		NR	
Topiramate	No effect (Wang-Tilz et al., 2006)	Animals	↑ (Nallani et al., 2003)	In vitro
Valproic acid	↑ (Eyal et al., 2006)↓ (Tang et al., 2004)	In vitro	↑ (Cerveny et al., 2007)↓ (Wen et al., 2001)	In vitro
Zonisamide	NR		NR	a

↑ = Inducer.

↓ = Inhibitor.

NR = not reported.

Epilepsy Research 2016;126:98–101

Antiepileptic drugs and reports about interaction with NOACs

Antiepileptic drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Carbamazepine	NR	1 CR (Risselada et al., 2013)	NR	NR
Ethosuximide	NR	NR	NR	NR
Gabapentin	NR	NR	NR	NR
Lamotrigine	NR	NR	NR	NR
Levetiracetam	NR	NR	NR	NR
Oxcarbazepine	NR	1 CR (Serra et al., 2015)	NR	NR
Phenobarbital	CS (Chin et al., 2014)	NR	NR	NR
Phenytoin	CS (Chin et al., 2014)CR (Wiggins et al., 2016)	NR	NR	NR
Pregabalin	NR	NR	NR	NR
Topiramate	NR	NR	NR	NR
Valproic acid	NR	1 CR (Stöllberger and Finsterer, 2014)	NR	NR
Zonisamide	NT	NR	NR	NR

CR = Case report.
CS = clinical series.
NR = not reported.

Epilepsy Research 2016;126:98–101

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Epilepsy Research 46 (2001) 93–99

Epilepsy Research

www.elsevier.com/locate/epilepsyres

Repeated administration of the novel antiepileptic agent levetiracetam does not alter digoxin pharmacokinetics and pharmacodynamics in healthy volunteers

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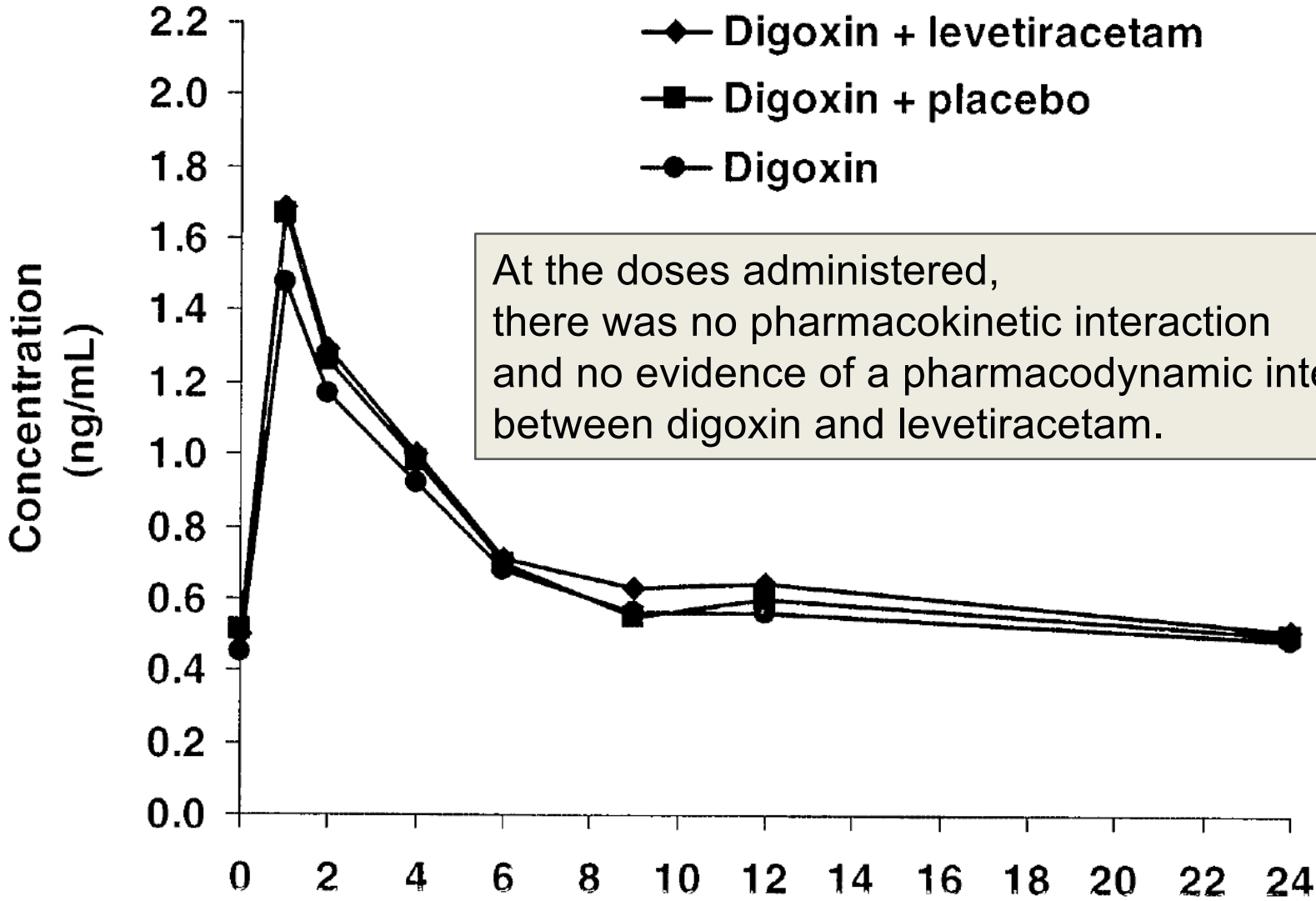
Epilepsy Research 2001;46: 93–99

- Two-way crossover design
- Double-blind, placebo-controlled study
- Seven men and four women (19–48 years old)
- Each received digoxin 0.25 mg once daily (0.5 mg on day 1) during the 1-week run-in period, followed by two 1-week periods of digoxin with levetiracetam (2000 mg/day) or placebo
- The pharmacokinetics of digoxin and levetiracetam were assessed by analysis of blood samples

Epilepsy Research 2001;46: 93–99

Evolution over time of serum concentrations (mean values; n=11) of digoxin at steady state in three conditions



At the doses administered,
there was no pharmacokinetic interaction
and no evidence of a pharmacodynamic interaction
between digoxin and levetiracetam.

Epilepsy Research 2001;46: 93–99

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 3800–3801
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DISCUSSION FORUM

Levetiracetam and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and epilepsy: a reasonable combination

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Online publish-ahead-of-print 20 September 2019

European Heart Journal 2019. 40: 3800–01

We are concerned about the expert advice given, classifying levetiracetam as contraindicated due to concerns over potentially reduced plasma levels of NOACs. We are arguing against such advice for the following reasons:

(1) The rate of post-stroke epilepsy (PSE) is expected in 8% of stroke patients after 5 years. Predictors include severity of stroke, cortical involvement, and territory of middle cerebral artery involvement, indicating a high proportion of patients with AF as stroke aetiology and the need of life-long oral anticoagulant and antiepileptic therapy.
(2) So far, there are no clinically relevant drug–drug interactions known with levetiracetam. Additional characteristics such as linear pharmacokinetics, renal clearance, and little risk for cognitive impairment are particular useful features for AED treatment with levetiracetam in the elderly with multimorbidity and polypharmacotherapy.

European Heart Journal 2019. 40: 3800–01

(3) Levetiracetam was shown to be superior to extended release carbamazepine in a randomized controlled trial in the elderly, mostly suffering from PSE. Superiority in AED trials is rarely reached, so this result is highly respected.
(4) PSE is a serious condition with increased mortality and reduced functional outcome. Withholding or switching a well-established therapy with levetiracetam according to the advice given in the guidance, puts patients on significant risk of break through seizures and status epilepticus including an additional risk for injuries including intracranial haemorrhage underNOAC therapy.

European Heart Journal 2019. 40: 3800–01

ESC European Society of Cardiology

Europace (2021) **00**, 1–65
doi:10.1093/europace/euab065

POSITION PAPER
EHRA PRACTICAL GUIDE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Jan Steffel[1]*, Ronan Collins[2], Matthias Antz[3], Pieter Cornu[4], Lien Desteghe[5,6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[12], Thomas Vanassche[12], Tatjana Potpara[13], A. John Camm[14], and Hein Heidbüchel[5,6]

Steffel J, et al. Europace 2021; 0:1-65

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29% [542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC [543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPc)			

- Colour coding is based on the respective NOAC SmPC (**Summary of Product Characteristics)**, drug interaction databases, or expert opinion.
- The hatched colour coding indicates no clinical or PK data available.
- Some of the colour codes will likely require adaptation as more data become available over time.
- White: No relevant drug–drug interaction anticipated.
- Blue (dark): Contraindicated due to reduced NOAC plasma levels.
- Blue (light): Caution required, especially in case of polypharmacy or in the presence of >_2 light blue interactions due to reduced NOAC plasma levels.

Steffel J, et al. Europace 2021; 0:1-65

POSTSTROKE EPILEPSY PREVENTION

Statin treatment reduces the risk of poststroke seizures

ABSTRACT

Objective: To examine the potential efficacy of statin treatment in reducing the risk of poststroke seizures.

Methods: In this cohort study, patients with a first-ever ischemic stroke and no history of epilepsy before stroke were enrolled. After a mean follow-up period of 2.5 years, a follow-up assessment was performed to identify poststroke epilepsy. Logistic regression and Cox regression analyses were used to assess the relationship between statin use and poststroke early-onset seizures or poststroke epilepsy.

Results: Of 1,832 enrolled patients, 63 (3.4%) patients had poststroke early-onset seizures and 91 (5.0%) patients had poststroke epilepsy. Statin use was associated with a lower risk of poststroke early-onset seizures (odds ratio [OR] 0.35, 95% confidence interval [CI] 0.20–0.60, $p < 0.001$), and this reduced risk was seen mainly in patients who used a statin only in the acute phase (OR 0.36, 95% CI 0.20–0.62, $p < 0.001$). No significant association was found between statin use and poststroke epilepsy (OR 0.81, 95% CI 0.52–1.26, $p = 0.349$). In 63 patients who presented with early-onset seizures, statin use was associated with reduced risk of poststroke epilepsy (OR 0.34, 95% CI 0.13–0.88, $p = 0.026$).

Conclusions: Statin use, especially in the acute phase, may reduce the risk of poststroke early-onset seizures. In addition, statin treatment may prevent the progression of initial poststroke seizure-induced neurodegeneration into chronic epilepsy. Because of the observational nature of the study, more studies are needed to confirm the results.

Classification of evidence: This study provides Class III evidence that in patients with a first-ever ischemic stroke, the early use of statins reduces the risk of early poststroke seizures. ***Neurology*®** **2015;85:701–707**

Guo J, et al. Neurology 2015;85:701-7

Table 3 Effect of statin treatment on poststroke early-onset seizures and poststroke epilepsy

	ES				PSE			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Statin use	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Anytime	0.32 (0.19-0.53)	<0.001	0.35 (0.20-0.60)	<0.001	0.64 (0.42-0.98)	0.041	0.81 (0.52-1.26)	0.349
Prestroke only	—	—	—	—	—	—	—	—
Acutely only	0.33 (0.20-0.55)	<0.001	0.36 (0.20-0.62)	<0.001	0.65 (0.42-1.01)	0.054	0.82 (0.52-1.28)	0.376
Prestroke and acutely	0.24 (0.06-1.00)	0.051	0.24 (0.05-1.07)	0.061	0.65 (0.26-1.67)	0.356	0.90 (0.34-2.38)	0.837

Abbreviations: CI = confidence interval; ES = poststroke early-onset seizures; OR = odds ratio; PSE = poststroke epilepsy.

Early use of statin appeared to reduce the risk of early poststroke seizure

Guo J, et al. Neurology 2015;85:701-7

PROGNOSIS

- PSE is often described as an easily manageable form of epilepsy, where monotherapy suffices to control seizures
- However, only reports from small case series existed with varying results

Silverman et al. 2002, Bryndziar et al. 2015, Zelano et al. 2015

- Compared with the information on the risk of developing PSE, there is less information on morbidity or mortality associated with the condition.
- In a prospective cohort of 631 patients with a transient ischemic attack or ischemic stroke, aged 18-50 years, poststroke epilepsy was associated with increased 30 day mortality (HR 4.8; 95% CI, 1.7–14.0) and long term mortality (HR 1.8; 95% CI, 1.2–2.9)

Arntz R, et al. Stroke 2015;46:2309-11

Frequency and Mortality of SE

	Proportion of Cases of SE, %	Associated Acute Mortality in Patients With SE, %
Drug reduction/withdrawal, poor compliance, or low AED levels	10-20	0-10
Cerebrovascular disease	10-40	20-60
Metabolic disorders	5-15	10-35
Acute CNS infections[b]	0-10	0-30
Anoxia	5-10	60-100
Alcohol abuse	5-15	0-10
Head trauma	0-10	0-25
Drug overdose/toxicity	0-10	10-25
Brain tumors	0-10	0-20
Cryptogenic/idiopathic	5-15	5-20

Neligan A. Arch Neurol 2010;67:931-40

CONCLUSION

- PSE is a major cause of epilepsy after middle age
- Consideration for treatment with AEDs in post stroke epilepsy
  - Efficacy
  - Side effects
  - Drug interaction

- Over the last decade, there have been remarkable improvements in the management of acute stroke.
- Advances in the knowledge of mechanism, management and prevention of poststroke seizures is still the subject that need further studies.