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Pillar of the Kingdom



Natural course and prognosis of epilepsy



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Natural course and prognosis of febrile seizures

Long-term prognosis of febrile seizures

- Population-based studies: risk of later developing epilepsy **between 2 and 7%** (depending on duration of follow up)

Chungath M and Shorvon S; Nat Clin Pract Neurol 2008

- 1980s to 2012, with a mean follow-up of 21.6 years
 - 6% of the children developed subsequent epilepsy** (compared with a population risk of 1.4%)

- age-specific incidence **risk of developing epilepsy is almost 10 times** (SIR = 9.7, 95% CI 5.7-16.4)

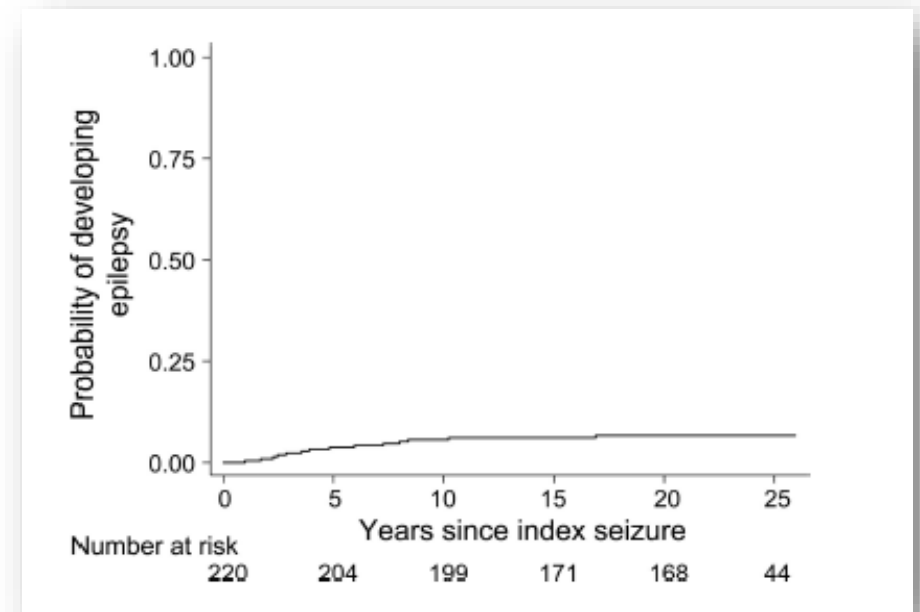
Neligan A et.al; Neurology 2012

- 12-yr F/U: 1/3 simple febrile convulsions


Risk factors: 1) number of FC:

The more febrile convulsions that occurred, the more likely was subsequent epilepsy

2) complex FC



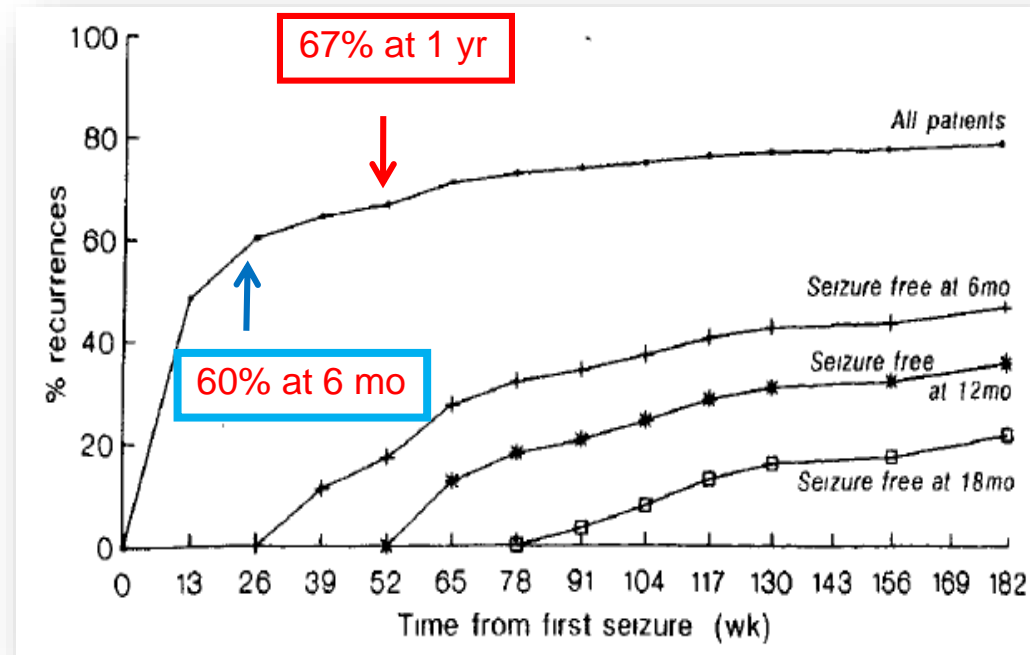
MacDonald BK et.al; Eur Neurol 1999



Natural course and prognosis of first unprovoked seizure

Early prognosis: Risk of recurrence after first unprovoked seizure

- ✓ Pooled estimate of 2 year recurrence risk = **42% (30-50%)**



78% at 3 yrs

44% at 3yrs

32% at 3yrs

17% at 3yrs



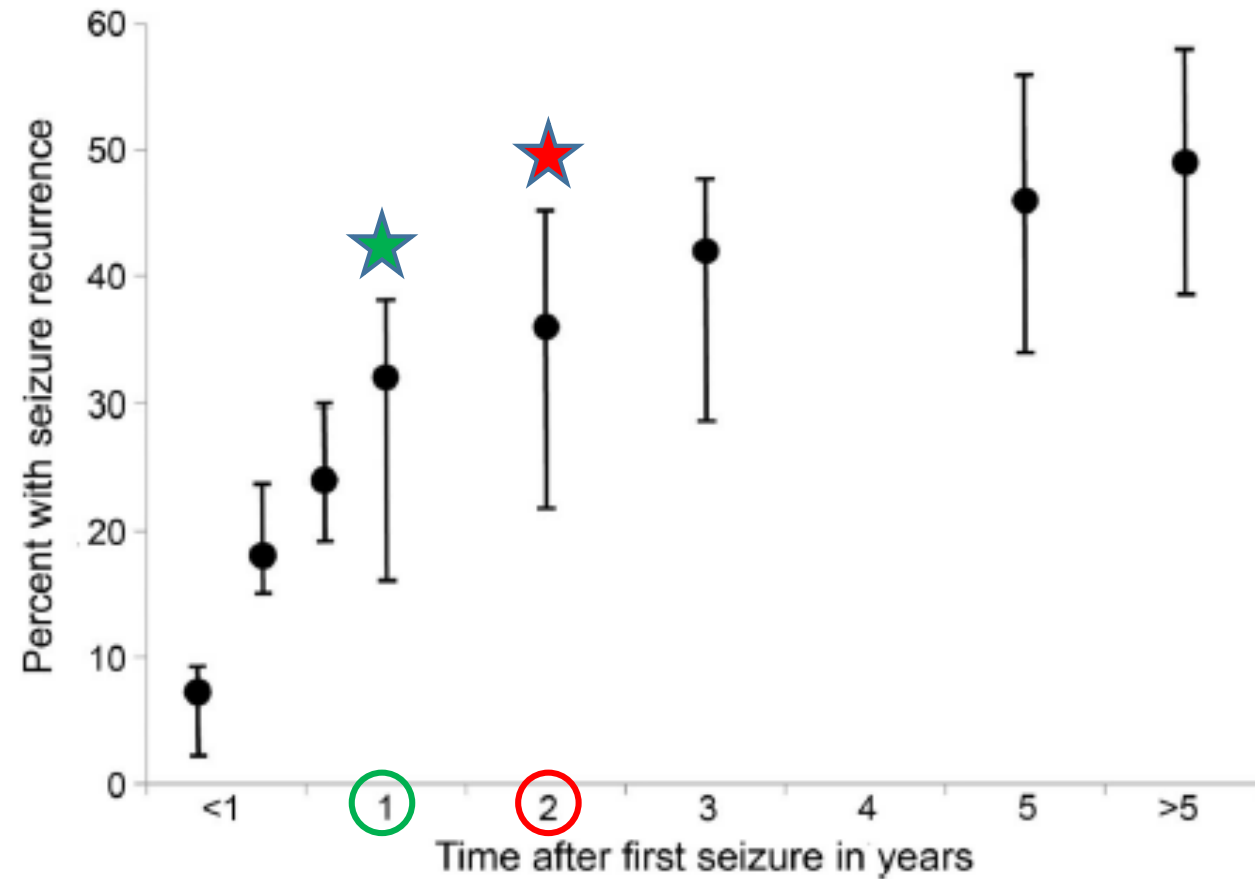
Management of an unprovoked first seizure in adults AAN and AES 2015

An adult with an unprovoked first seizure is at greatest risk of a recurrence relatively early within the **first 2 years (21-45%)** and especially in the first year

Table 1 Risk of seizure recurrence after an unprovoked first seizure in adults (Class I and II studies)

Ref.	Class	Age, y	No.	Treated	Seizure recurrences at various times, n (%)							
					1 mo	3 mo	6 mo	1 y	2 y	3 y	5 y	>5 y
10, 11	I	70% >19	238	164 (69)	—	—	—	38 (16)	50 (21)	60 (29)	70 (34)	81 (39)
12, 13	I	72% >16	397	204 (51)	24 (6)	58 (15)	75 (19)	98 (25)	111 (28)	—	—	—
17	II	≥16	147	62 (42)	—	—	39 (27)	50 (34)	60 (41)	61 (41)	—	—
18	II	Mean >20	76	36 (47)	2 (3)	18 (24)	20 (26)	22 (29)	—	—	—	—
16	II	≥16	306	41 (13)	—	55 (18)	79 (26)	111 (36)	136 (44)	144 (47)	—	—
19	II	75% >15	424	?	38 (9)	89 (21)	127 (30)	153 (36)	191 (45)	204 (48)	237 (56)	244 (58)
20	II	14-91	497	127 (26)	—	—	—	191 (38)	—	—	—	—
15	II	60% >20	812	404 (50)	—	—	179 (22)	—	288 (35)	—	378 (46)	398 (49)
21	II	≥16	228	113 (50)	—	—	—	68 (30)	—	—	—	—
22	II	18-50	87	45 (52)	—	—	—	30 (34)	37 (43)	39 (45)	—	—
Total			3,212	1,196 (43)	64 (7)	220 (18)	519 (24)	761 (32)	873 (36)	508 (42)	685 (46)	723 (49)

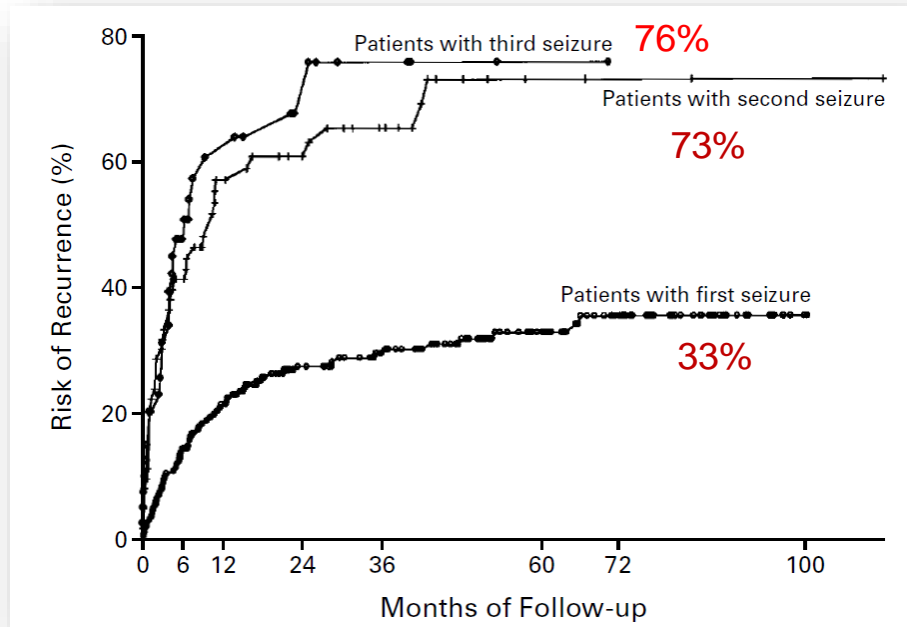
Figure 1 Percentages of patients with first seizure experiencing a recurrent seizure over time



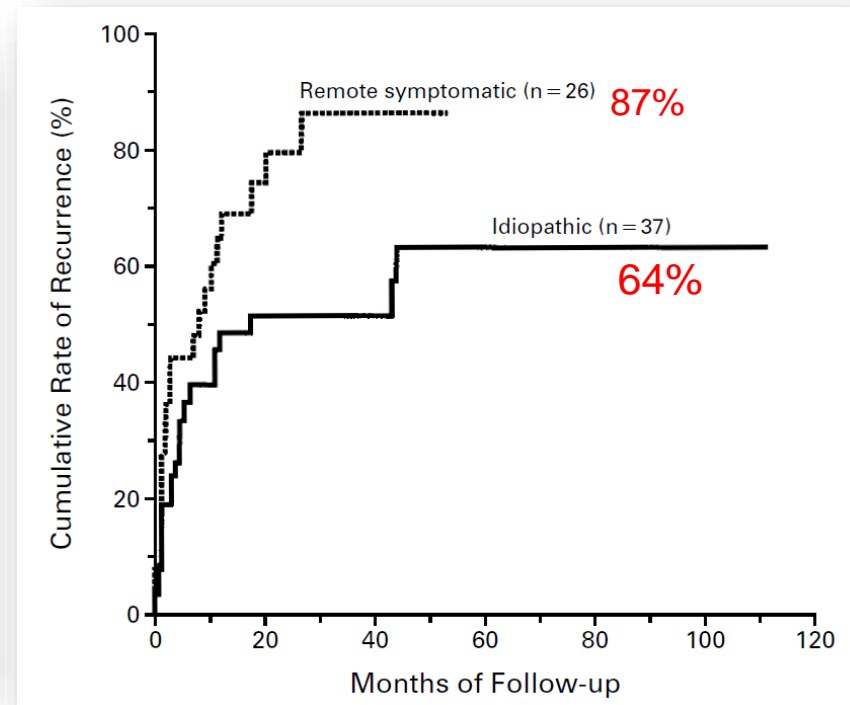
This graph is based on a fixed-effect pooled percentage model from data in table 1 and shows the cumulative average and the range for each time period from 1 month to more than 5 years.

Risk of recurrence

After first, second and third seizure



Etiology



What are the predictors of recurrence?

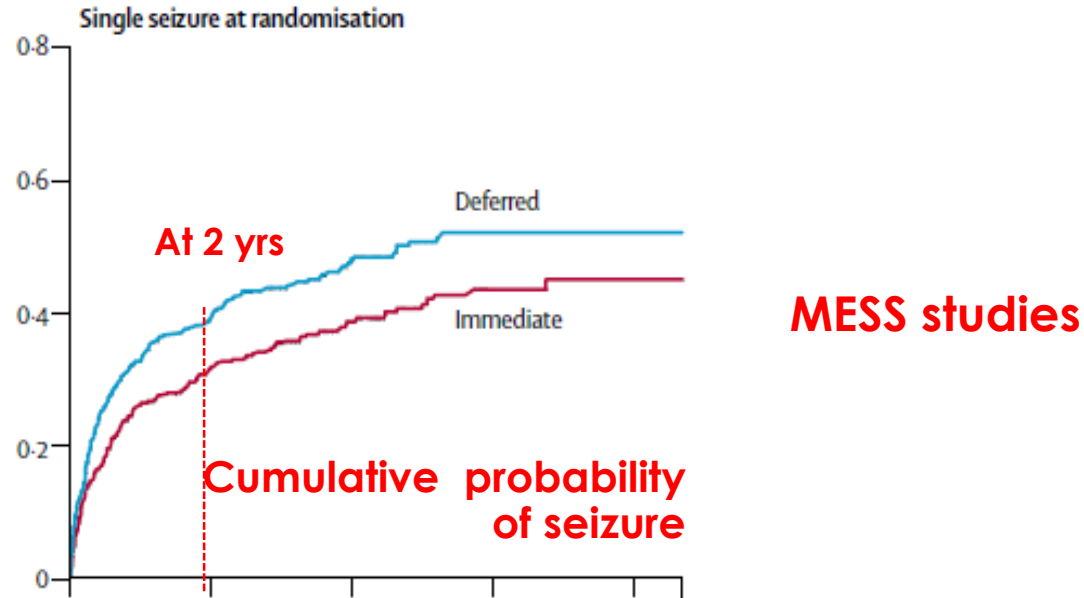
**Abnormal
neurological status
and abnormal EEG**

Predictor	Pooled RR of recurrence	Pooled risk of 2 year recurrence (%)
Abnormal neurological status	1.8	57
<u>Normal EEG</u>		27
<u>Epileptiform abnormalities in EEG</u>	2.0	58
Non-epileptiform abnormalities in EEG	1.3	37
Aetiology and EEG combined		
Idiopathic + normal EEG		24
Idiopathic + abnormal EEG	1.9	48
Remote symptomatic + normal EEG		48
Remote symptomatic + abnormal EEG	1.4	65

EEG, electroencephalogram; RR, relative risk.

Immediate vs deferred treatment after a first unprovoked seizure

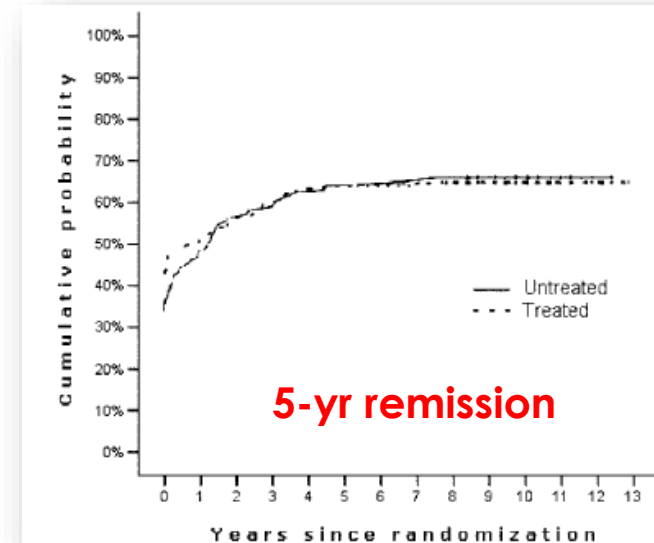
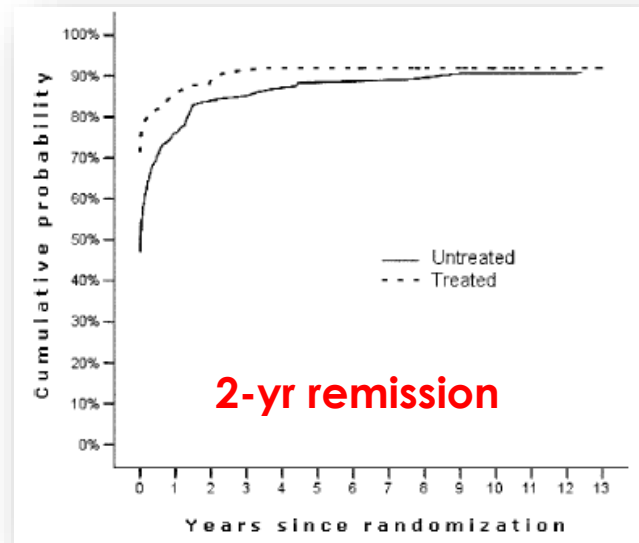
Marson A et.al *The Lancet* 2005



- 2 yr-remission: 69% vs 61%
 - At 3 yrs: 1-3 yrs sz remission: 74% vs 71%
 - At 5 yrs: 3-5 yr sz remission: 76% vs 77%
- “Immediate antiepileptic drug treatment reduces the occurrence of seizures in the next 1–2 years, but does not affect long-term remission in individuals with single or infrequent seizures”**

Immediate vs deferred treatment after a first unprovoked seizure

FIR.S.T. (First Seizure Trial) studies



- Treatment of the first seizure increased the probability of a 2-year remission in the first 3 years; however, the difference disappeared after a longer period of follow-up

(only patients with GTCs were included)

Prediction of risk of seizure recurrence

MESS studies

	Prognostic index
Starting value	
- 1 seizure prior to presentation	0
- 2 or 3 seizures prior to presentation	1
- 4 or more seizures prior to presentation	2
Add if present	
- Neurological disorder or deficit, <i>learning disability</i> or <i>developmental delay</i>	1
- Abnormal EEG	1
Risk classification group for seizure recurrence	
- Low risk	0
- Medium risk	1
- High risk	2-4

"There is little benefit to immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk"

"Should treat"

First unprovoked seizure with
➤ **Abnormal neurological signs**

and/or

➤ **Epileptiform discharges on EEG**



Natural course and prognosis of untreated epilepsies

Introduction

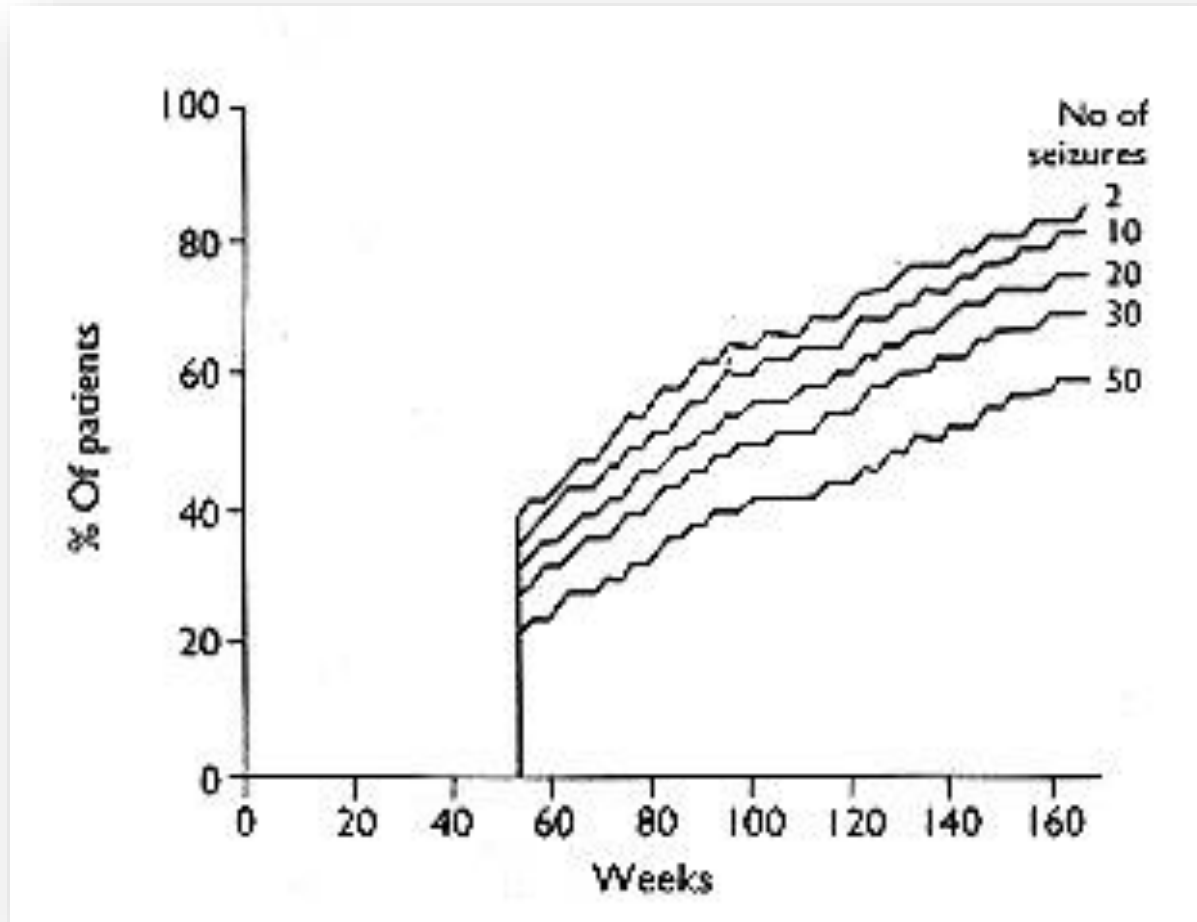
- **The course of disorders from onset to resolution, without interventions (Last, 1988)**
- **Evidence-based treatments with proven efficacy alter the natural course of disorders**
- **Prospective studies in untreated patients are thus not possible.**

Effect of duration of epilepsy on long-term prognosis

Gower's observation and Reynolds EH studies pointed out that the longer the history of epilepsy the worse the longer term prognosis

*Gowers WR 1881
Reynolds EH; BMJ 1995
Reynolds EH et.al; Epilepsia 1989*

Effect of number of seizure prior to treatment

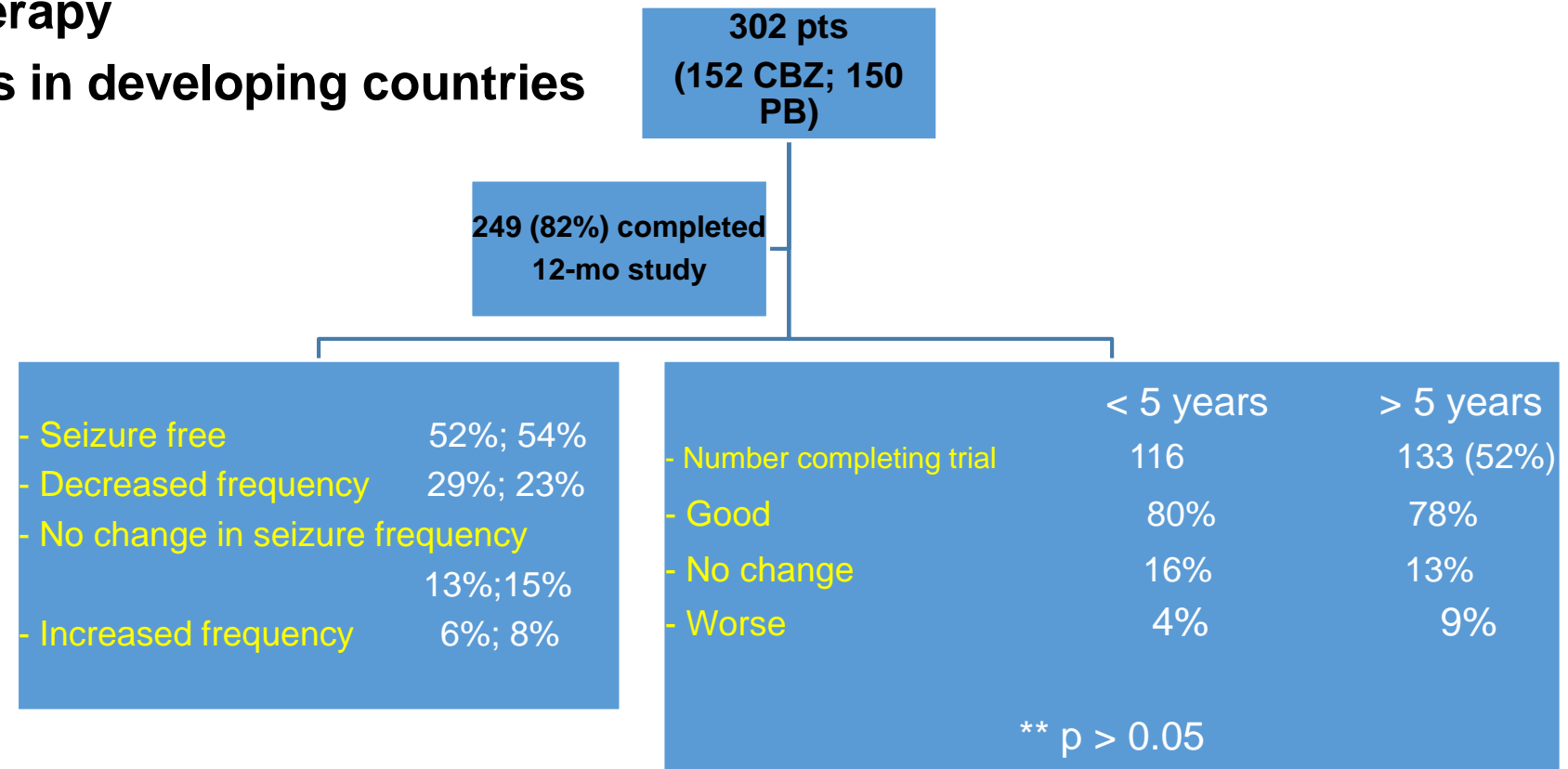


**Prospective study:
241 adults with newly
diagnosed epilepsy
treated with one drug**

*Gowers WR 1881
Reynolds EH; BMJ 1995
Reynolds EH et.al; Epilepsia 1989*

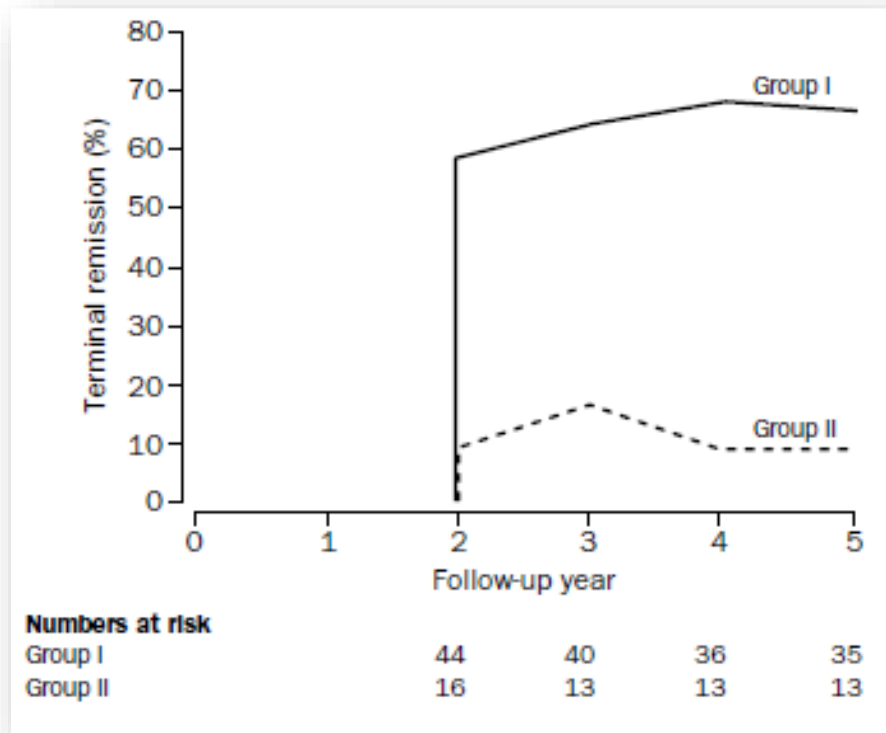
The effects of AEDs on long-lasting untreated epilepsy

- A study in Kenya (Lancet, 1991) : a finding that does not support the suggestion that the disorder becomes intractable if not treated early.
- Neither length of history of epilepsy nor number of seizures before treatment influenced effect of therapy
- Similar to other studies in developing countries (Malawi and Ecuador)



Feksi AT et.al; Lancet 1991
Watts AE; Br Med J 1989
Placencia et.al; JNNP 1994

Effect of number of seizure prior to treatment



135 adult patients with partial seizure or GTCs

- Treated with either PB or PHT
- Primary outcome: 2-year seizure freedom

Group I: good compliance coupled with lifetime total of ≤ 30 GTCs

Group II: poor compliance and lifetime total ≥ 30 GTCs



Natural course and prognosis of treated epilepsies

“2001”

TABLE 2. SUCCESS OF ANTIPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

VARIABLE	No. (%)
Response to first drug	222 (47)
Seizure-free during continued therapy with first drug	207 (44)
Remained seizure-free after discontinuation of first drug	15 (3)
Response to second drug	61 (13)
Seizure-free during monotherapy with second drug	41 (9)
Remained seizure-free after discontinuation of second drug	20 (4)
Response to third drug or multiple drugs	18 (4)
Seizure-free during monotherapy with third drug	6 (1)
Seizure-free during therapy with two drugs	12 (3)
Total	301 (64)

- 470 patients with newly-diagnosed epilepsy
- Seizure-free for at least 1 year
 - 1st drug: 47%
 - 2nd drug mono: 13%
 - 3rd drug mono: 1%
 - Two drugs: 3%

Medically controlled: 64%
Medically refractory: 36%

Effectiveness of AEDs

“2012”

Drug regimens	No. of patients	Seizure-free on monotherapy	Seizure-free on combination	Total no. seizure-free	% of cohort seizure-free	% Seizure-free on regimen
First	1,098	543	0	543	49.5	49.5
Second	398	101	45	146	13.3	36.7
Third	168	26	15	41	3.7	24.4
Fourth	68	6	5	11	1.0	16.2
Fifth	32	1	3	4	0.4	12.5
Sixth	16	1	1	2	0.2	12.5
Seventh	9	1	1	2	0.2	22.2
Eighth	3	0	0	0	0.0	0.0
Ninth	2	0	0	0	0.0	0.0

Medically controlled: 68%

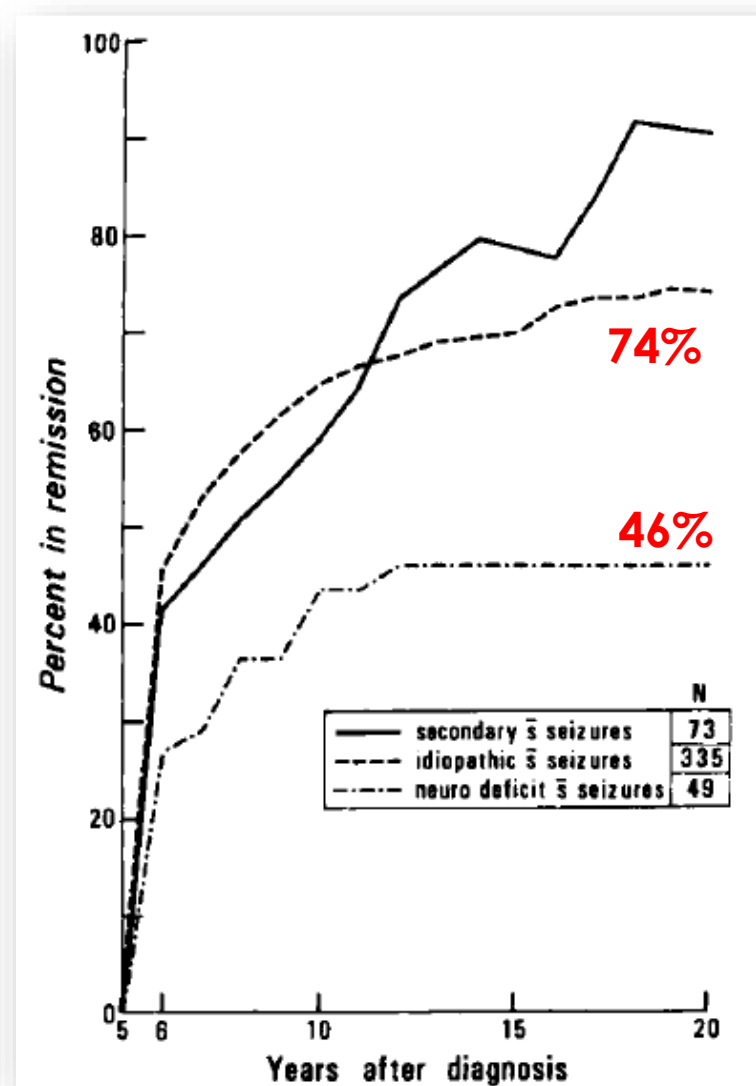
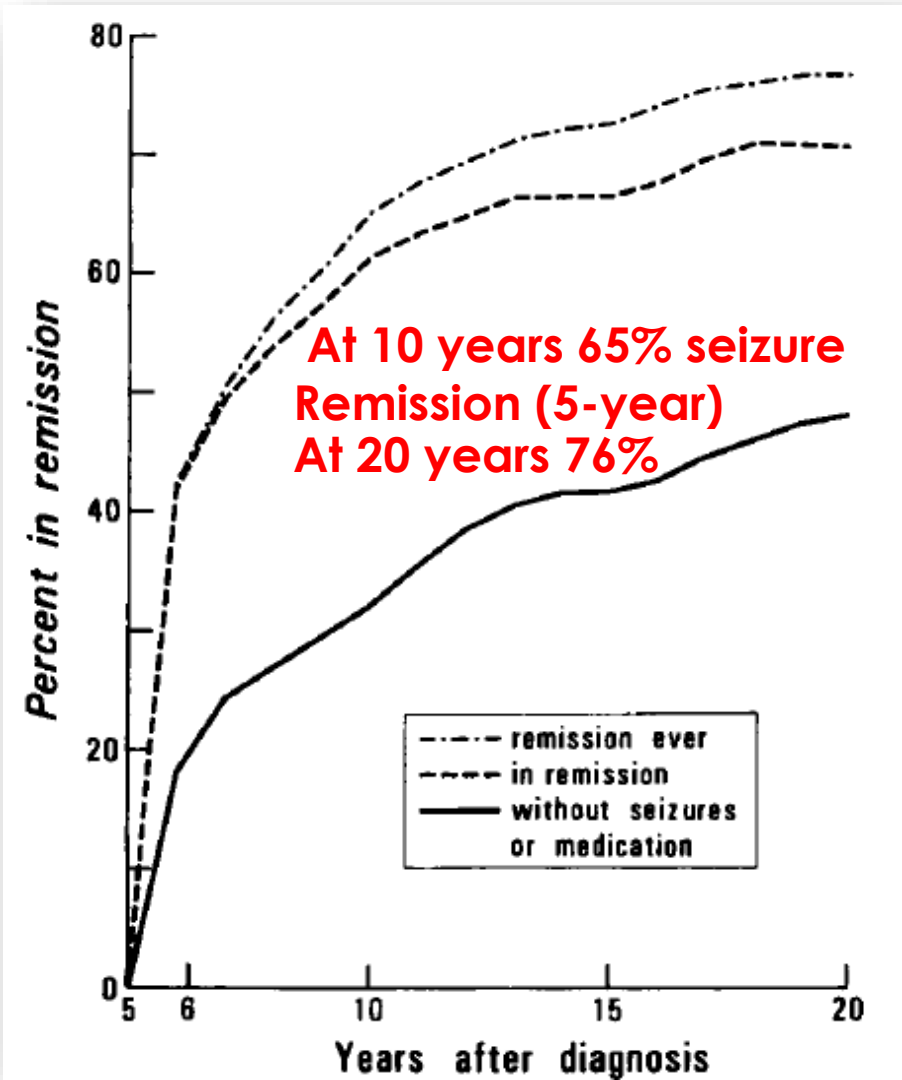
Medically refractory: 32%

- Despite the introduction of more than **15 new AEDs** (since 1985), there is limited evidence endorsing improved outcomes in the common adult epilepsies **over the past 30 years**
- Based on two large studies by the same group, there has been **slightly increased rate of seizure freedom** from **64% to 68%**

Late prognosis

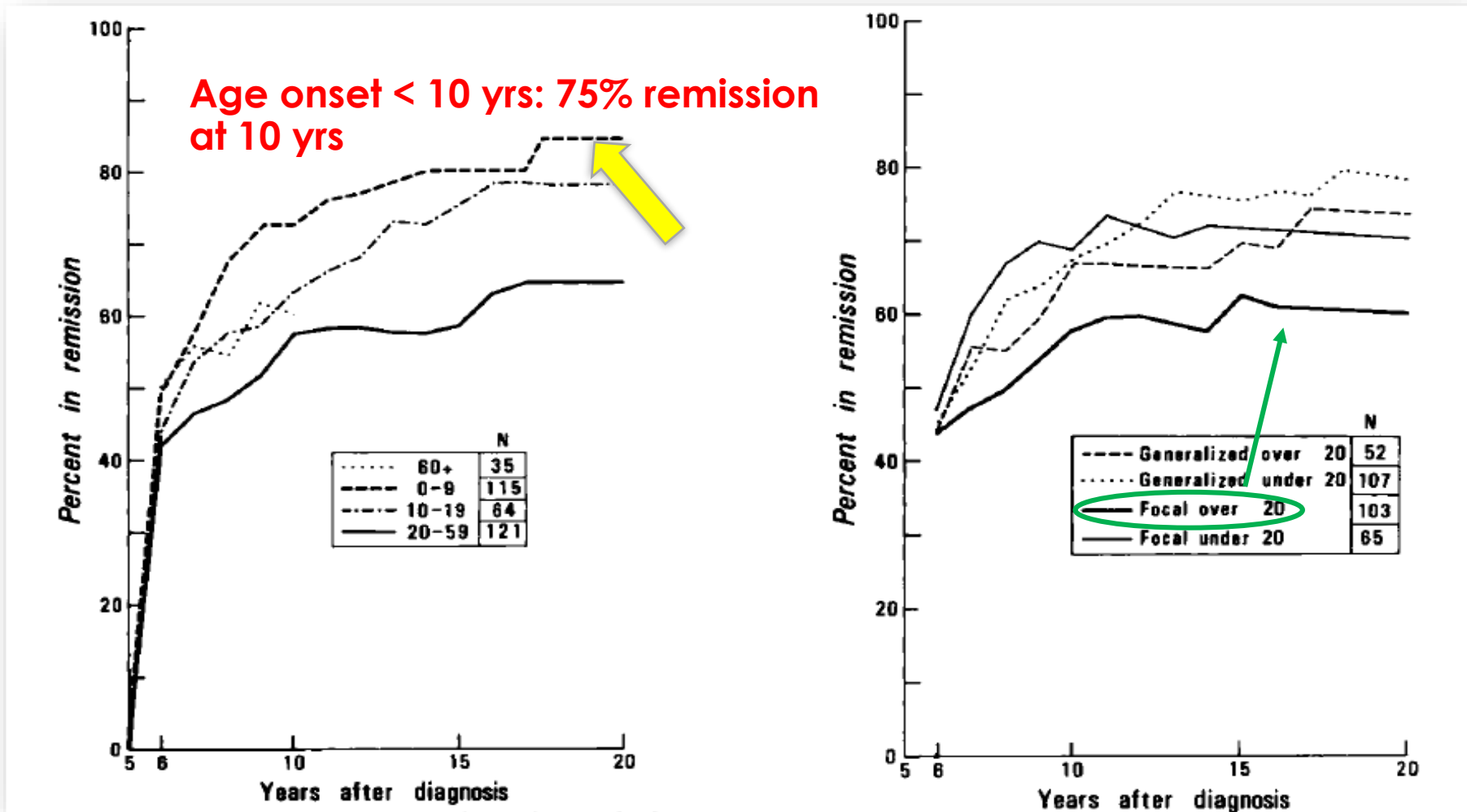
- **Based on 3 longitudinal community-based studies with long-term follow up**
 - **Mayo Clinic Record linkage study (US)**
 - **Tonbridge study (UK)**
 - **Turku study (Finland) (childhood-onset epilepsy)**

Mayo clinic study (20 years follow up)



- 475 pts followed at least 5 yrs
- 141 pts > 20 yrs

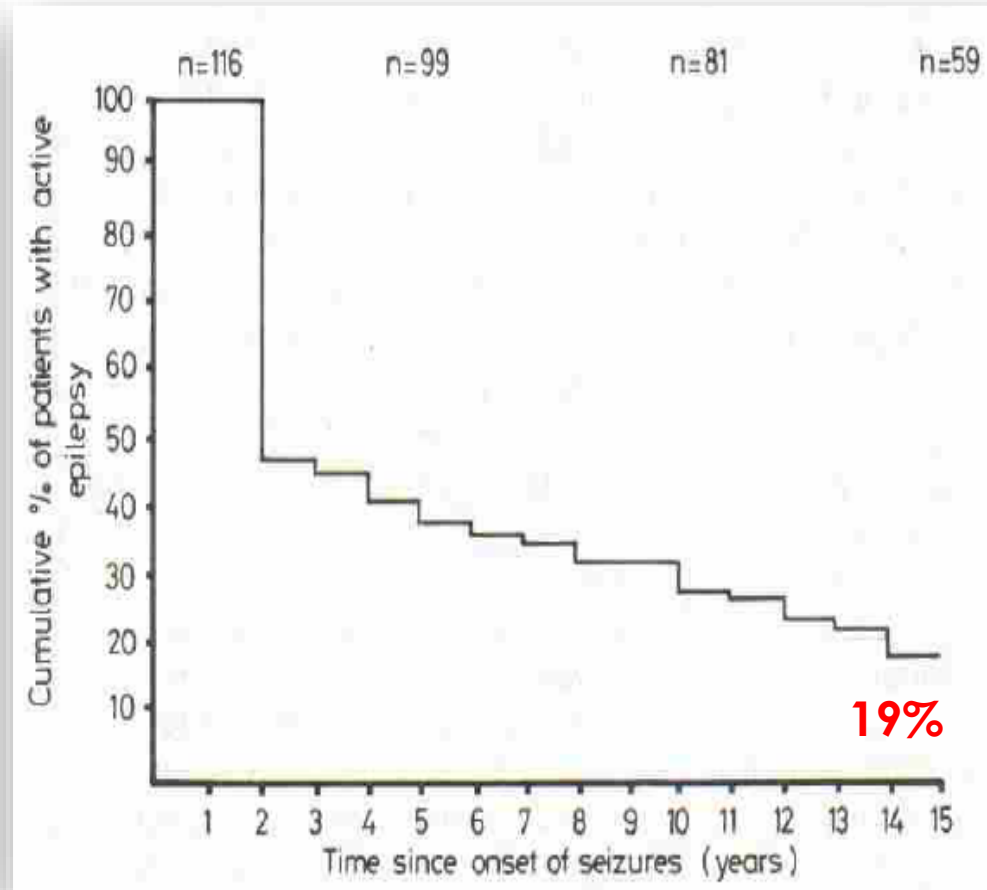
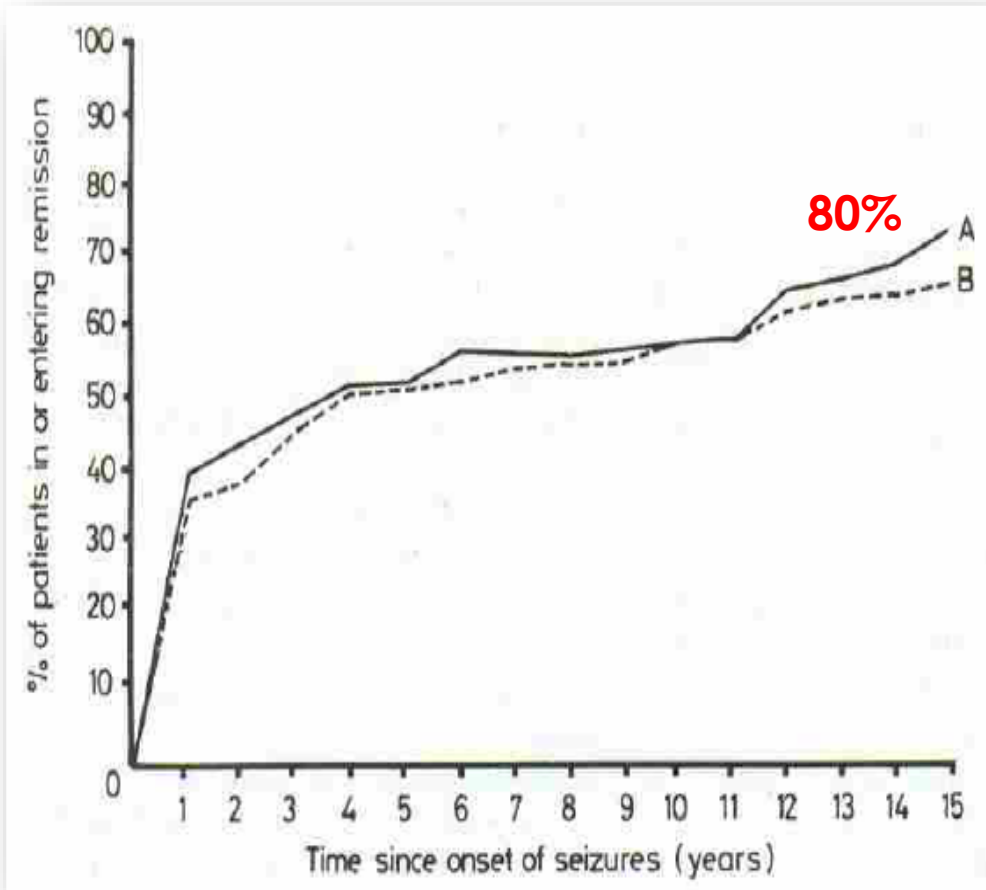
Mayo clinic study



Higher remission: generalized-onset seizure diagnosed < 10 yrs

Lower remission: CPS with adult onset

Tonbridge study (15 years follow up)



About one fifth (20%) of the patients continued to have seizure (chronic epilepsy)

Tonbridge study

- **At 5 years after the first seizure**
 - **of those whose epilepsy was still active, only 21% achieved subsequent terminal remission as compared with 96% of those who were already in remission**

“ the longer seizure continues to occur, the lower the probability for subsequent remission ”

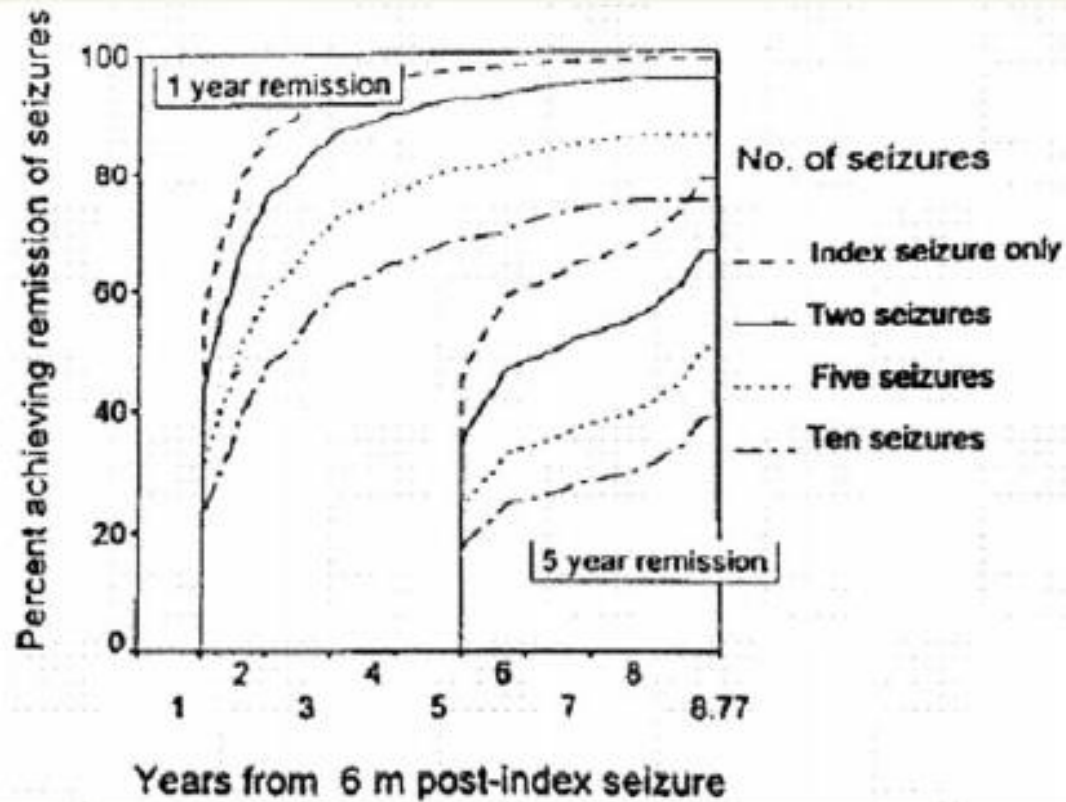
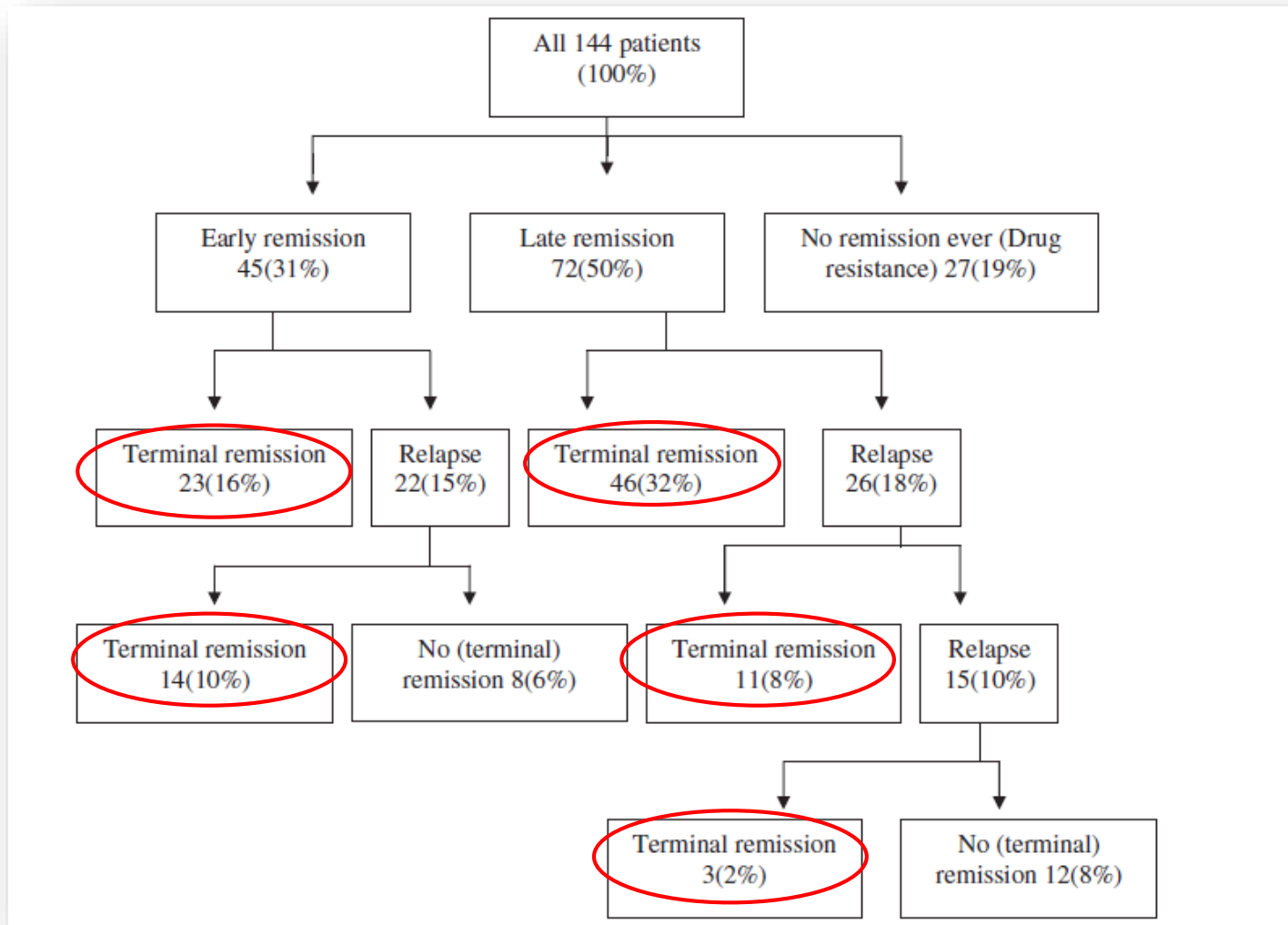


Figure 2 NGPSE: the influence of seizure density on long-term remission. The percentage of patients achieving remission in those who had experienced one (dashed line), two (solid line), five (dotted line), or 10 (dashed and dotted line) seizures in the period from the index seizure to 6 months.

The more number of seizure in the 6 months after the first seizure, the lesser is the chance of long-term remission

Turku study (37 years follow up)

- Seizure before the age of 16 years



- 67% achieved terminal remission (5-year seizure freedom at the end of follow up)
- 19% drug resistant
- 19% entered terminal remission after a relapse

Conclusion

- **2/3 of the patients (58-65%)** achieved 5-year cumulative terminal remission at 7-10 years follow up
- **3/4 of the patients (67-78%)** with childhood-onset epilepsy achieved 3-5 year remission at 12-37 years follow up

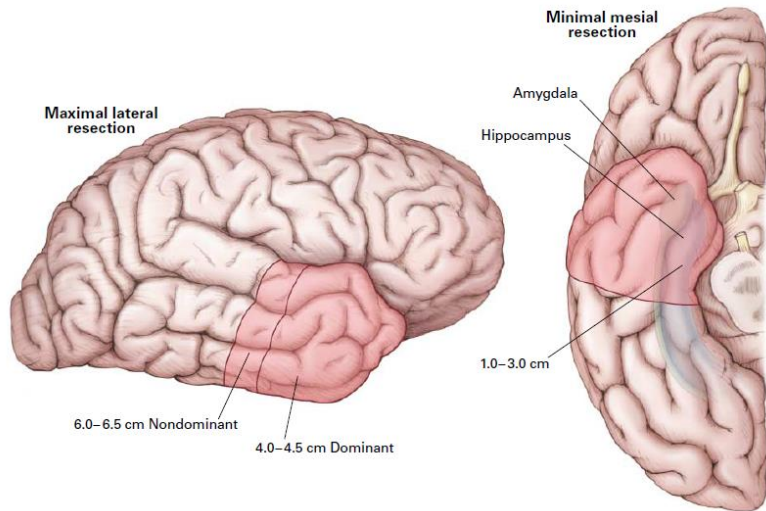
Factors which influence on long-term remission rate

- ✓ Neurological deficits
- ✓ Age onset
- ✓ Seizure type
- ✓ Number of early seizure



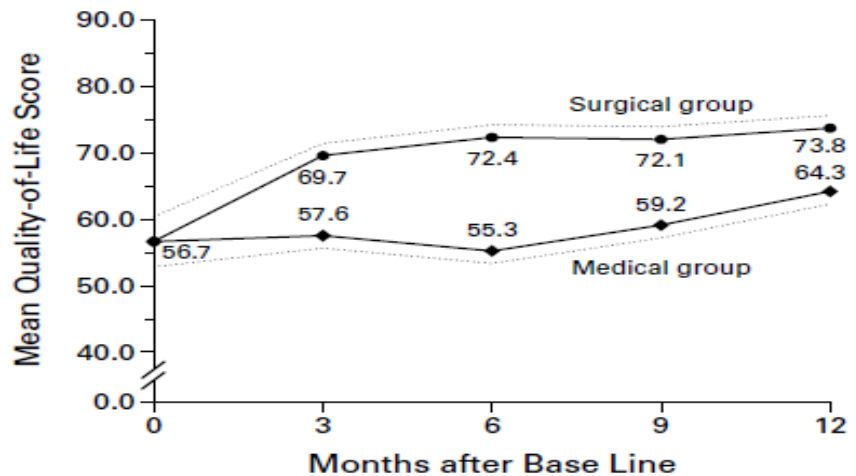
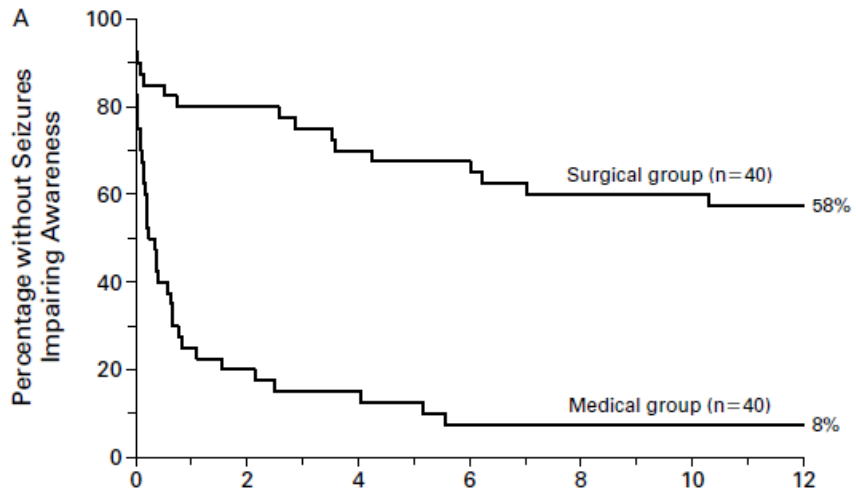
Natural course and prognosis of medically intractable epilepsy with surgeries

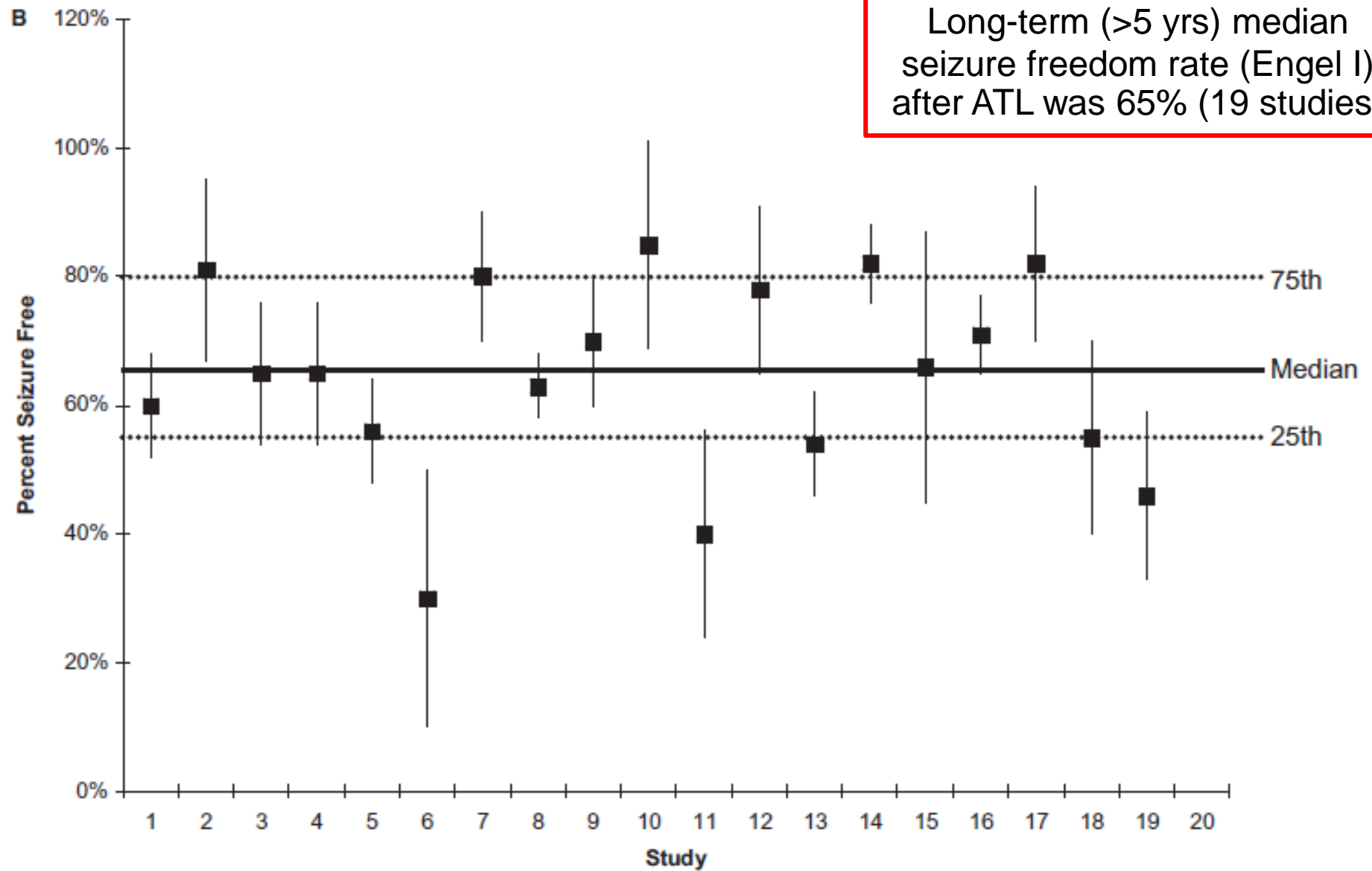
RCT of surgery for temporal lobe surgery

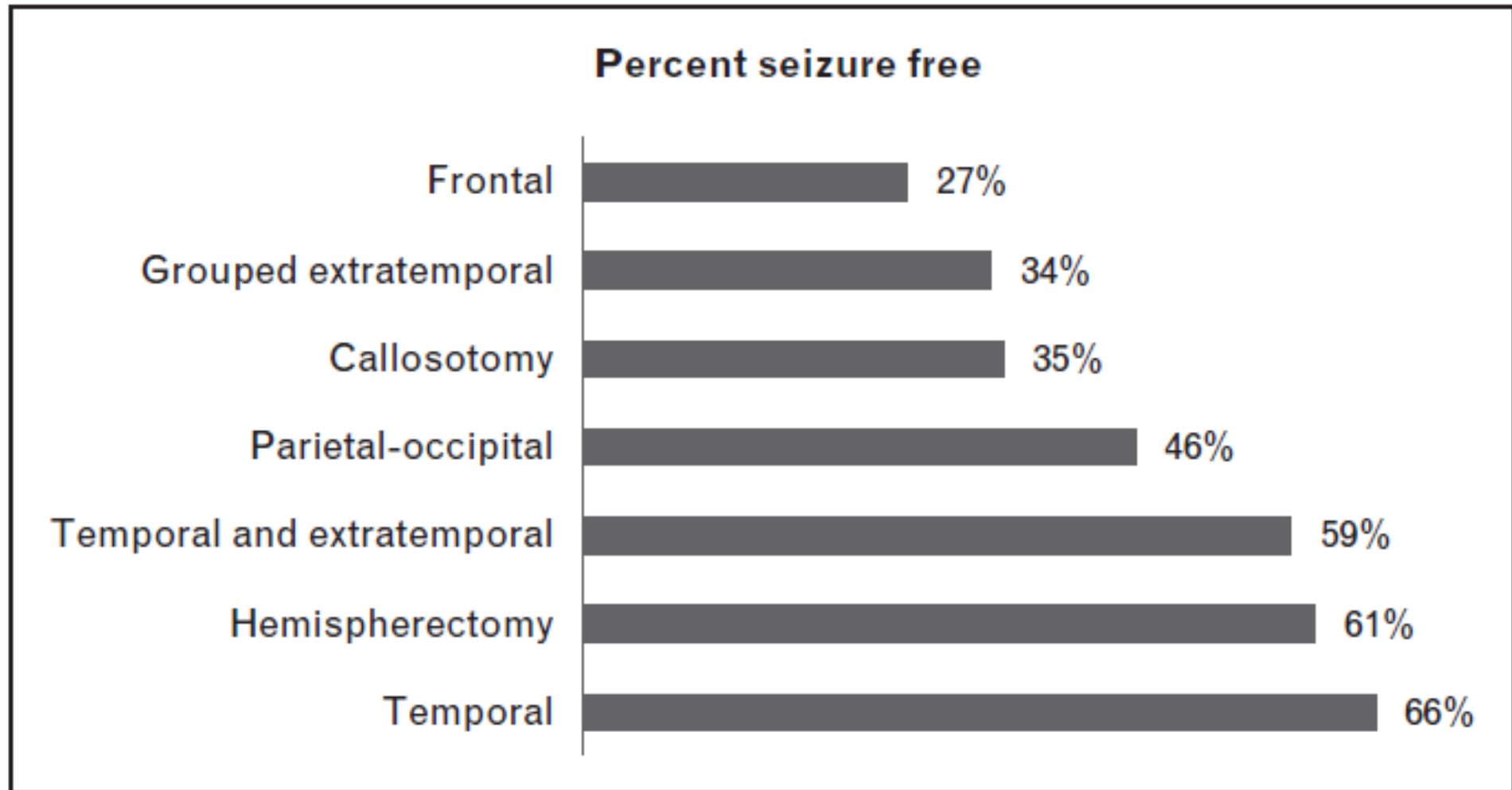


The patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life ($P < 0.001$ for both comparisons) than the patients in the medical group

Wiebe S et.al; NEJM 2001

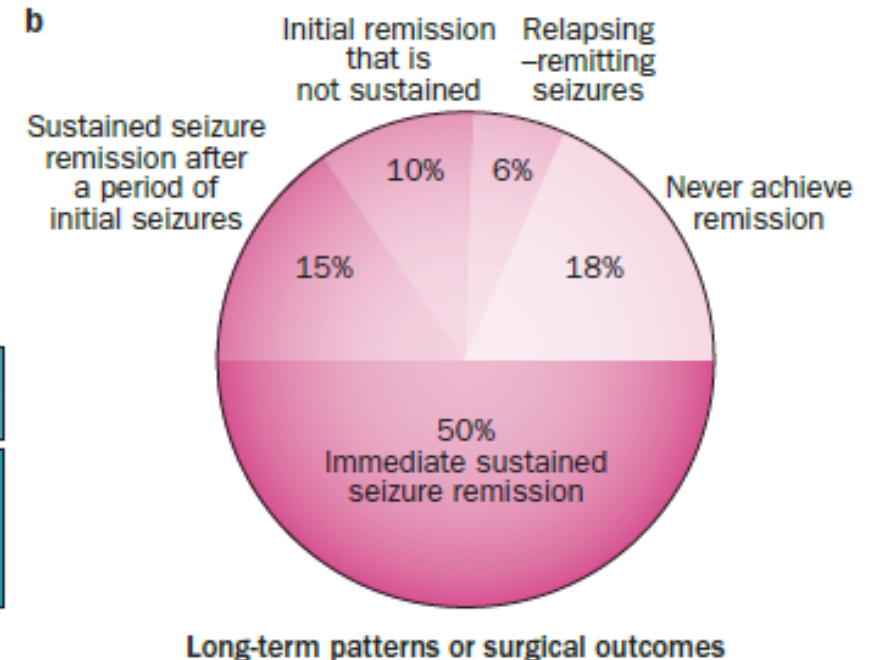
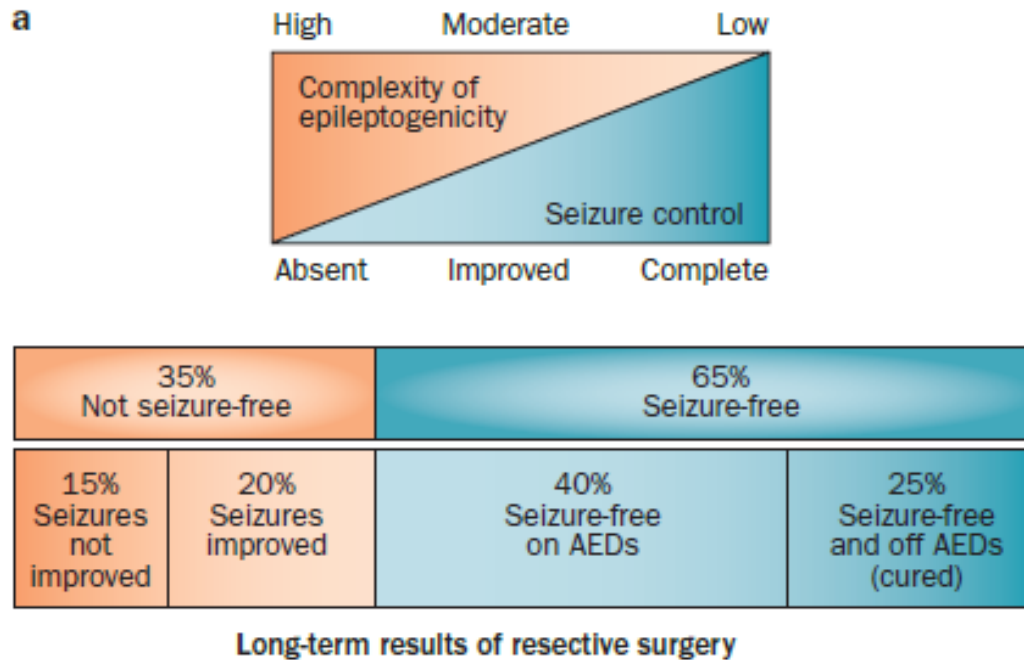






*Tellez-Zenteno JF et.al; Brain 2005
Weibe S and Jette N; Curr Opin Neurol 2012*

The outcome of surgical treatment in patients with epilepsy





Thank you for your attention