Interaction between Antiseizure and Stroke Treatment Highlight in Poststroke Epilepsy

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Outline

- Post stroke seizure/Epilepsy
- Pathophysiology of PSE
- Treatment of PSE
- AEDs and stroke medicine drug interaction

Post Stroke Epilepsy (PSE)

"Seizures that occur after a stroke without a previous history of epilepsy "

Early seizures occur ≤2weeks after the stroke

Late seizures occur > 2 weeks after the insult

Fu et al. Acta Epileptologica (2021)

Pathophysiology of PSE

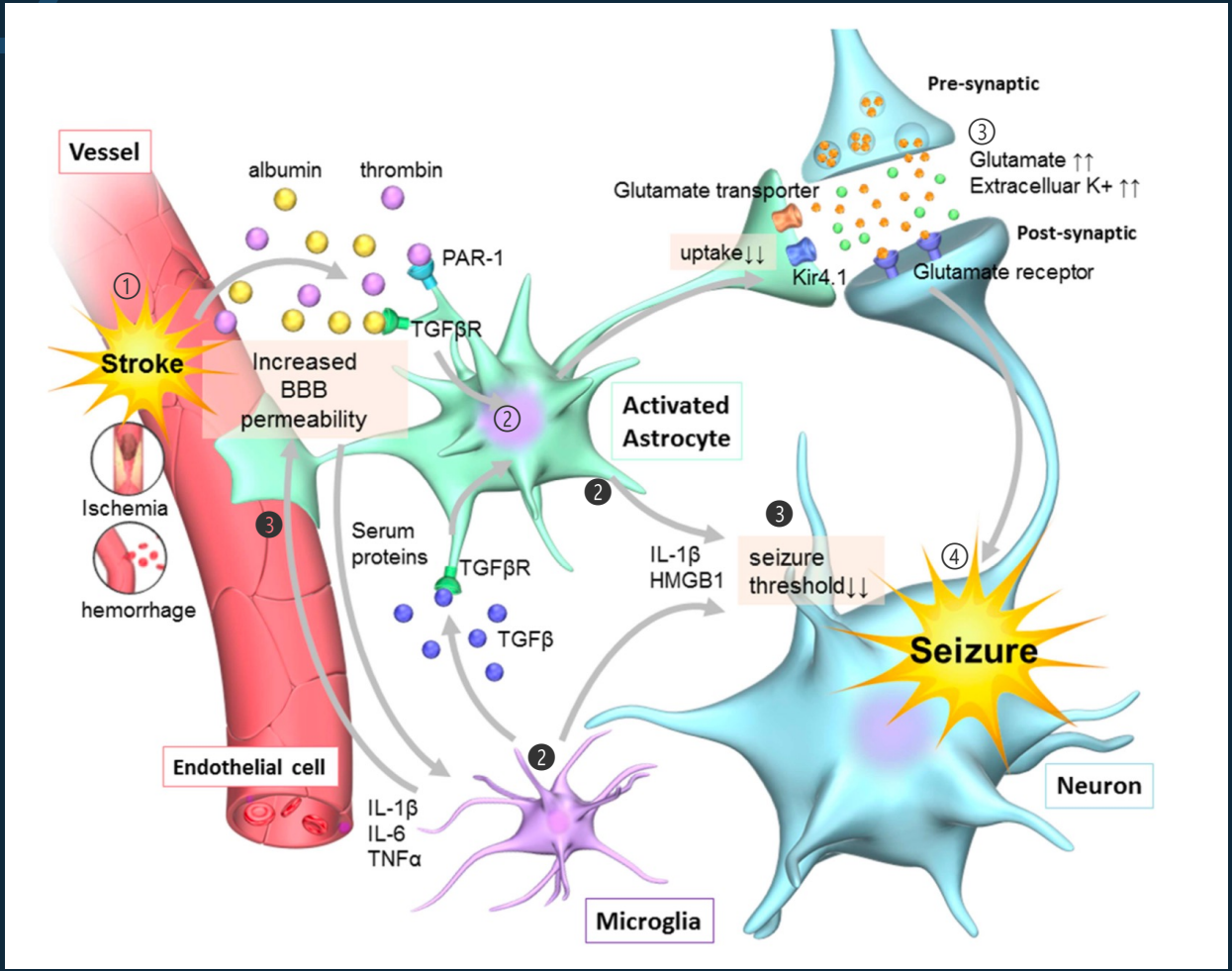
Acute PSE

- Electrophysiological instability
- Neurotransmitter imbalance

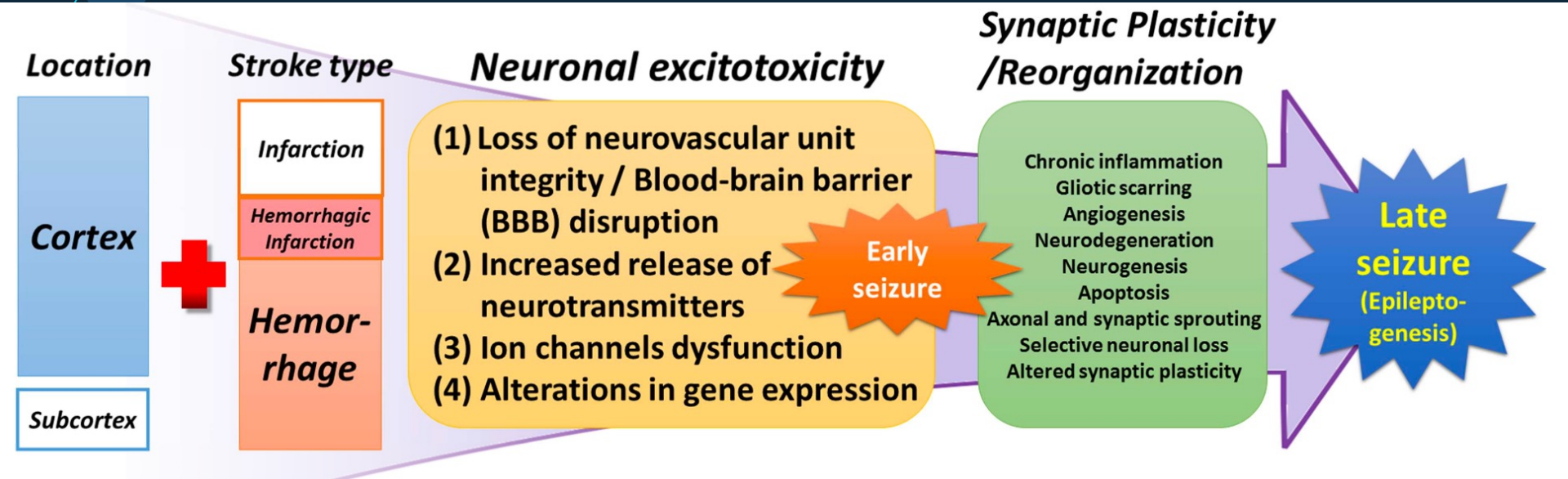
Late PSE

- Neurovascular unit imbalance
- Disruption of the neuronal network
- Glial activation
- Genetic factor

Fu et al. Acta Epileptologica (2021)



Tanaka, T., Ihara, M., Post stroke epilepsy, Neurochemistry International (2017), doi: 10.1016/j.neuint.2017.02.002.



Tanaka, T., Ihara, M., Post stroke epilepsy, Neurochemistry International (2017), doi: 10.1016/j.neuint.2017.02.002.

SVN Stroke and Vascular Neurology

Poststroke seizure: optimising its management

To cite: Xu MY. Poststroke seizure: optimising its management. *Stroke and Vascular Neurology* 2019;**4**: e000175. doi:10.1136/svn-2018-000175

Table 1 Seven items of the Post-Stroke Epilepsy Risk Scale

Item	Weight
Supratentorial stroke	2
ICH involving cortical areas	2
Ischaemia involving cortical or cortical-subcortical areas	1
Ischaemia + ongoing neurological deficit	1
Stroke caused neurological deficit with mRS > 3	
Seizure occurred up to 14 days after stroke	1
Seizure occurred 15 days or later after stroke	2

ICH, intracerebral haemorrhage; mRS, modified Rankin scale.

Table 2 CAVE score (for LS from ICH)

CAVE	Risk of LS
C: cortical involvement (1 point)	0 point: 0.6%
A: age <65 years (1 point)	1 point: 3.6%
V: volume >10 mL (1 point)	2 points: 9.8%
E: early seizure (1 point)	3 points: 34.8%
	4 points: 46.2%

ICH, intracerebral haemorrhage; LS, late seizure.

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Statin treatment reduces the risk of poststroke seizures

Neurology® 2015;85:1–7

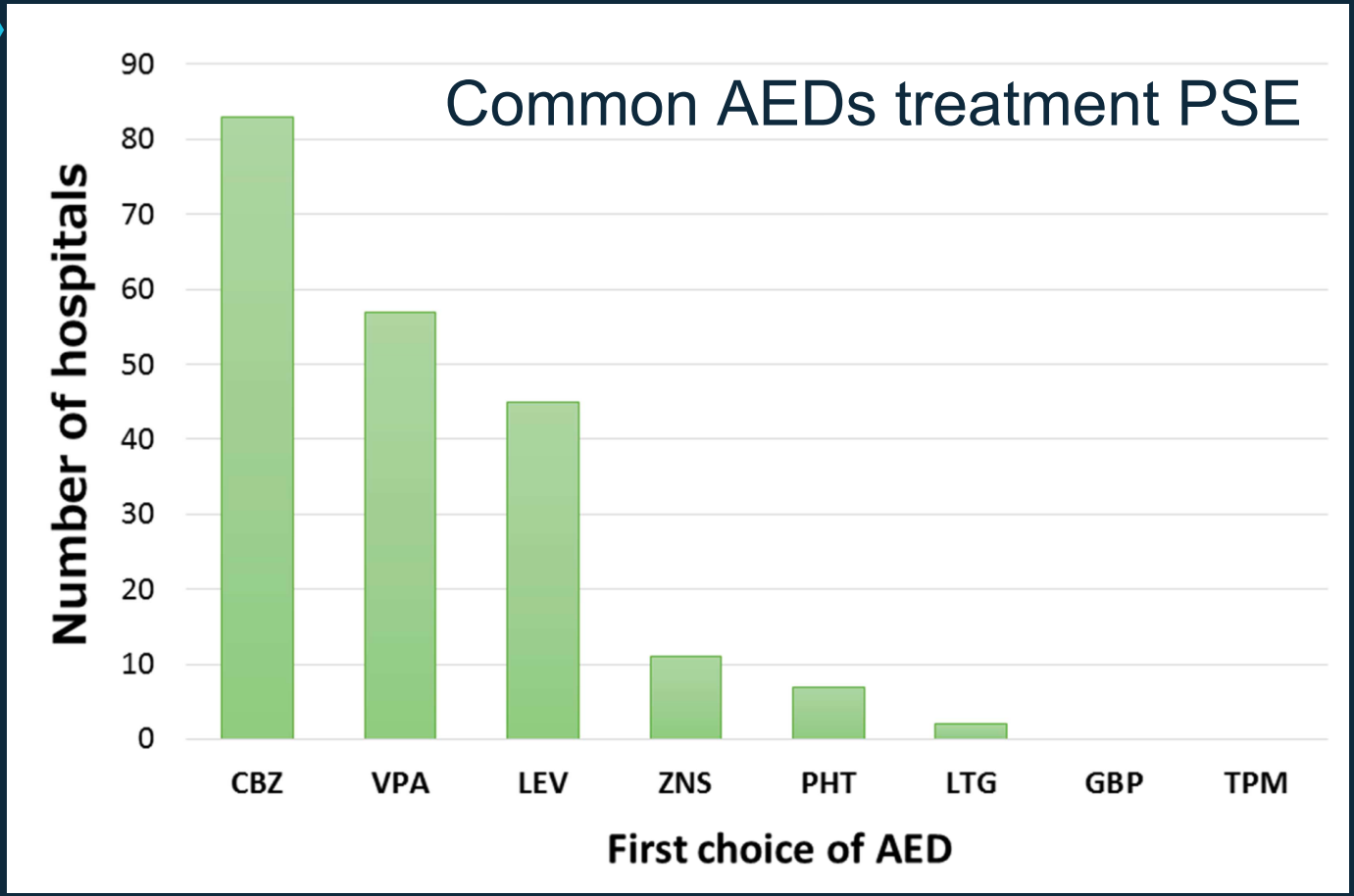
Cohort study. Patients with a first-ever ischemic stroke and no history of epilepsy before stroke

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.**

In 63 patients who presented with early-onset seizures, statin use was associated with reduced risk of poststroke epilepsy.

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.

Common AEDs treatment PSE



Tanaka, T., Ihara, M., Post stroke epilepsy, Neurochemistry International (2017), doi: 10.1016/j.neuint.2017.02.002.

Interaction between ASMs and antiplatelet drugs

- Valproic acid and its derivatives impair platelet functions
- Levetiracetam was reported to induce an alteration of platelet functions
- Restoration of platelet functionality was observed after cessation of levetiracetam treatment
- Bleeding is a potential complication when statins are used in combination with antiplatelet drugs

Zhao L, Li J, Kälviäinen R, Jolkkonen J, Zhao C. Impact of drug treatment and drug interactions in post-stroke epilepsy. Pharmacol Ther. 2022;233:108030. doi:10.1016/j.pharmthera.2021.108030

Clopidogrel

- **Phenobarbital, phenytoin, carbamazepine and topiramate** increase the level or effect of clopidogrel by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.
- Clopidogrel increases levels of phenytoin by decreasing metabolism. Minor/Significance Unknown.
- **Oxcarbazepine** decreases effects of clopidogrel by affecting hepatic enzyme CYP2C19 metabolism. Avoid or Use Alternate Drug.

Clopidogrel efficacy may be reduced by drugs that inhibit CYP2C19 or CYP3A4. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. Clopidogrel is metabolized to this active metabolite in part by CYP2C19 and in part by CYP3A4 (CYP3A4 inducers may increase the metabolism of clopidogrel to its active metabolite).

Magdalena Bosak. Co-medication and potential drug interactions among patients with epilepsy . *Seizure:European Journal of Epilepsy 66 (2019)*

Atorvastatin

- **Carbamazepine** will decrease the level or effect of atorvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or **Use Alternate Drug**.
- **Phenobarbital, phenytoin, oxcarbazepine and topiramate** will decrease the level or effect of atorvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Use Caution/Monitor.
- **phenobarbital** will decrease the level or effect of atorvastatin by P-glycoprotein (MDR1) efflux transporter. Use Caution/Monitor.
- **carbamazepine** increases toxicity of atorvastatin. Use Caution/Monitor. Comment: OATP1B1 inhibitors may increase risk of myopathy.

Magdalena Bosak. Co-medication and potential drug interactions among patients with epilepsy . *Seizure:European Journal of Epilepsy 66 (2019)*

Treatment with antiepileptic drugs in patients with stroke. A change in clinical practice may be required

	All n = 82	AED before stroke[a] n = 32 (39%)	AED after stroke[a] n = 50 (61%)
Age: average (range)	74 (44–98)	72 (47–92)	75 (44–98)
Sex: female – n (%)	36 (45%)	15 (47)	21 (42)
Type of stroke[a] - n (%)			
ICH	13 (16)	5 (16)	8 (16)
TIA	8 (10)	6 (19)	2 (4)
Large vessel ischemic	41 (50)	10 (31)	31 (62)
Small vessel ischemic	19 (23)	11 (34)	8 (16)
Unknown ischemic	1 (1)	0 (0)	1 (2)
Mechanism of ischemic stroke[a] - n (%)			
Embolic	32 (53)	7 (33)	25 (63)
Thrombotic	27 (44)	14 (67)	13 (33)
Unknown	2 (3)	0 (0)	2 (5)
Indication for AED – n (%)[b]			
Epilepsy	65 (79)	20 (62)	45 (90)
Pain	12 (15)	7 (22)	5 (10)
Psychiatric	6 (7)	6 (19)	0 (0)

Ali Jabareen. *Journal of the Neurological Sciences 395 (2018)*

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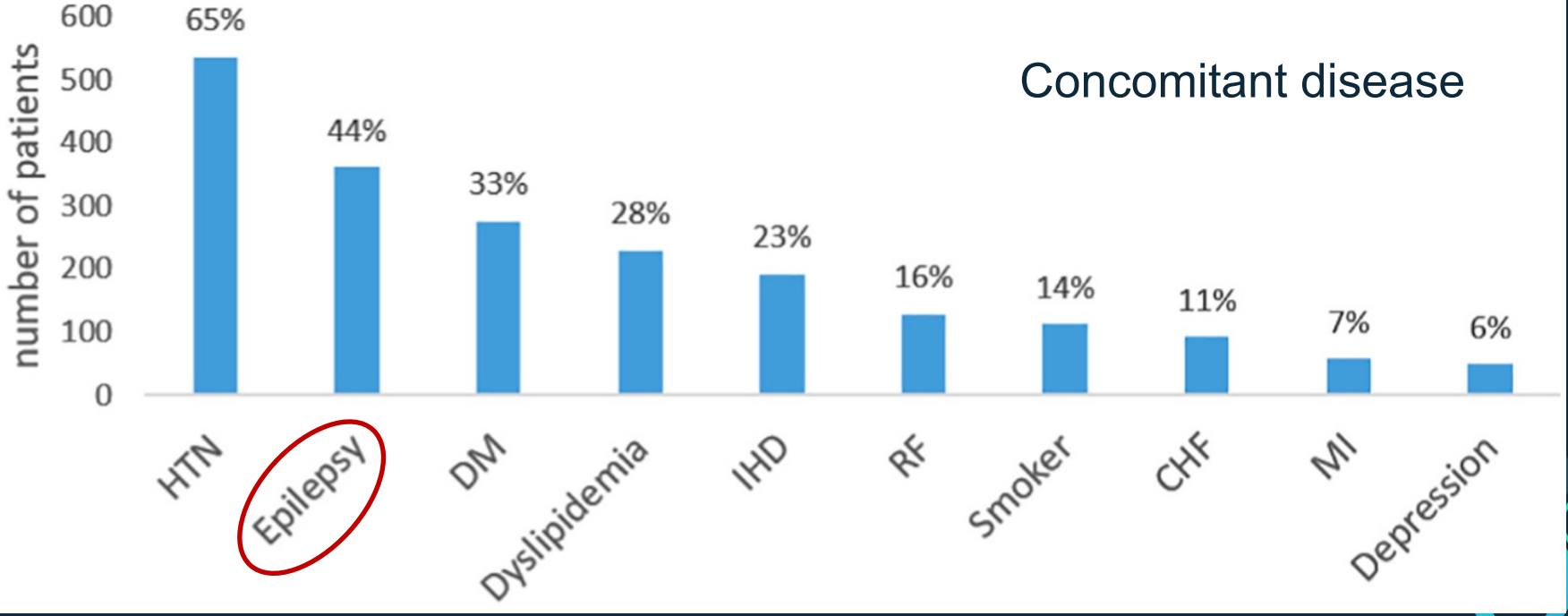

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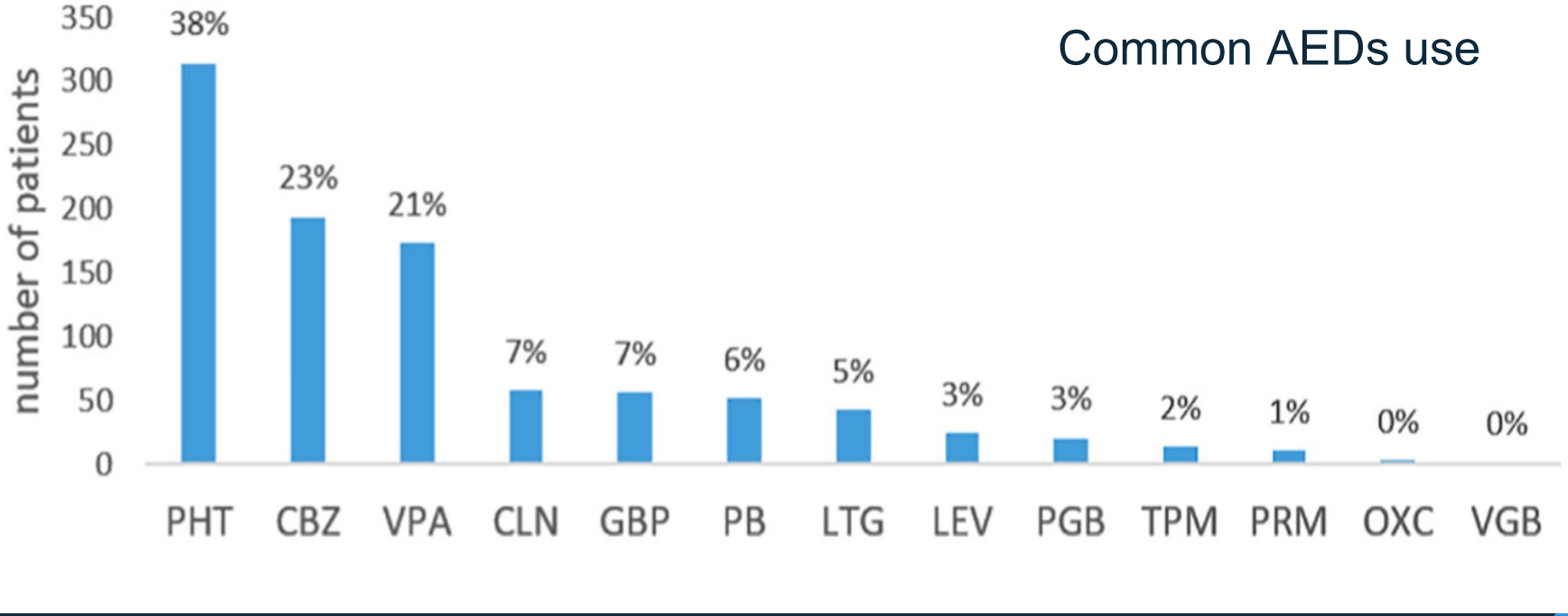

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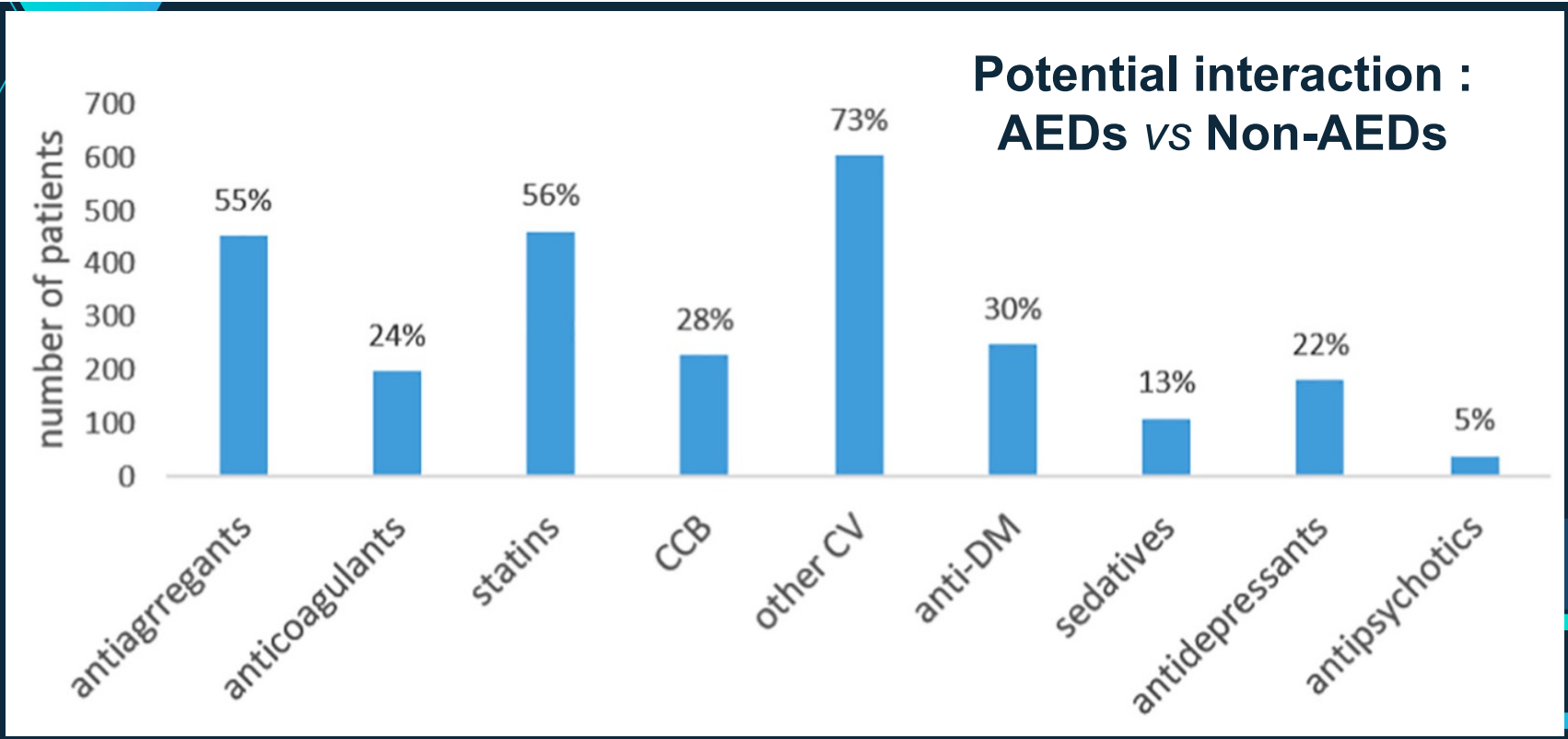

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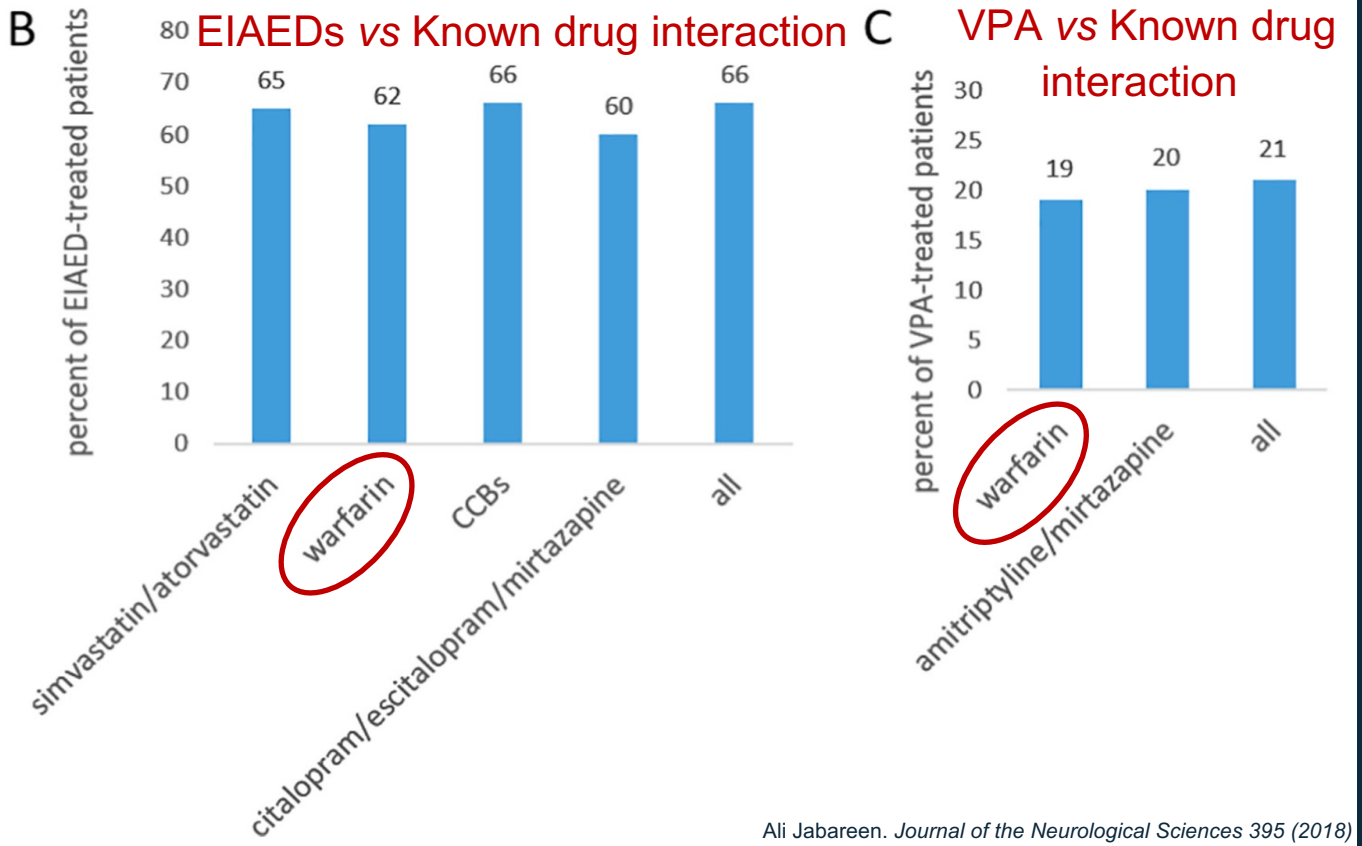


Ali Jabareen. *Journal of the Neurological Sciences 395 (2018)*

Table 2. AED Interactions With Commonly Used Drugs

AED	Affected Drugs	Effect
Enzyme inducers (phenobarbital, phenytoin, carbamazepine, felbamate, topiramate, oxcarbazepine)	Oral contraceptives, doxycycline, amitriptyline, nortriptyline, imipramine, paroxetine, bupropion, citalopram, haloperidol, risperidone, quetiapine, olanzapine, ziprasidone, atorvastatin, simvastatin, lovastatin, fluvastatin	Decreased levels and effect
Phenobarbital, carbamazepine, phenytoin	Warfarin	Decreased levels and effect
Valproic acid	Warfarin, amitriptyline, nortriptyline, paroxetine, atorvastatin, lovastatin, simvastatin, fluvastatin	Increased levels and effect

AED: antiepileptic drug. Source: Reference 24.

Hien Ha. Epilepsy: Treatment and Management. *US Pharm.* 2013

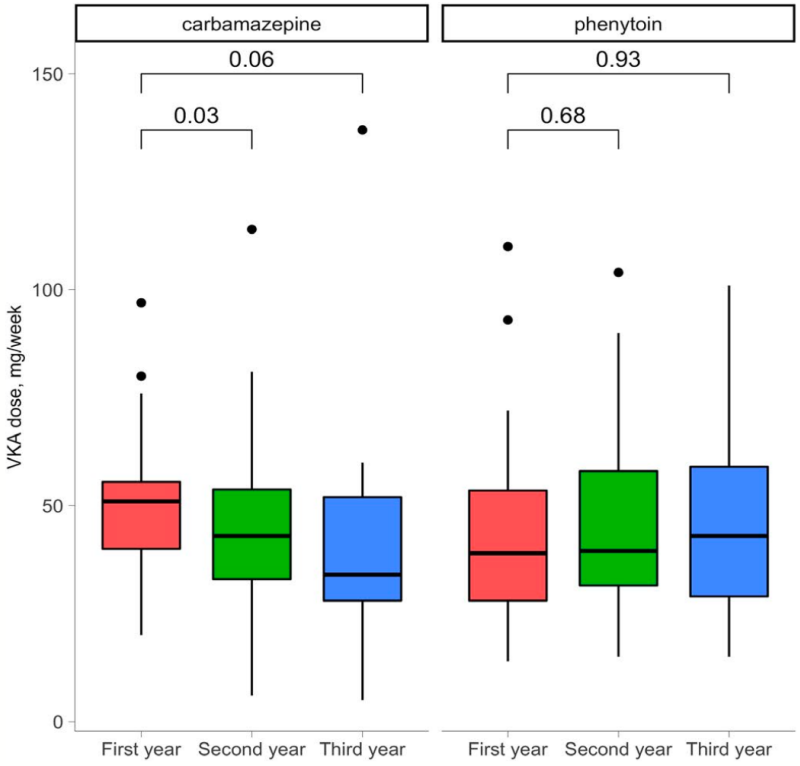
Received: 21 October 2021 | Revised: 26 November 2021 | Accepted: 1 December 2021

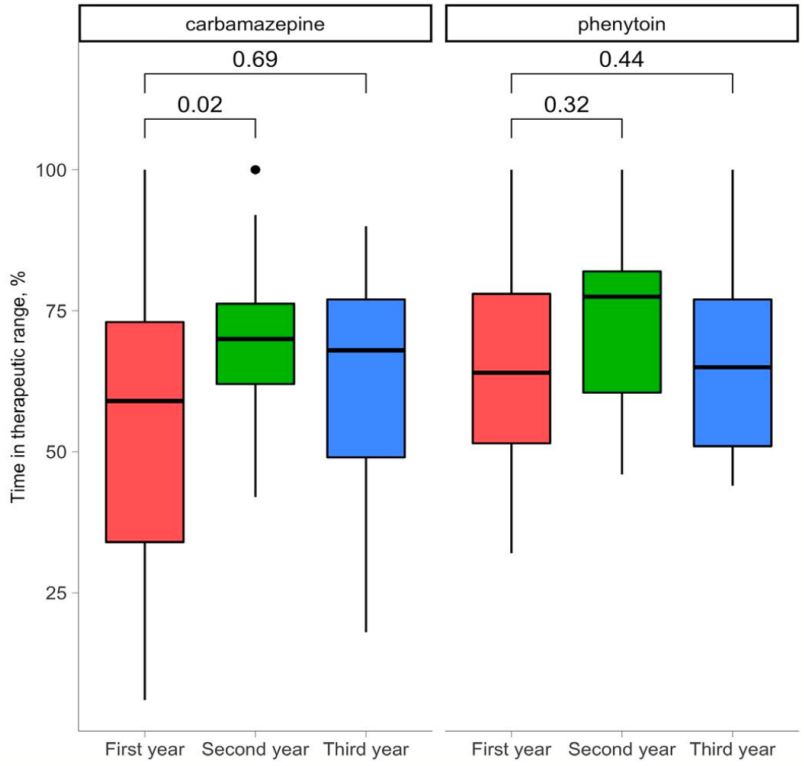
DOI: 10.1002/rth2.12650

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

Carbamazepine, phenytoin, and oral anticoagulants: Drug-drug interaction and clinical events in a retrospective cohort





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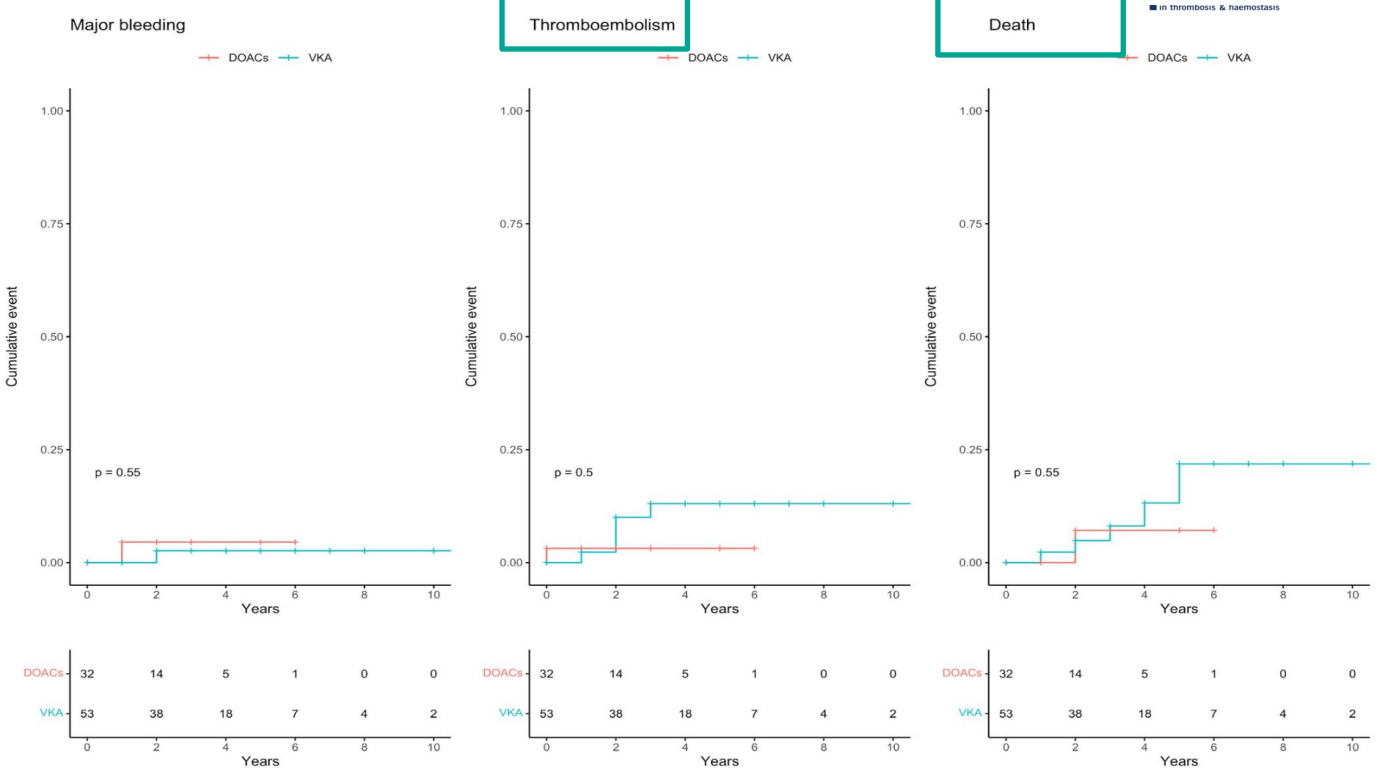

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	All patients *N* = 85 *n* (%)	Cases per 100 p-y (95% CI)	VKA *N* = 56[a] *n* (%)	Cases per 100 p-y (95% CI)	DOAC *N* = 39[a] *n* (%)	Cases per 100 p-y (95% CI)	Incidence rate ratio VKA/DOAC (95% CI)
Thromboembolism	9 (11)	3.8 (3.5–4.5)	6 (11)	3.6 (3.1–4.2)	3 (8)	4.4 (3.5–5.6)	0.8 (0.2–3.3)
Major bleeding	4 (5)	1.7 (1.9–2.5)	3 (5)	1.8 (1.5–2.1)	1 (3)	1.5 (1.2–1.9)	1.2 (0.1–11.5)
All-cause death	7 (8)	3.0 (2.6–3.4)	6 (11)	3.6 (3.1–4.2)	1 (3)	1.5 (1.2–1.9)	2.4 (0.3–19.9)

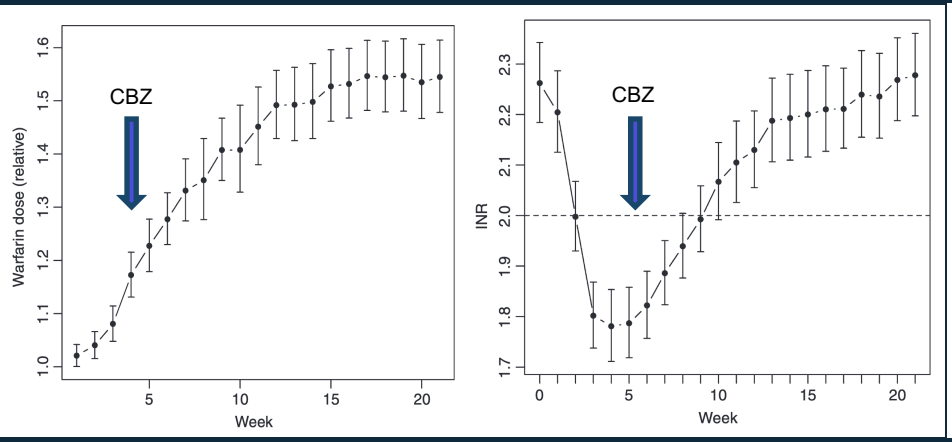
Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; p-y, person-years; VKA, vitamin K antagonist.

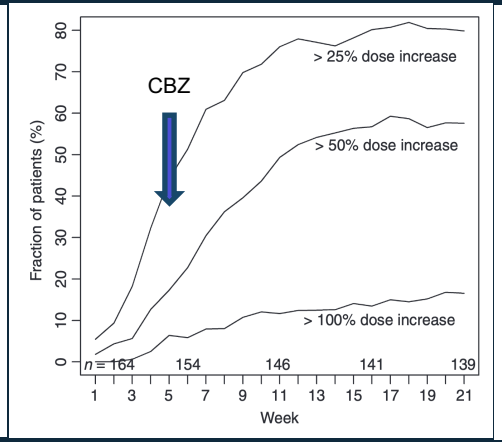
[a]These groups include patients who switched the anticoagulant.

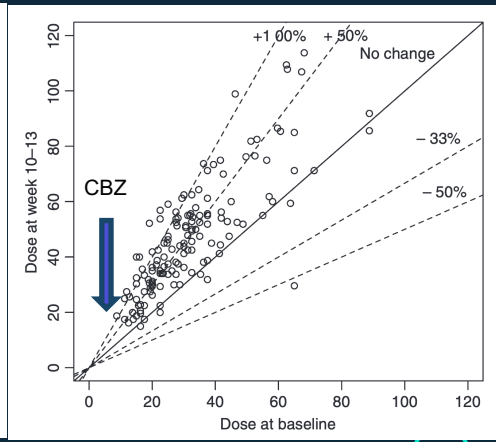
Journal of Thrombosis and Haemostasis, **14**: 765–771 DOI: 10.1111/jth.13268

ORIGINAL ARTICLE

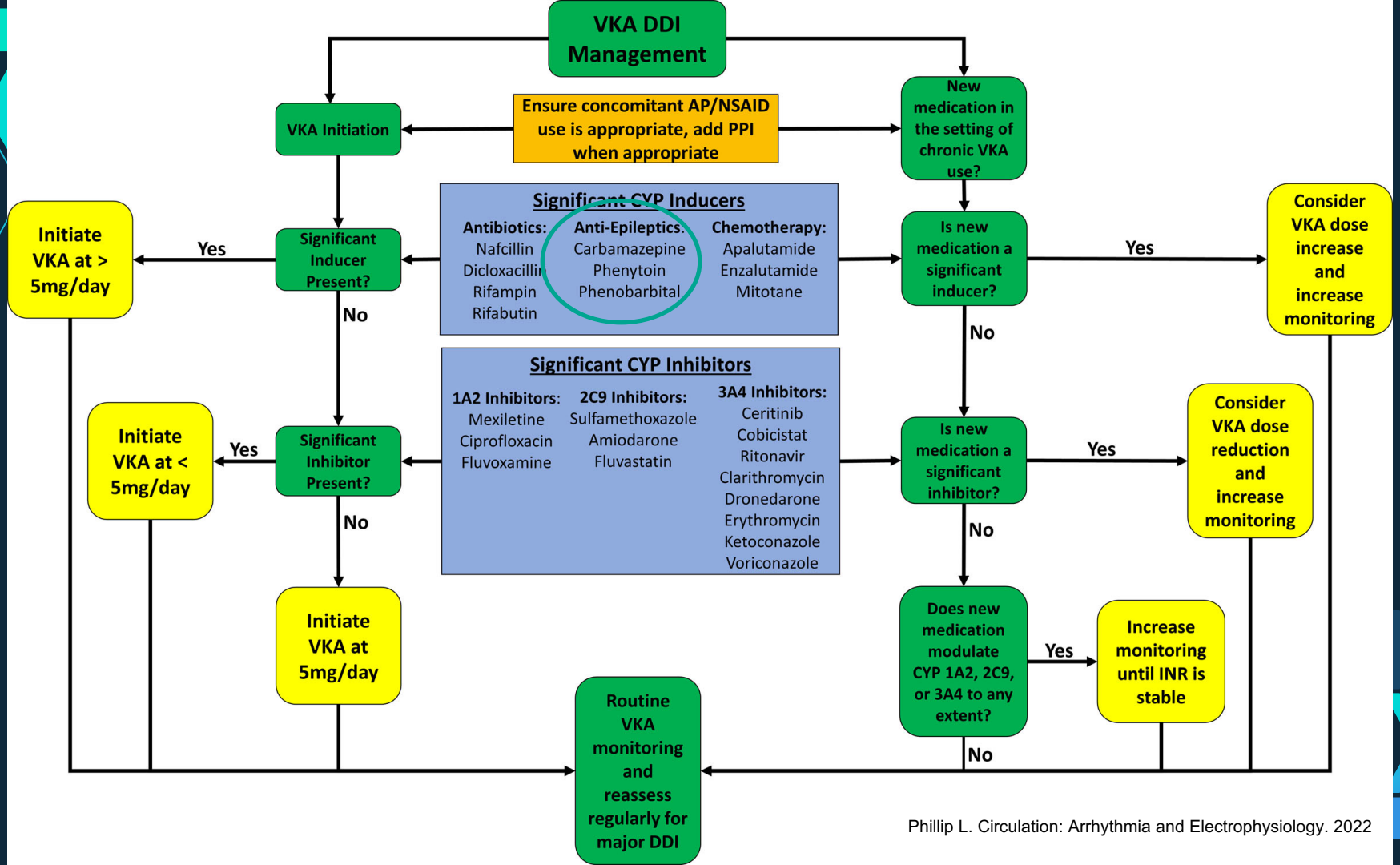
The effect of carbamazepine on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population







B. MANNHEIMER. The effect of carbamazepine on warfarin anticoagulation:a register-based nationwide cohort study involving the Swedish population.J Thromb Haemost2016



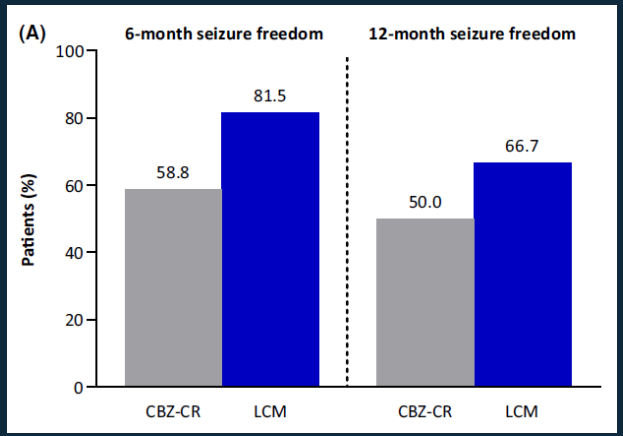
Phillip L. Circulation: Arrhythmia and Electrophysiology. 2022

Enoxaparin

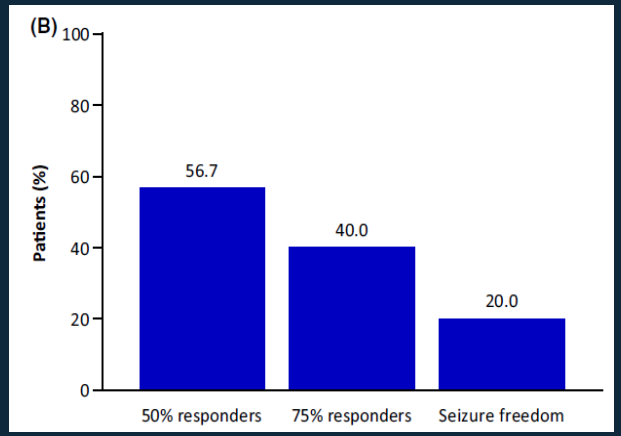
- Phenobarbital decreases effects of enoxaparin by increasing metabolism. Avoid or Use Alternate Drug.
- Enoxoparin increases levels of phenytoin by unknown mechanism. Use Caution/Monitor.
- Phenytoin, decreases the effect of enoxaparin. Use Caution/Monitor. Comment: Hydantoin anticonvulsants increase anticoagulant effects at first, then decrease those effects with continued use (2+ wks). There are multiple mechanisms involved, including enzyme induction, plasma protein binding site competition, and additive effects on prothrombin time.
- Carbamazepine decreases levels of enoxaparin by increasing metabolism. Use Caution/Monitor.

Magdalena Bosak. Co-medication and potential drug interactions among patients with epilepsy . *Seizure:European Journal of Epilepsy 66 (2019)*

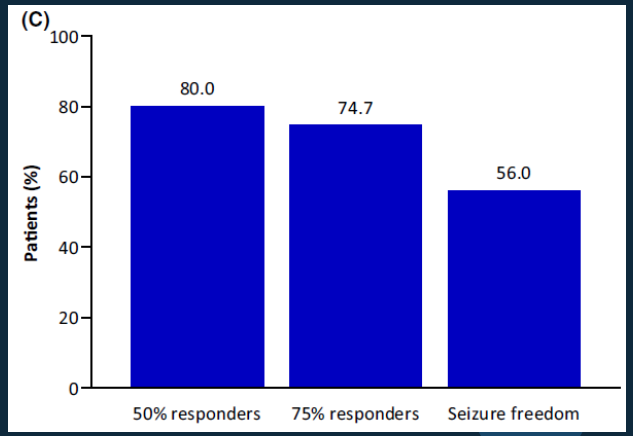
LCM in patients with epilepsy of cerebrovascular etiology



Initial monotherapy



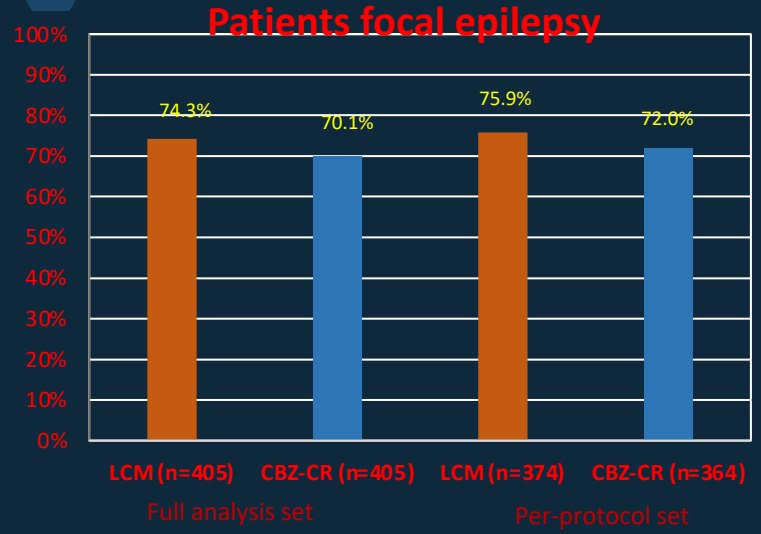
Conversion to LCM monotherapy

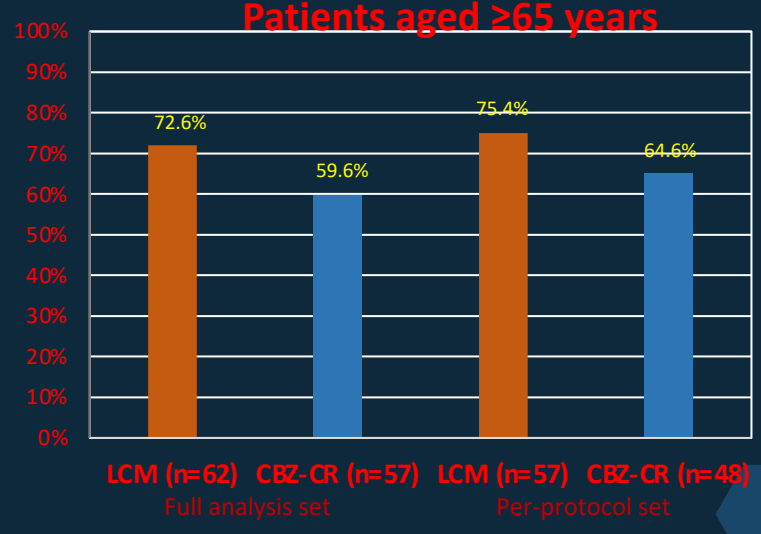


LCM as adjunctive therapy to one baseline AED

Rosenow F, Brandt C, Bozorg A, et al. Lacosamide in patients with epilepsy of cerebrovascular etiology. *Acta Neurol Scand*. 2020;141(6):473-482. doi:10.1111/ane.13230

LCM useful as first-line monotherapy





Lacosamide similar Carbamazepine (Seizure free)

Michel Baulac et al. Lancet Neurol, 16, 43-54, 2017

Lack of effect of lacosamide on the pharmacokinetic and pharmacodynamic profiles of warfarin

*Armel Stockis, †Jan Jaap van Lier, ‡Willi Cawello, ‡Thomas Kumke, and ‡Klaus Eckhard

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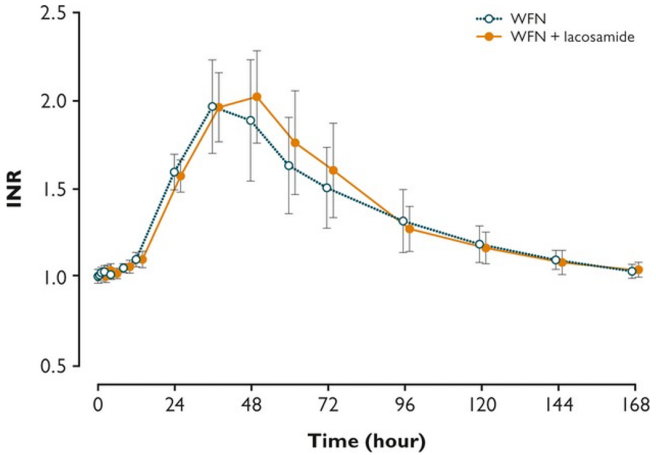
Epilepsia

Lack of effect of lacosamide on the pharmacokinetic and pharmacodynamic profiles of warfarin



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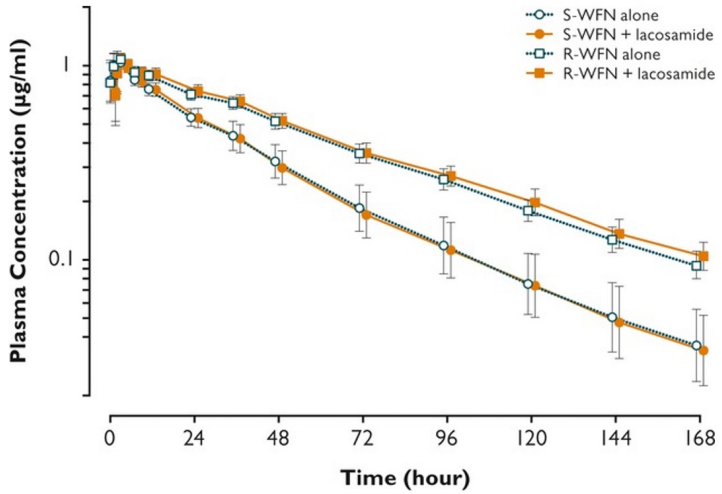

Epilepsia, Volume: 54, Issue: 7, Pages: 1161-1166, First published: 24 April 2013, DOI: (10.1111/epi.12192)

Trends in Oral Anticoagulant Co-Prescription with Antiepileptic Drugs Among Adults with Epilepsy, 2010-2018

Epilepsy Behav. 2020 December ; 113: 107550. doi:10.1016/j.yebeh.2020.107550.

Emily K. Acton, BS[a,b,c], Michael A. Gelfand, MD, PhD[d], Sean Hennessy, PharmD, PhD[a,c,e], Sharon X. Xie, PhD[a], John R. Pollard, MD[f], Scott E. Kasner, MD, MSCE[d,*], Allison W. Willis, MD, MS[a,b,c,d,*]

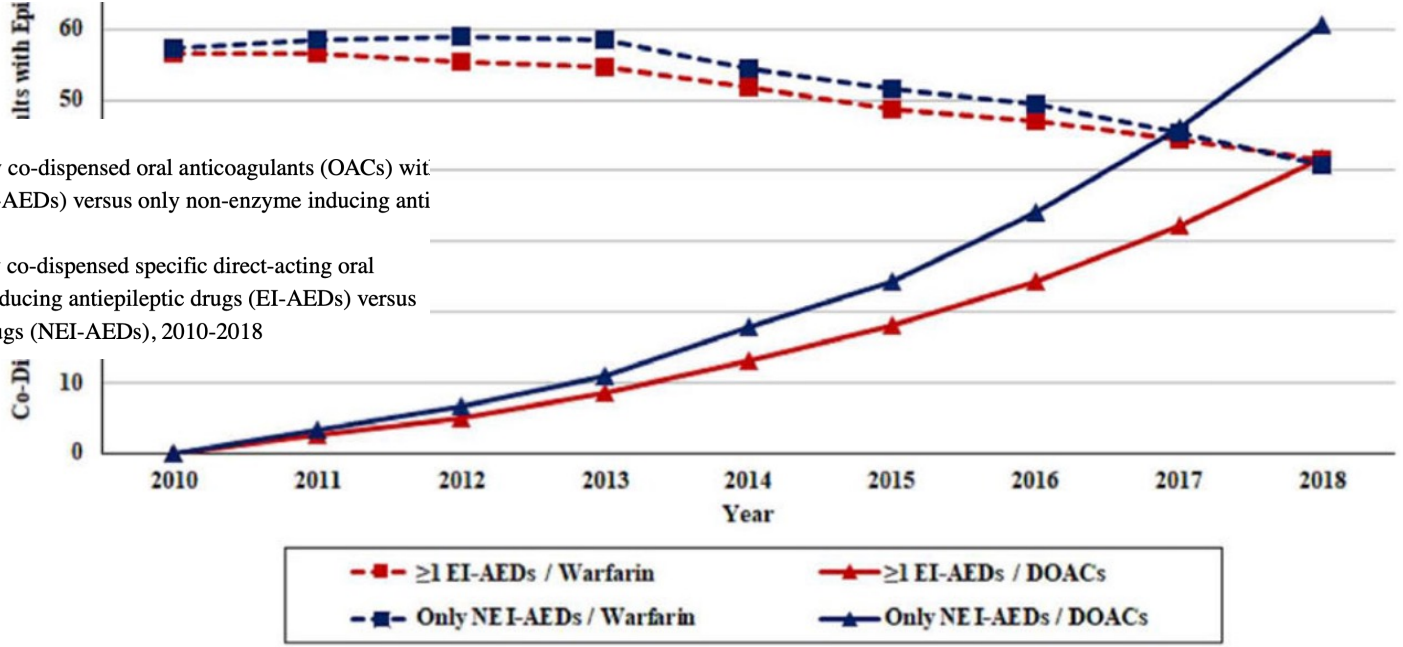

Figure 1.

A. Yearly prevalence of adults with epilepsy co-dispensed oral anticoagulants (OACs) wit ≥1 enzyme inducing antiepileptic drugs (EI-AEDs) versus only non-enzyme inducing anti epileptic drugs (NEI-AEDs), 2010-2018

B. Yearly prevalence of adults with epilepsy co-dispensed specific direct-acting oral anticoagulants (DOACs) with ≥1 enzyme inducing antiepileptic drugs (EI-AEDs) versus only non-enzyme inducing anti epileptic drugs (NEI-AEDs), 2010-2018

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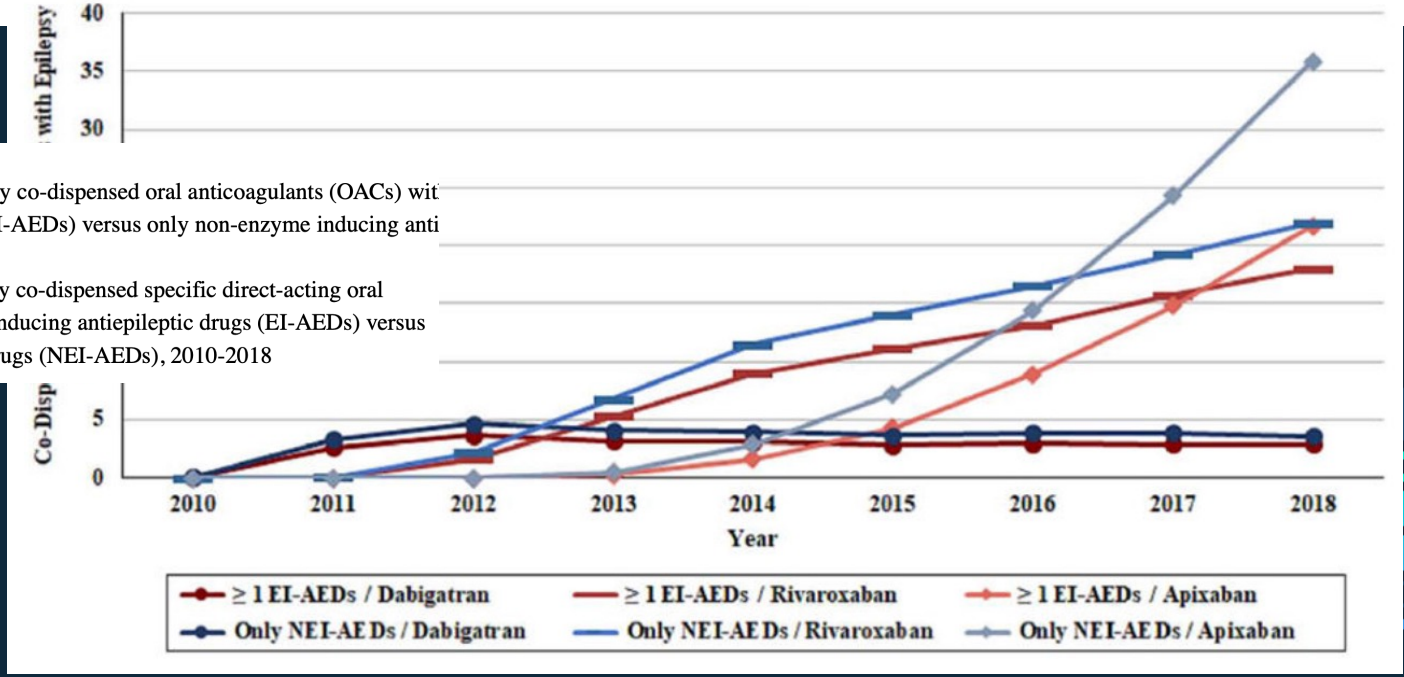

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- Among those on AEDs, the prevalence of concurrent OACs rose to 92.0/1,000 by 2018
- DOAC use with AEDs rapidly increased, reaching 53.9 per 1,000 by 2018 (ρ= 1.00)
- Warfarin use with AEDs decreased to 42.0 per 1,000 by 2018 (ρ= –0.97)
- Enzyme-inducing AED use with OACs was associated with net worth and education level

Pharmacokinetic Interactions of Clinical Interest Between Direct Oral Anticoagulants and Antiepileptic Drugs

Alessandro


Giovambatt


Emilio Russ

AEDs	P-gp	References	CYP3A4	CYP3A5/CYP2J2
Eslicarbazepine acetate	Substrate (*in vitro*)	(35)	Weak inductor (*in vitro e vivo*)	NR
Felbamate	Substrate (*in vivo*)	(36)	Weak inductor/No effects (*in vitro*)	NR
Gabapentin	Not substrate	(38)	NR	NR
Lamotrigine	No effects/substrate	(39)	No effects	No effects
Levetiracetam	Inductor/substrate (*in vivo*)	(41)	Weak inductor (*in vitro*)	No effects
Oxcarbazepine	NR		Inductor (*in vivo e vitro*)	Inductor 3A5 (*in vivo e vitro*)
Perampanel	No effects	(44)	Weak inductor (*in vitro*)	Weak inductor 3A5 (*in vitro*)
Pregabalin	No effects	(45)	No effects	No effects
Rufinamide	NR		Mild induction (*in vitro*)	No effects
Stiripentol	NR		Inhibitor (*in vitro*)	No effects
Tiagabine	NR		Substrate	No effects
Topiramate	No effects/substrate	(39)	Mild inductor (*in vitro*)	No effects
Lacosamide	No effects	(51)	No effects (*in vitro*)	No effects
Vigabatrin	NR		No effects	No effects
Zonisamide	Weak inhibitor	(34)	No effects/substrate	No effects
Phenobarbital	Inductor/substrate	(54)	Inductor	No effects
Phenytoin	Inductor/substrate (*in vivo*)	(56)	Inductor/substrate (*in vivo*)	NR
Ethosuximide	NR		Substrate	NR
Carbamazepine	Inductor (*in vivo*)	(57)	Substrate/inductor (*in vitro and vivo*)	NR
Valproate	Inductor/inhibitor (*in vitro*)	(59, 60)	Inductor/weak inhibitor (*in vitro*)	NR

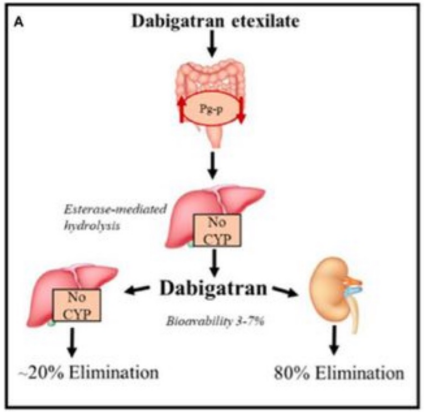
Front. Neurol., 07 December 2018
Sec.Epilepsy
https://doi.org/10.3389/fneur.2018.01067

Pharmacokinetic Interactions of Clinical Interest Between Direct Oral Anticoagulants and Antiepileptic Drugs

frontiers in Neurology

Alessandro Galgani[1], Caterina Palleria[2], Luigi Francesco Iannone[2], Giovambattista De Sarro[2], Filippo Sean Giorgi[1], Marta Maschio[3] and Emilio Russo[2]*

Nicola Ferri. Drug-Drug Interactions of Direct Oral Anticoagulants (DOACs): From Pharmacological to Clinical Practice *Pharmaceutics* 2022



Concomitant Drug		Effect on DOACs Concentration			
Antiepileptic Drugs	**Effect on P-gp and CYP**	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	•Strong decrease in AUC	•Strong decrease in AUC	•Possible decrease in AUC predicted	•Possible decrease in AUC predicted
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed	No significant effect on AUC predicted			
Gabapentin	No relevant interactions known/assumed	No significant effect on AUC predicted			
Lamotrigine	P-gp competition; No relevant interaction known/assumed	No significant effect on AUC predicted			
Levetiracetam	P-gp induction; P-gp competition	•Possible decrease in AUC predicted			
Oxcarbazepine	CYP3A4 induction; P-gp competition	No significant effect on AUC predicted			
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competition	•Decrease in AUC	•Decrease in AUC	•Possible decrease in AUC	•Possible decrease in AUC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	•Decrease in AUC	•Decrease in AUC	•Possible decrease in AUC	•Possible decrease in AUC
Valproic acid	CYP3A4/P-gp induction	•Possible decrease in AUC predicted			
Pregabalin	No relevant interactions known/assumed	No significant effect on AUC predicted			
Topiramate	CYP3A4 induction; CYP3A4 competition	No significant effect on AUC predicted			
Zonisamide	CYP3A4 competition; No relevant interactions known/assumed	No significant effect on AUC predicted			

AUC = Area under the curve; CYP = Cytochrome P 450; P-gp = P-glycoprotein. White: No relevant DDI anticipated. Yellow: caution/careful monitoring required, especially in case of polypharmacy or in the presence of ≥2 yellow/bleeding risk factors. Orange: Consider dose reduction or avoiding concomitant use. Red: Contraindicated/not advisable. Blue dot indicates PK interaction.

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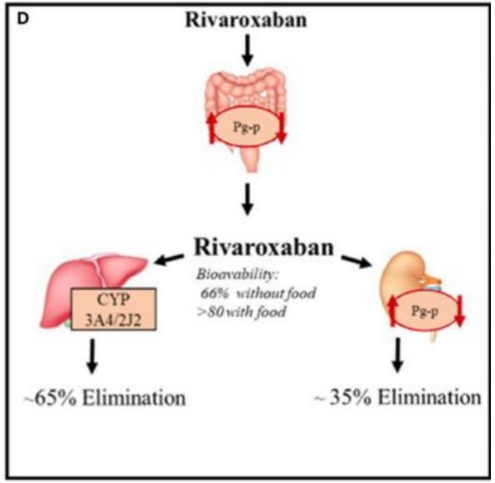

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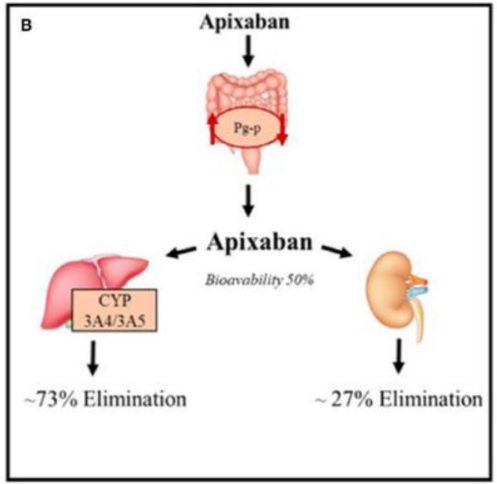

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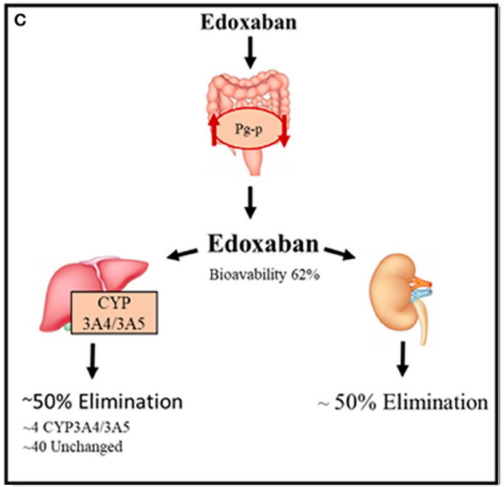

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Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels

ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–64
doi:10.1093/eurheartj/ehy136

levels

	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				
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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				
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Valproic acid	CYP3A4/P-gp induction				Ref.[149]
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Anticipated effects of common antiepileptic drugs on NOACs plasma levels.[147,150]
The hatched colour coding indicates no clinical or PK data available, and recommendations are based on the respective NOAC SmPC, where available, or expert opinion. Some of the colour codes will likely require adaptation as more data become available over time.
White: No relevant drug–drug interaction anticipated.
Brown (dark): Contraindicated due to *reduced* NOAC plasma levels.
Brown (light): Use with caution or avoid—either the label for the respective NOAC mentions that co-administration is possible despite a decreased plasma level, which are deemed not clinically relevant (nevertheless, since not tested prospectively, such concomitant use should be used with caution, and avoided when possible) or expert opinion.
Where no data or SmPC instructions were available, expert opinion was based on the following principles:

Thanks!

Any questions?