

# The risk of taking antiepileptic drugs



Jakob Christensen, Department of Neurology, Aarhus University Hospital

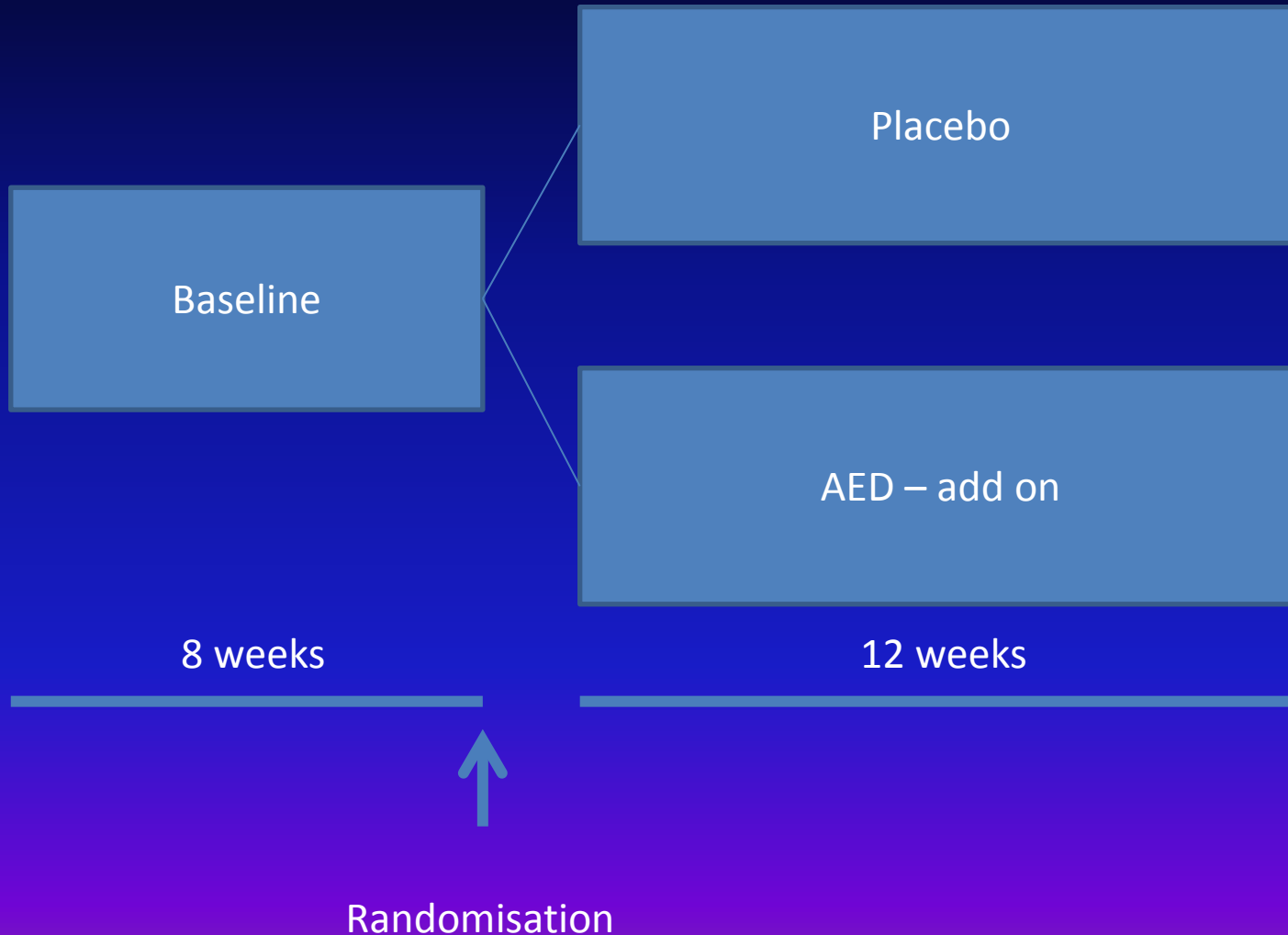
# Disclosure

## Company Name

## Nature of Affiliation

- UCB  
Serving on a scientific advisory board, and honoraria for speaking engagements
- Eisai  
Serving on a scientific advisory board, and editorial board, and honoraria for speaking engagements
- Novartis  
PI of clinical trial
- Pfizer  
PI of clinical trial
- Non-profit organization  
The Danish Epilepsy Association

# Randomized AED trials in epilepsy



# Food and Drug Administration



# FDA - suicidality

199 placebo-controlled trials

27,863 patients in drug arms

16,029 patients in placebo arms

from 11 drugs

# Information

0	No Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Not enough information, non-fatal

# Suicidal Behavior or Ideation

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# Type of disorder

Epilepsy	Psychiatric	Other
Epilepsy	Anxiety	Agitation
	Binge eating disorder	Chronic pain
	Bipolar disorder	Fibromyalgia
	Depression	Impaired cognition
	Panic disorder	Insomnia
	Post-Traumatic Stress Disorder	Migraine
	Schizophrenia	Neuropathy
	Social phobia	Obesity
		Radiculopathy
		Spasticity
		Tremor



# Drug groups

## 1. Sodium Channel Blocking Drugs

- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Topiramate
- Zonisamide

## 2. GABAergic Drugs and GABA-mimetic Drugs

- Divalproex
- Gabapentin
- Pregabalin
- Tiagabine
- Topiramate

## 3. Carbonic Anhydrase Inhibitors

- Topiramate
- Zonisamide

# Other factors

age

gender

race

setting

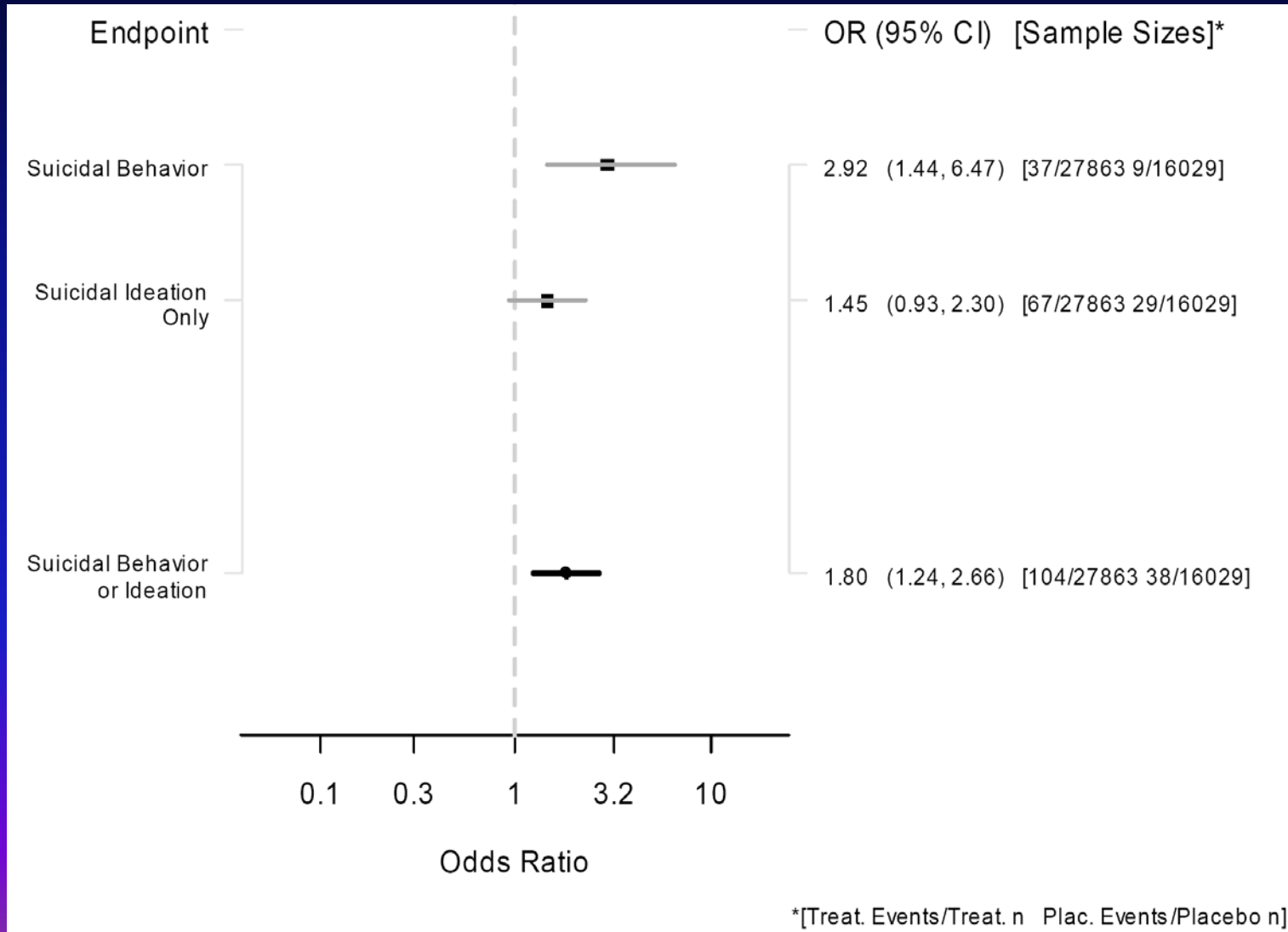
prespecified drug groups (GABAergic etc.)

# Suicidal Behavior or Ideation

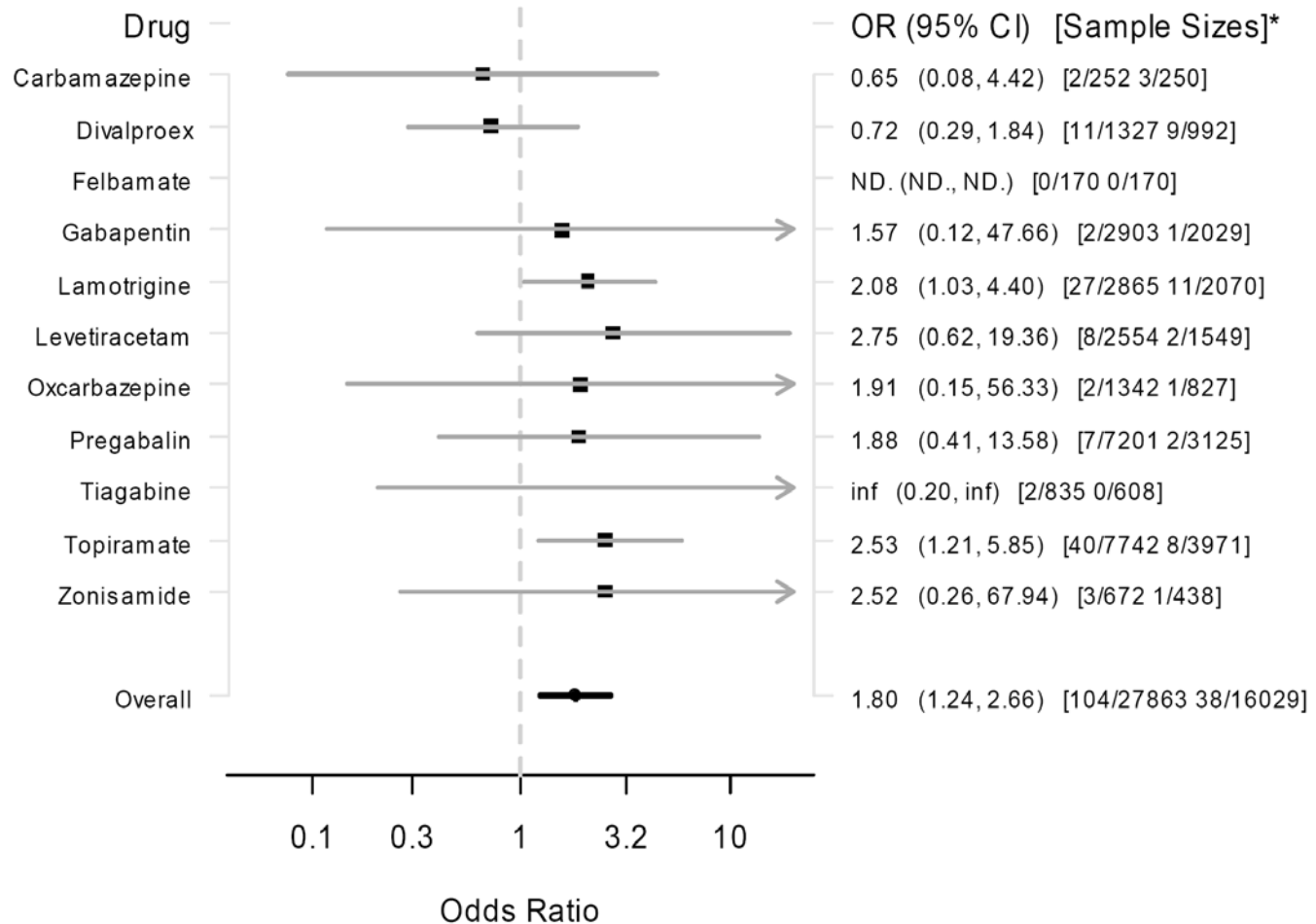
Event	Drug	Placebo	Total
Completed suicide	4	0	4
Suicide attempt	30	8	38
Preparatory acts	3	1	4
Suicidal ideation	67	29	96
Total	104	38	142

Notes: Events include only the most critical event for each patient.

# Type of suicide intention

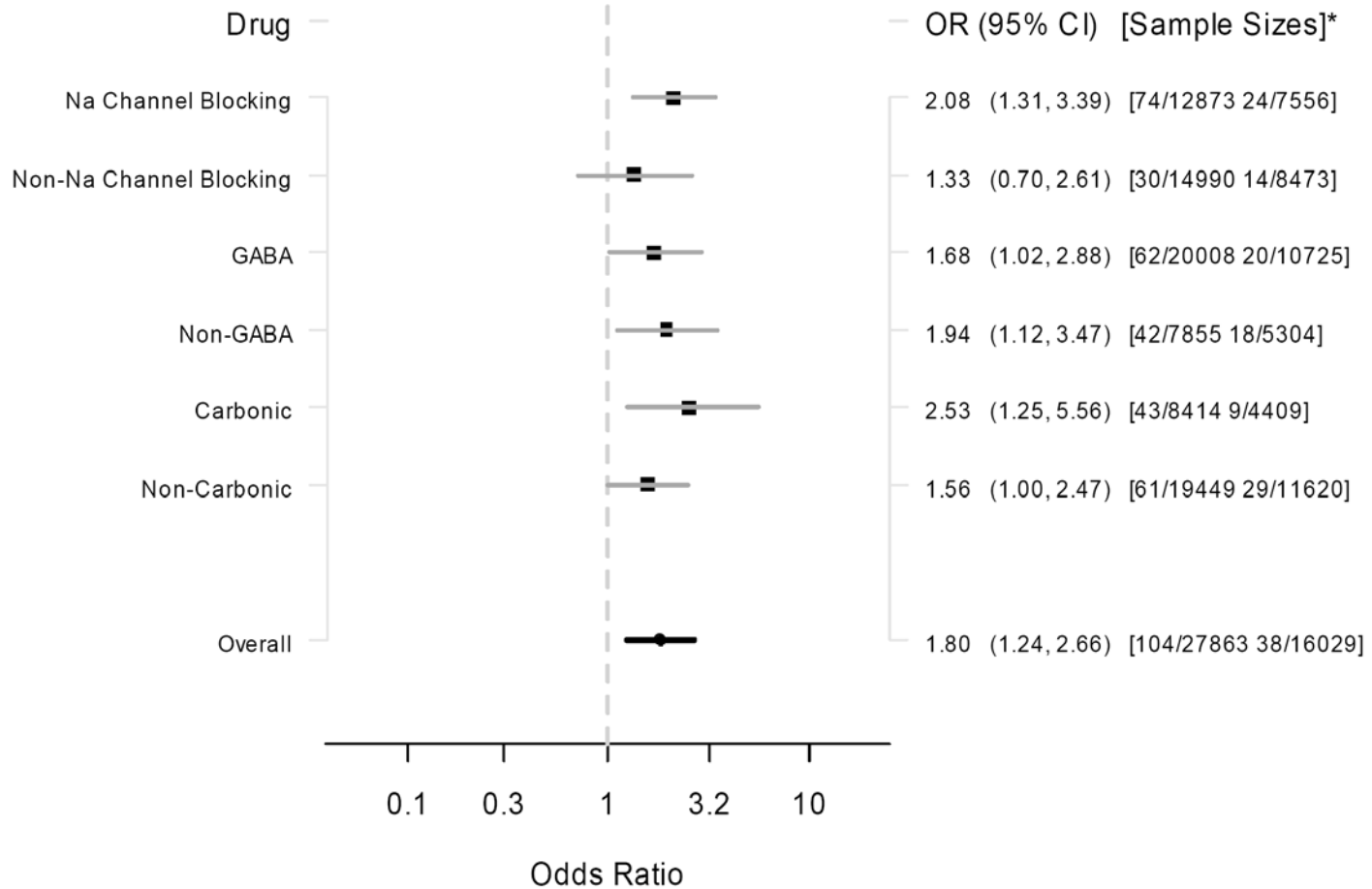


# Type of drugs



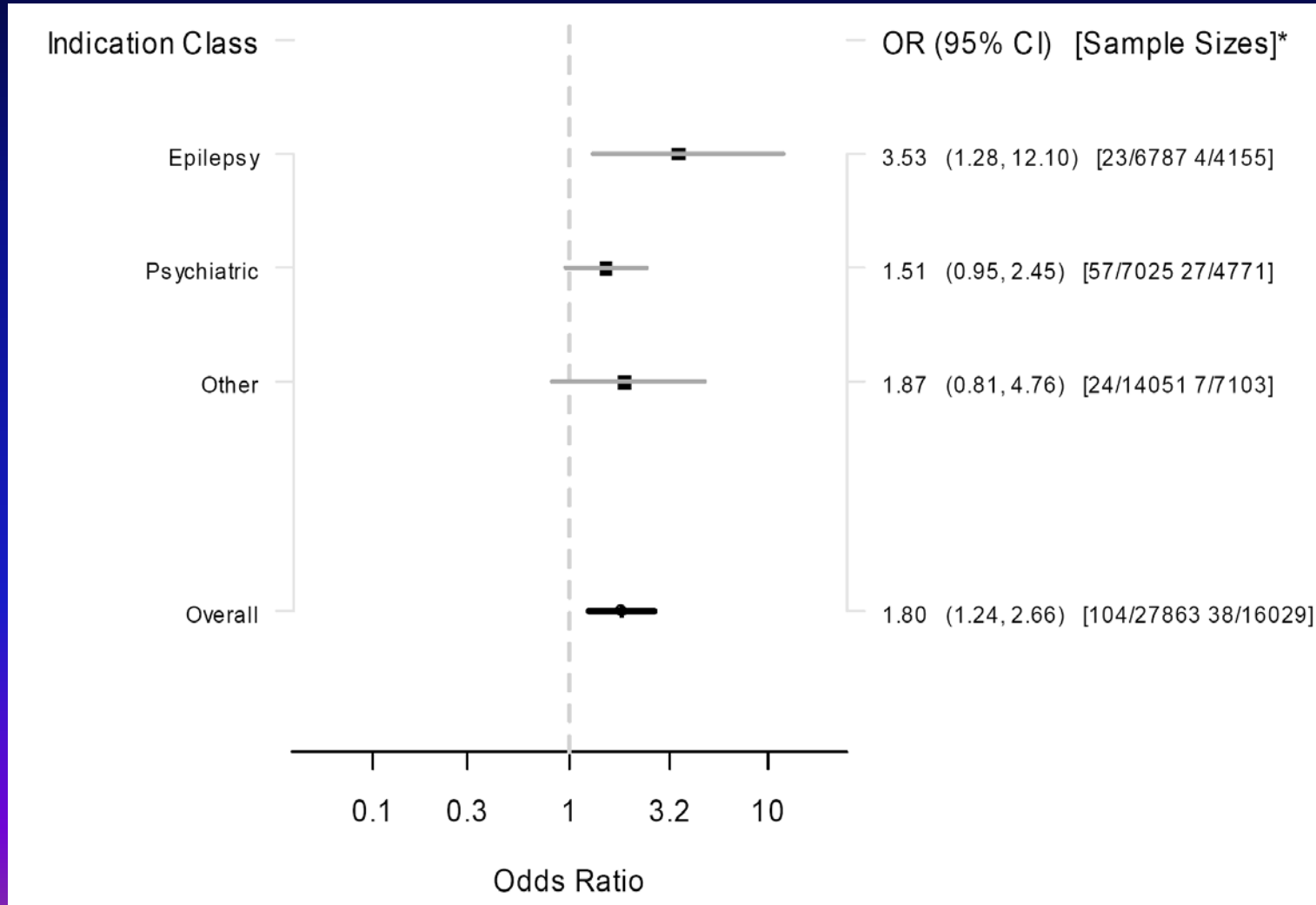
\*[Treat. Events/Treat. n Plac. Events/Placebo n]

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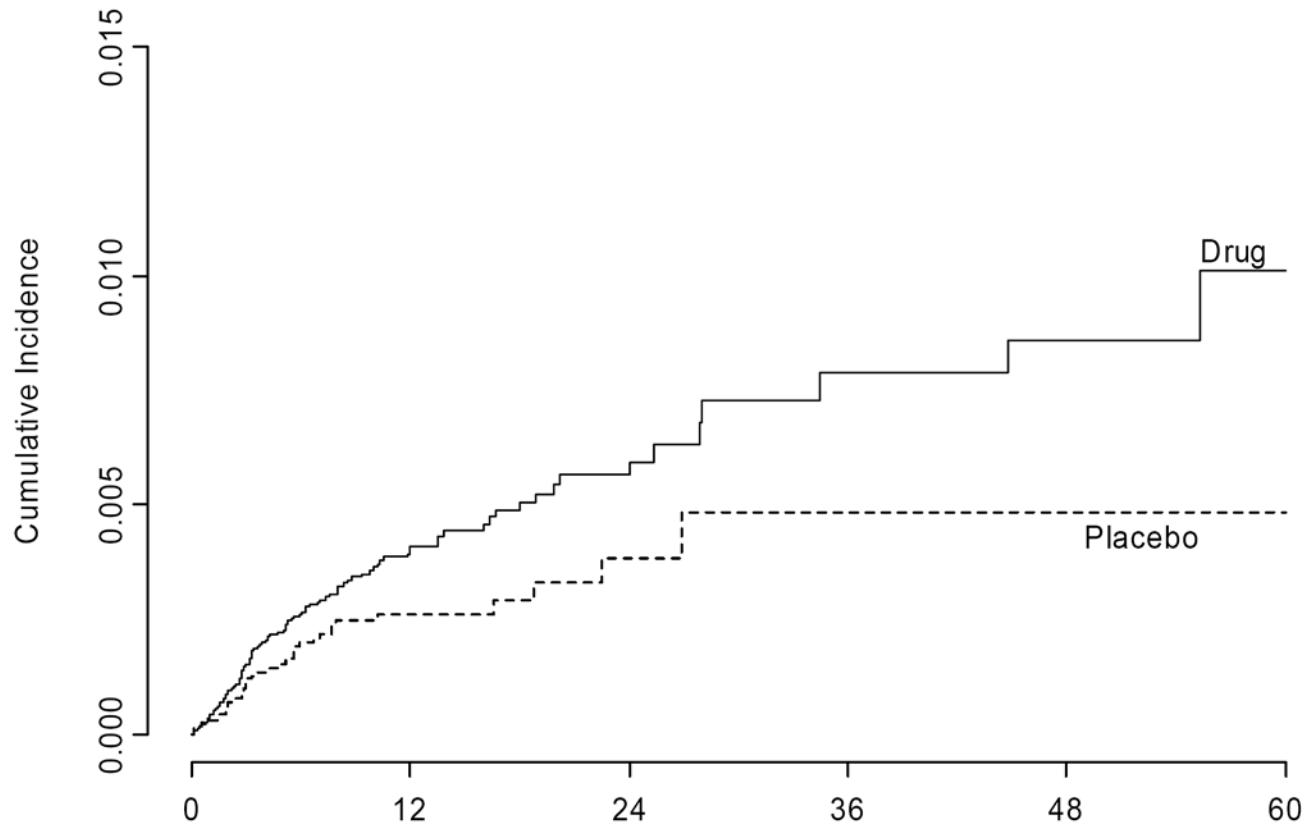


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# Type of disorder



# Time from initiating treatment



Number At Risk

Weeks

27854	12549	3716	1610	1178	494	Drug
16021	7410	1770	714	465	153	Placebo



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# Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials

*\*Philippe Ryvlin, Michel Cucherat, \*Sylvain Rheims*

# Mortality

112 eligible trials

- 106 (95%) in refractory partial epilepsy and
- six (5%) in refractory primary generalised tonic-clonic seizures

21,224 patients (5589 patient-years)

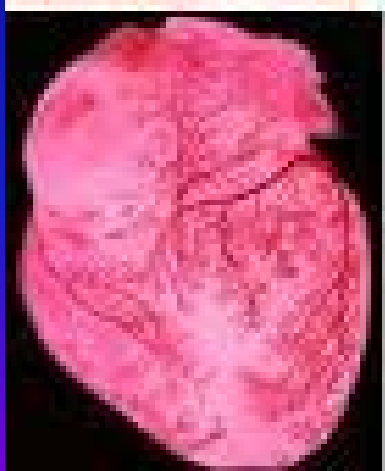
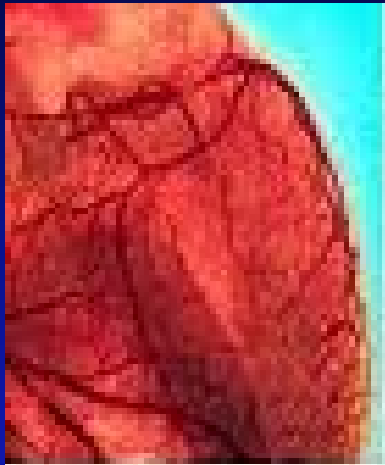
27 AEDs

Total of 33 deaths occurred

# Overall Mortality

	Exact Mantel-Haenszel OR, zero-event trials excluded			
	Number of trials	OR (95% CI)	p value	$I^2$ (% 95% CI)*
<b>Primary analysis: efficacious AED doses vs placebo</b>				
Definite and probable SUDEP (primary endpoint)	12	0.17 (0.05–0.57)	0.0046	0 (0–35.3)
Definite, probable, and possible SUDEP	12	0.17 (0.05–0.57)	0.0046	0 (0–35.3)
Other causes of death (non-SUDEP)	7	0.89 (0.28–2.79)	0.8407	0 (0–72.4)
All causes of death	17	<u>0.37 (0.17–0.81)</u>	<u>0.0131</u>	0 (0–29.8)

# The real big killers



# Cardiovascular Risk

Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study

Jonas Bjerring Olesen<sup>1\*</sup>, Steen Zabell Abildstrøm<sup>2,3</sup>, Jesper Erdal<sup>4</sup>, Gunnar H. Gislason<sup>1</sup>, Peter Weeke<sup>1</sup>, Charlotte Andersson<sup>1</sup>, Christian Torp-Pedersen<sup>1</sup> and Peter Riis Hansen<sup>1</sup>

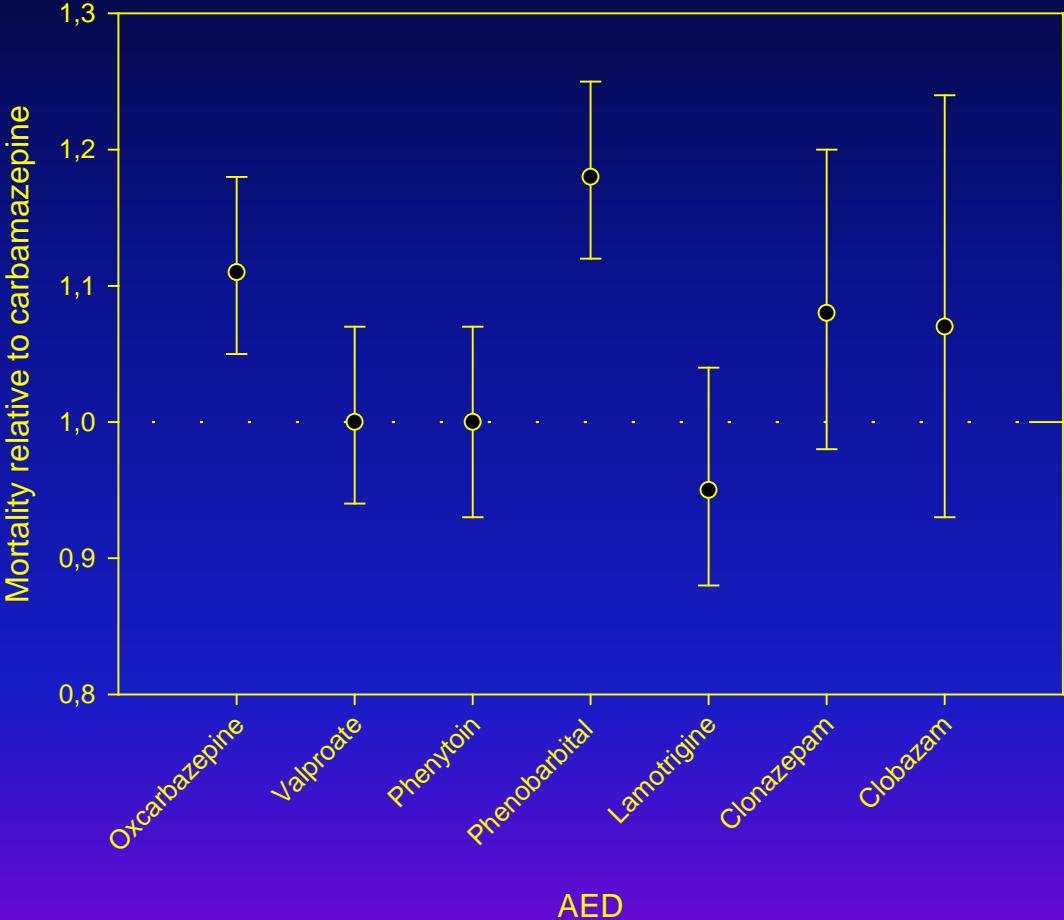
<sup>1</sup>*Department of Cardiology, Copenhagen University Hospital, Gentofte, Denmark*

<sup>2</sup>*National Institute of Public Health, Copenhagen, Denmark*

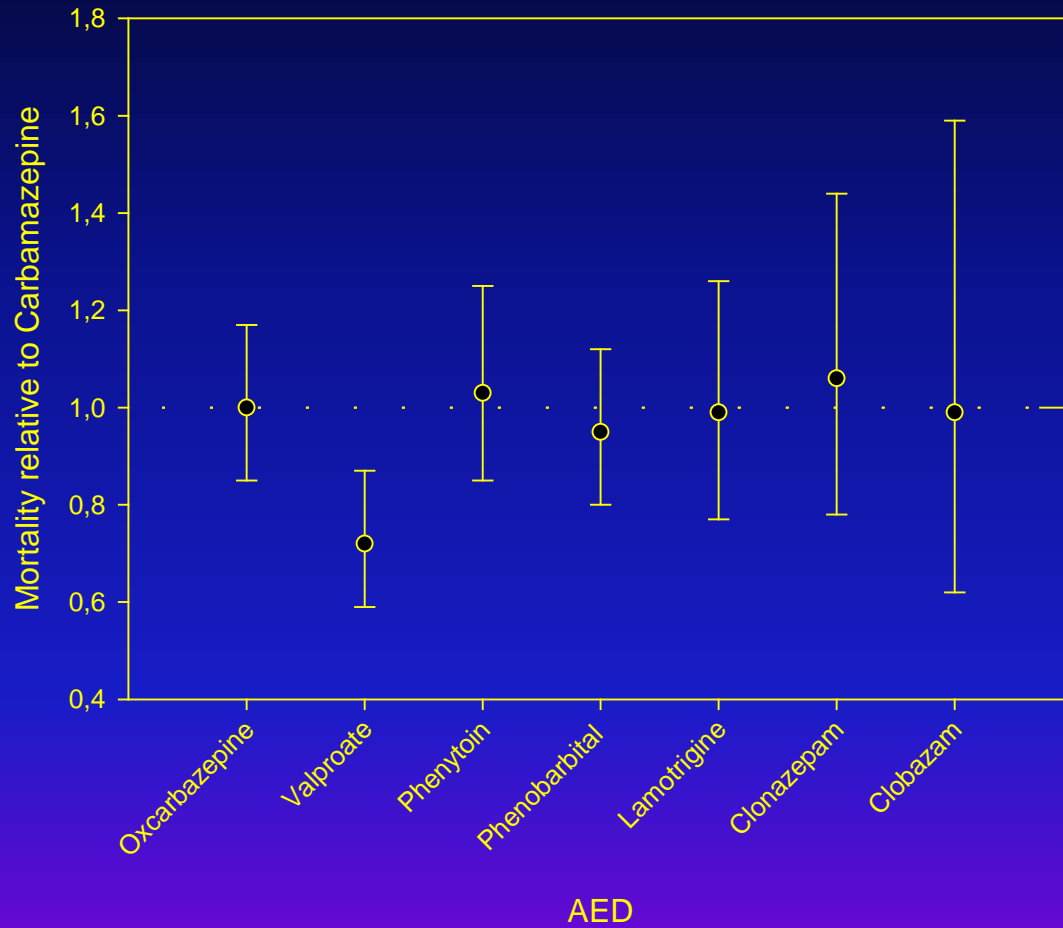
<sup>3</sup>*Department of Cardiology, Copenhagen University Hospital, Bispebjerg, Denmark*

<sup>4</sup>*Department of Neurology, Copenhagen University Hospital, Herlev, Denmark*

### All-Cause death in patients with epilepsy



## Risk of myocardial infarction in patients with epilepsy



# Cancer



IJC  
International Journal of Cancer

## Epilepsy, anti-epileptic medication use and risk of cancer

Jeanette Kaae<sup>1,2</sup>, Lisbeth Carstensen<sup>1</sup>, Jan Wohlfahrt<sup>1</sup>, Mads Melbye<sup>1</sup> and Heather Allison Boyd<sup>1</sup>

<sup>1</sup> Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen, Denmark

<sup>2</sup> Department of Oncology, Herlev University Herlev Ringvej 75, DK-2730 Hospital, Herlev, Denmark

Int. J. Cancer: 134, 932–938 (2014)



# Type of Cancer

Table 1. Incidence rate ratios<sup>1</sup> for cancer by epilepsy status and use of anti-epileptic medication, Denmark 1996–2010

Type of cancer	No epilepsy				Epilepsy			
	No use of anti-epileptic medication		Anti-epileptic medication used		No use of anti-epileptic medication		Anti-epileptic medication used	
	No. of cases	IRR (95% CI) <sup>2</sup>	No. of cases	IRR (95% CI) <sup>1</sup>	No. of cases	IRR (95% CI) <sup>1</sup>	No. of cases	IRR (95% CI) <sup>1</sup>
Bone	456	1 (ref)	42	0.74 (0.52–1.07)	1	0.50 (0.07–3.53)	6	1.21 (0.50–2.95)
Breast	41,123	1 (ref)	9,848	1.10 (1.07–1.12)	131	1.06 (0.88–1.27)	419	0.99 (0.89–1.09)
CNS	4,759	1 (ref)	782	1.10 (1.01–1.19)	32	2.00 (1.38–2.80)	180	3.91 (3.34–4.55)
Connective tissue	2,095	1 (ref)	348	1.06 (0.93–1.20)	8	0.96 (0.45–2.00)	29	1.26 (0.84–1.86)
Digestive organs	59,342	1 (ref)	12,649	1.04 (1.02–1.06)	207	1.17 (1.01–1.34)	707	1.06 (0.98–1.15)
Endocrine	1,827	1 (ref)	261	0.95 (0.82–1.10)	7	1.01 (0.47–2.08)	15	0.86 (0.51–1.42)
Female genital tract	17,645	1 (ref)	3,884	0.99 (0.95–1.02)	54	0.98 (0.74–1.28)	146	0.79 (0.66–0.93)
Hematologic	7,178	1 (ref)	1,354	0.98 (0.91–1.04)	24	1.13 (0.73–1.66)	69	0.84 (0.64–1.08)
Liver	2,439	1 (ref)	714	1.59 (1.45–1.74)	12	1.07 (0.50–2.04)	42	1.41 (1.02–1.92)
Lymphatic	8,115	1 (ref)	1,648	1.05 (1.00–1.12)	29	0.98 (0.64–1.41)	84	0.83 (0.65–1.04)
Male genital tract	34,628	1 (ref)	5,320	1.06 (1.03–1.09)	112	1.04 (0.85–1.25)	326	0.85 (0.76–0.95)
Mouth and throat	6,751	1 (ref)	1,672	1.46 (1.38–1.55)	82	3.09 (2.45–3.84)	209	2.25 (1.94–2.59)
Respiratory organs	39,008	1 (ref)	10,642	1.40 (1.37–1.43)	167	1.35 (1.15–1.57)	614	1.30 (1.20–1.41)
Skin	95,110	1 (ref)	19,459	1.10 (1.08–1.12)	271	0.92 (0.81–1.04)	1,025	1.03 (0.97–1.10)
Urinary tract	14,527	1 (ref)	2,961	1.09 (1.04–1.14)	34	0.80 (0.55–1.11)	183	1.14 (0.98–1.32)
Other <sup>3</sup>	13,423	1 (ref)	3,256	1.23 (1.17–1.28)	48	1.25 (0.92–1.65)	218	1.49 (1.28–1.72)
All cancers <sup>4</sup>	345,356	1 (ref)	73,984	1.11 (1.10–1.12)	1,207	1.12 (1.06–1.19)	4,222	1.12 (1.08–1.15)

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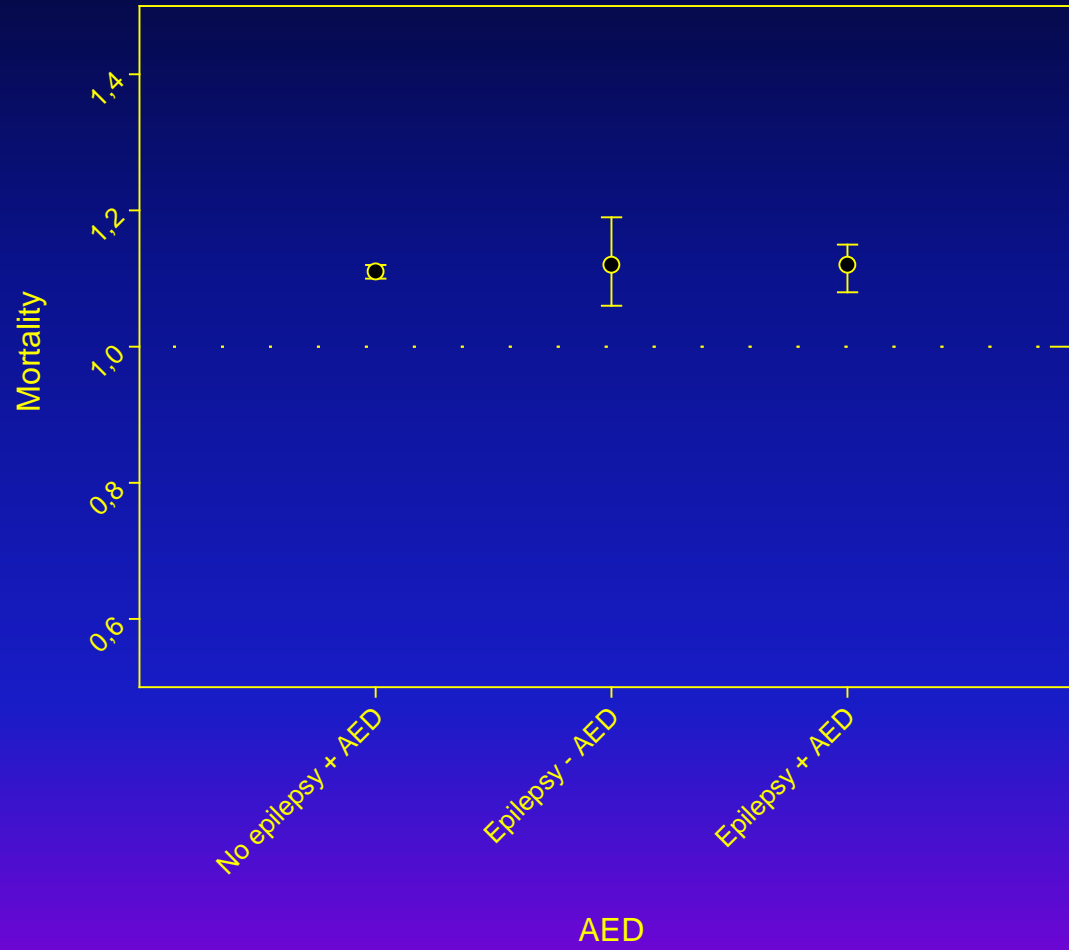
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## AED use and risk of Cancer



# Conclusions

Low risk of suicide (0.43% versus 0.24%) ☹️

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Reduced overall mortality 😊

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Reduced overall mortality 😊

Small risk from "big killers" 😊

Cancer 😐

Cardiovascular disease 😊



Thank you

