Chulalongkorn Comprehensive Epilepsy Centre

Chulalongkorn University
จุฬาลงกรณ์มหาวิทยาลัย
Pillar of the Kingdom

Natural course and prognosis of epilepsy

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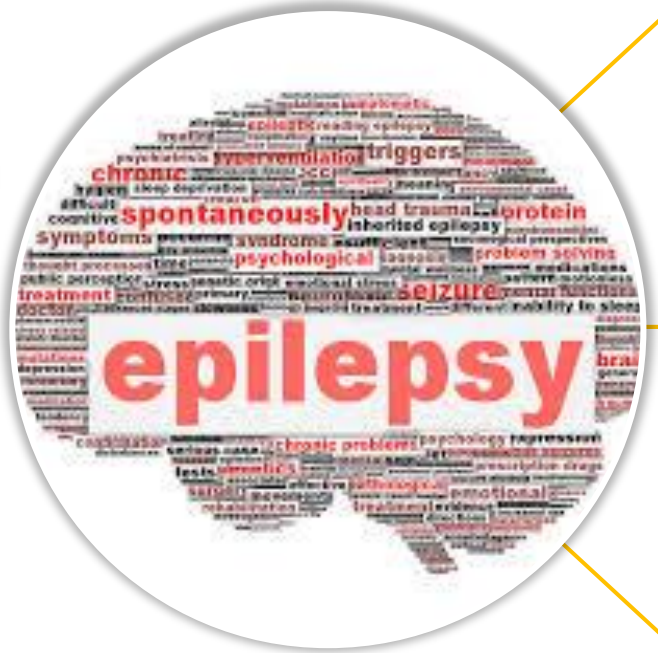
Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC)
The Thai Red Cross Society

Febrile seizures

First unprovoked seizure



Untreated epilepsy

Treated epilepsy

Medically intractable epilepsy with surgeries

Natural course and prognosis of febrile seizures

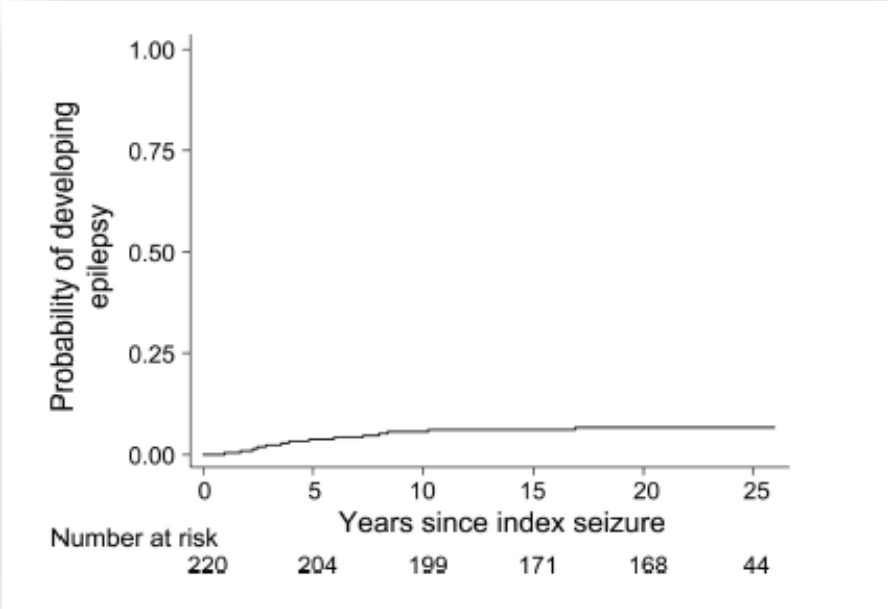
Long-term prognosis of febrile seizures

- **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

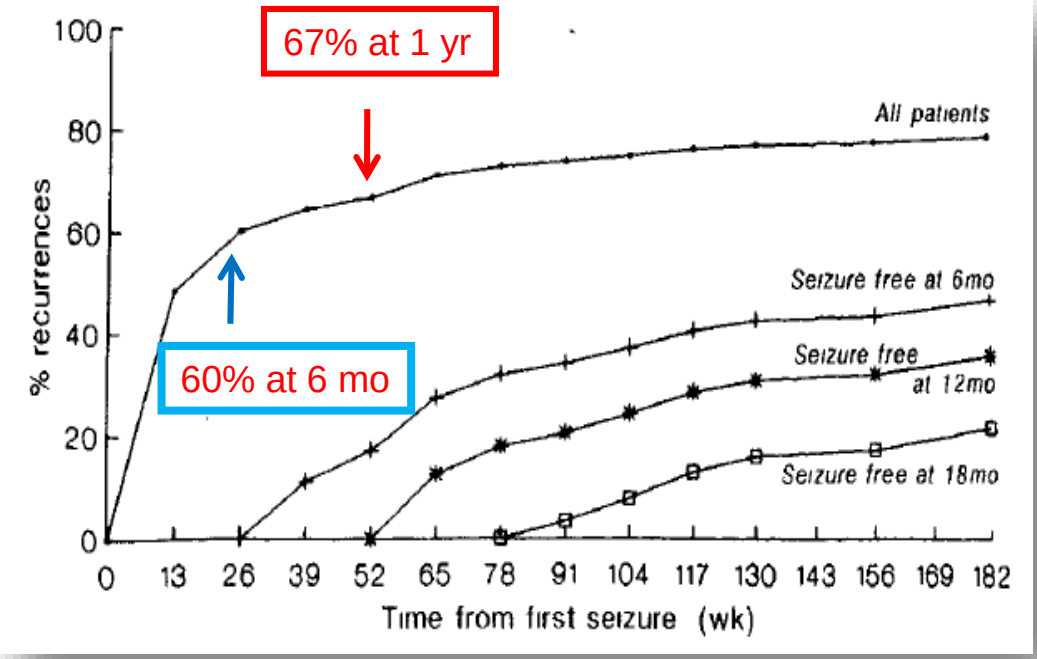
MacDonald BK et,al; Eur Neurol 1999

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

Berg AT and Shinnar S Neurology 1991
Hart YM et.al; The Lancet 1990

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

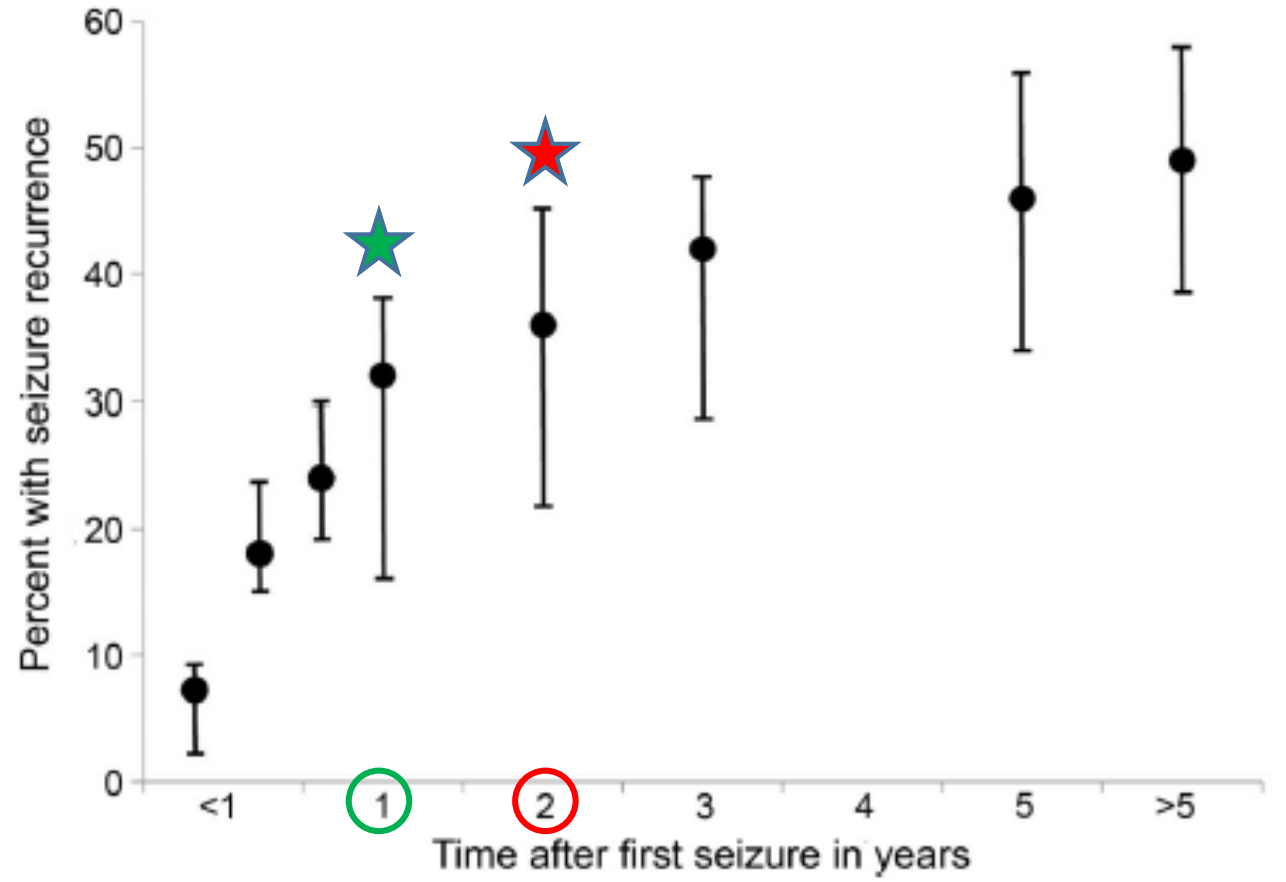
An adult with an unprovoked first seizure is at greatest risk of a recurrence relatively early within the first 2 years (21-45%) and especially in the first year

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

				Seizure recurrences at various times, n (%)								
Ref.	Class	Age, y	No.	Treated	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)

Krumholz et al; Neurology 2015

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

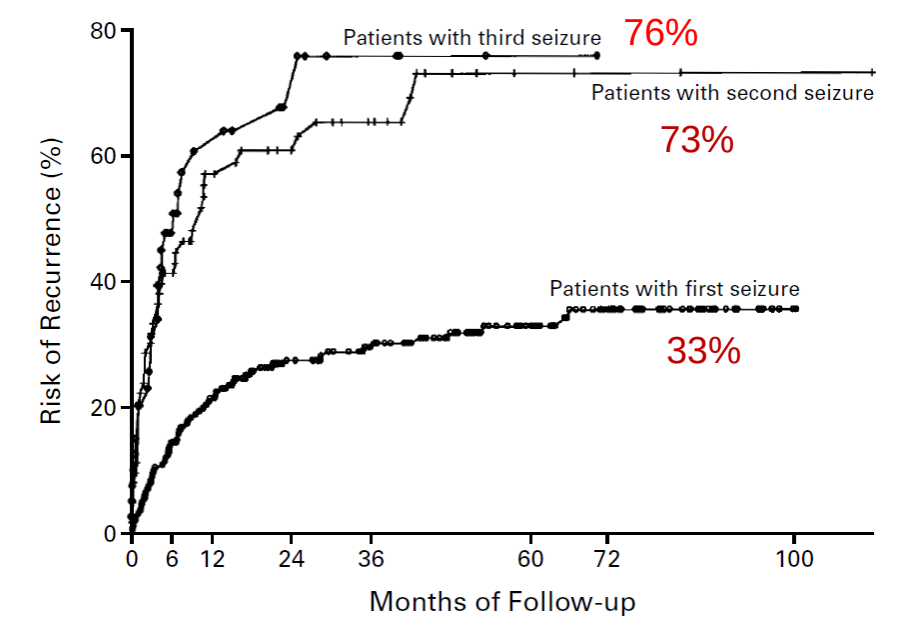


This graph is based on a fixed-effect pooled percentage model from data in table 1 and shows the cumulative average and the range for each time period from 1 month to more than 5 years.

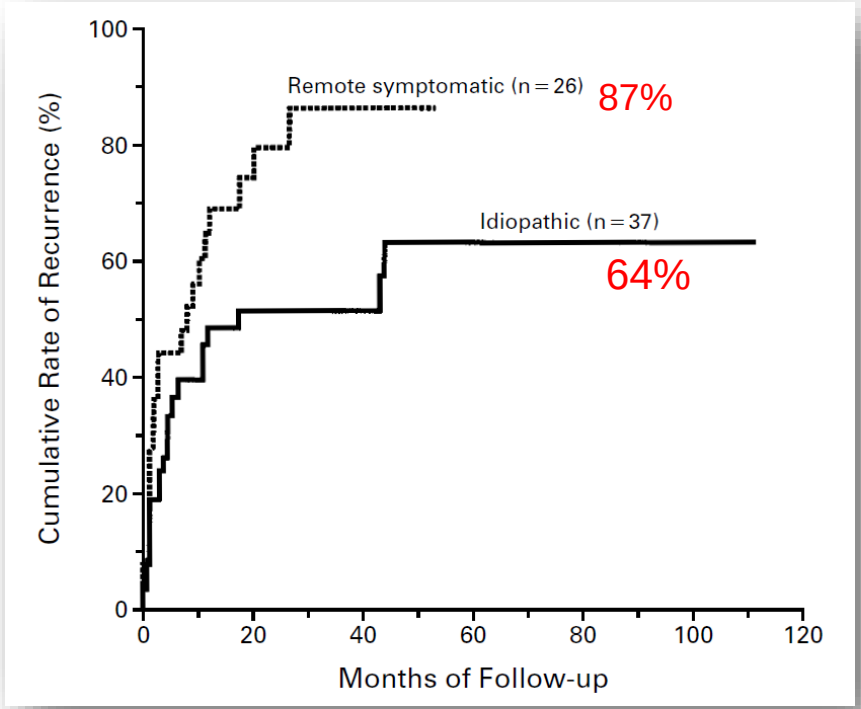
Krumholz et al; Neurology 2015

Risk of recurrence

After first, second and third seizure



Etiology



Hauser WA et.al; NEJM 1998

What are the predictors of recurrence?

Abnormal neurological status and abnormal EEG

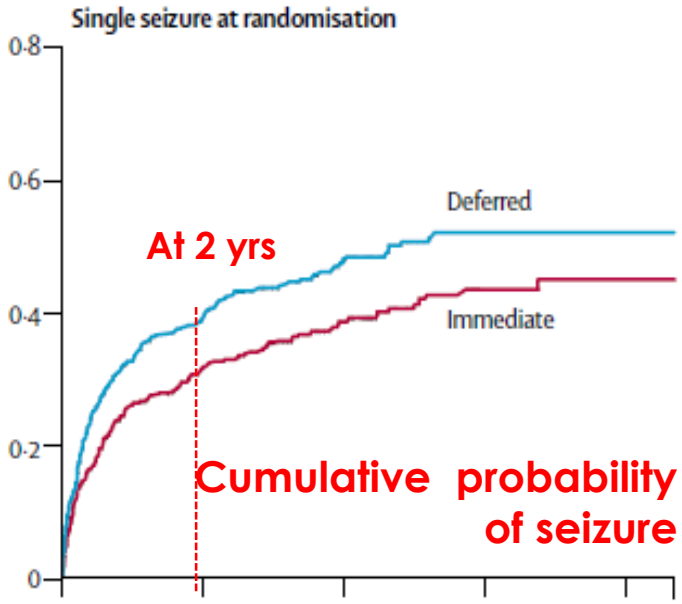
Predictor	Pooled RR of recurrence	Pooled risk of 2 year recurrence (%)
Abnormal neurological status	1.8	57
Normal EEG		27
Epileptiform abnormalities in EEG	2.0	58
Non-epileptiform abnormalities in EEG	1.3	37
Aetiology and EEG combined		
Idiopathic + normal EEG		24
Idiopathic + abnormal EEG	1.9	48
Remote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

EEG, electroencephalogram; RR, relative risk.

Camfield P and Camfield C Epilepsia 2000

Immediate vs deferred treatment after a first unprovoked seizure

Marson A et.al The Lancet 2005



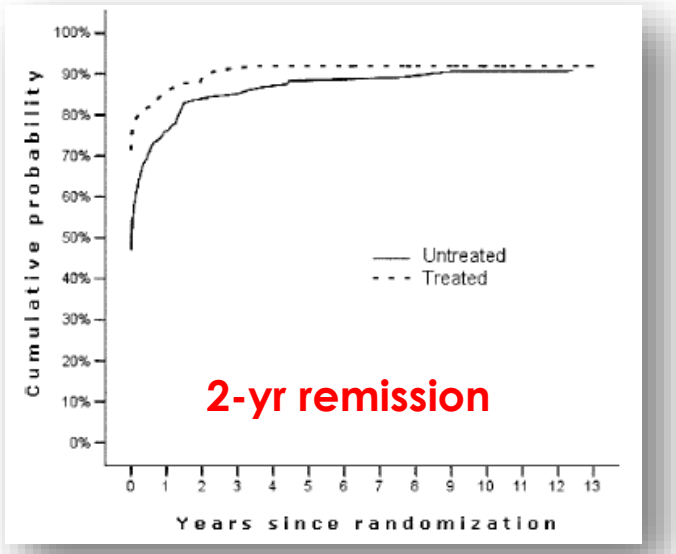
MESS studies

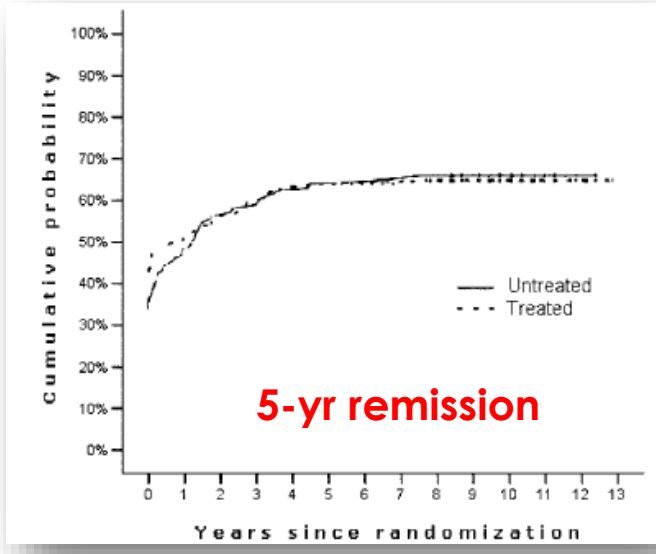
- 2 yr-remission: 69% vs 61%
  - At 3 yrs: 1-3 yrs sz remission: 74% vs 71%
  - At 5 yrs: 3-5 yr sz remission: 76% vs 77%

"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)

Maurizio AL et.al Neurology

Prediction of risk of seizure recurrence

	Prognostic index
Starting value	
One seizure prior to presentation	0
Two or three seizures prior to presentation	1
Four or more seizures prior to presentation	2
Add if present	
Neurological disorder or deficit, learning disability, or developmental delay	1
Abnormal EEG	1
Risk classification group for seizure recurrence*	**Final score**
Low risk	0
Medium risk	1
High risk	2–4

*See table 3 for probabilities of no seizure recurrence at specific time points for each of these subgroups.

Table 4: Prognostic index, with integer values

MESS studies

"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"

Kim LG et.al The Lancet 2006

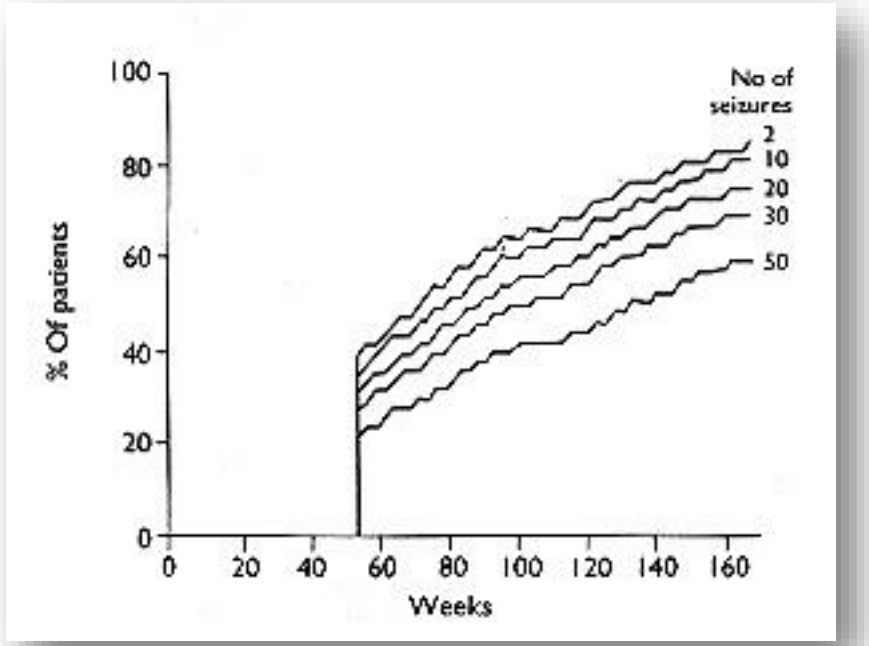
Natural course and prognosis of untreated epilepsies

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 and number of seizure prior to treatment

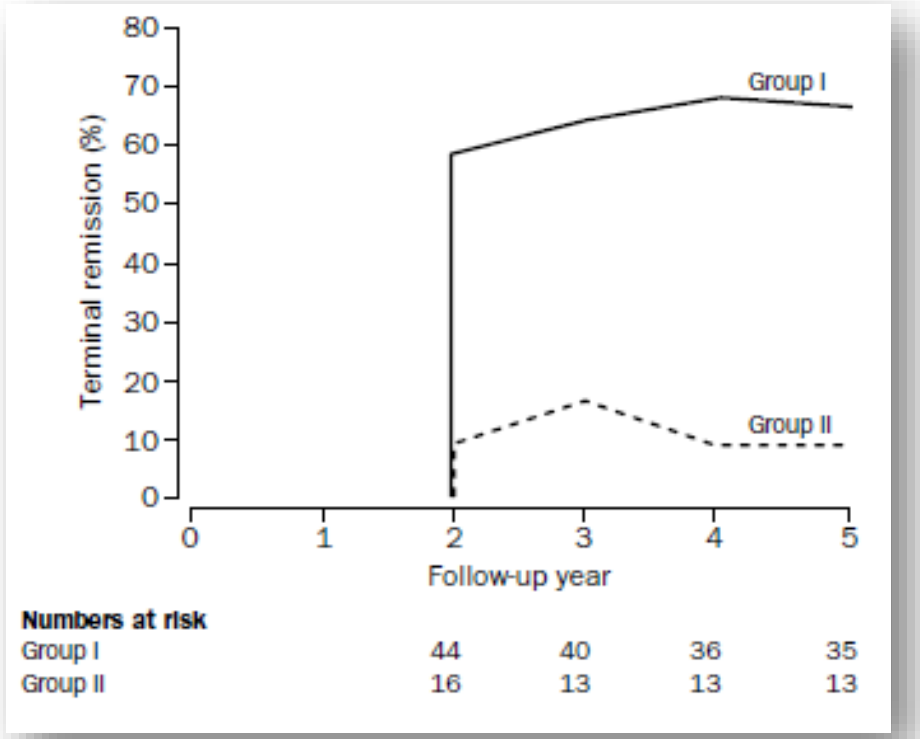
- **Gower's observation and Reynolds EH studies pointed out that the longer the history of epilepsy the worse the longer term prognosis**



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

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**

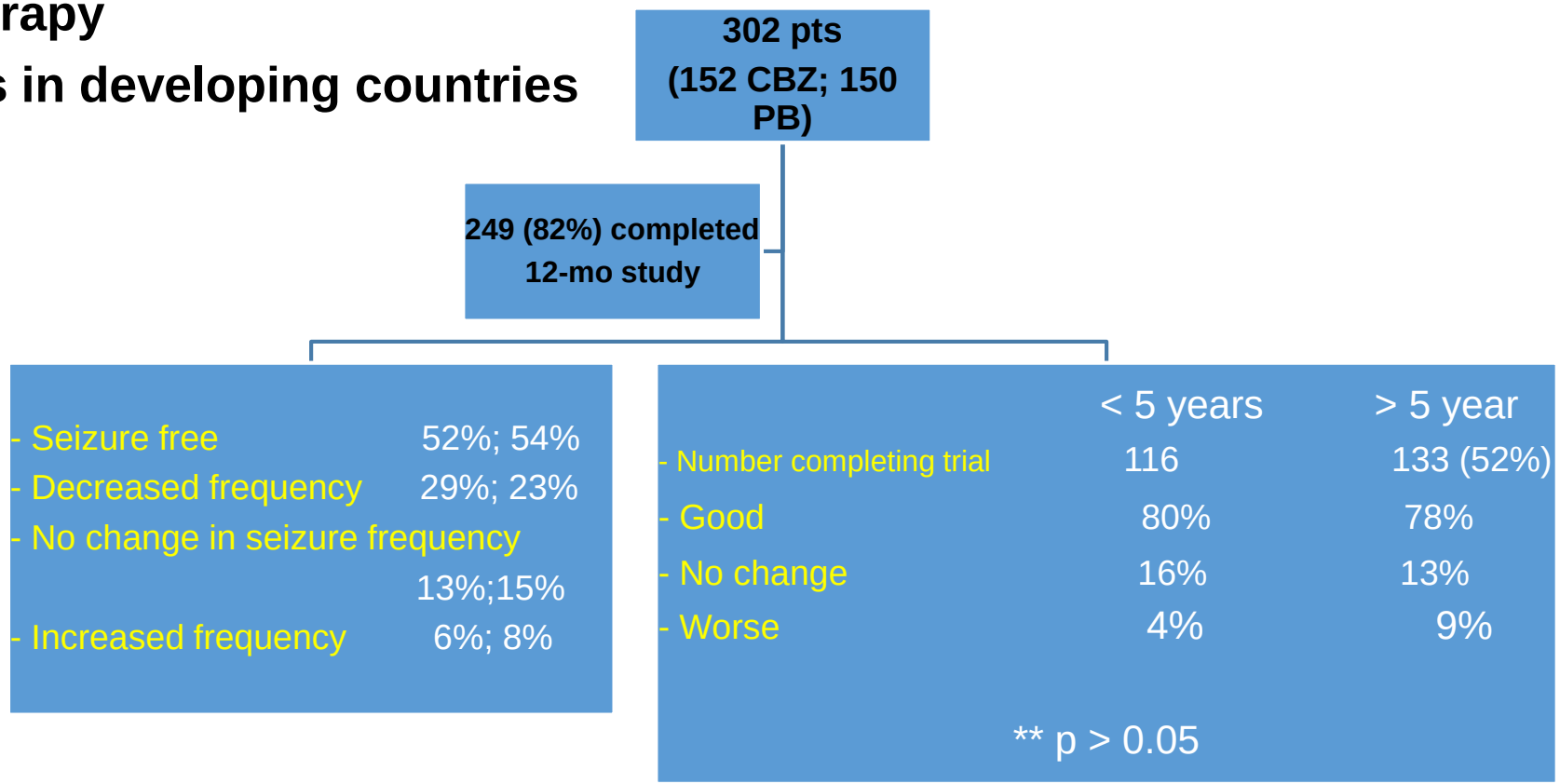
Group I: good compliance coupled with lifetime total of ≤ 30 GTCs
Group II: poor compliance and lifetime total ≥ 30 GTCs

Mani et.al; Lancet 2001

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

Natural course and prognosis of treated epilepsies

"2001"

TABLE 2. SUCCESS OF ANTIEPILEPTIC-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

Kwan P and Brodie M; Epilepsia 2001

“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%

Brodie MJ et.al: Neurology 2012

- **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%**

Loscher W. and Schmidt D; Epilepsia 2011

Late prognosis

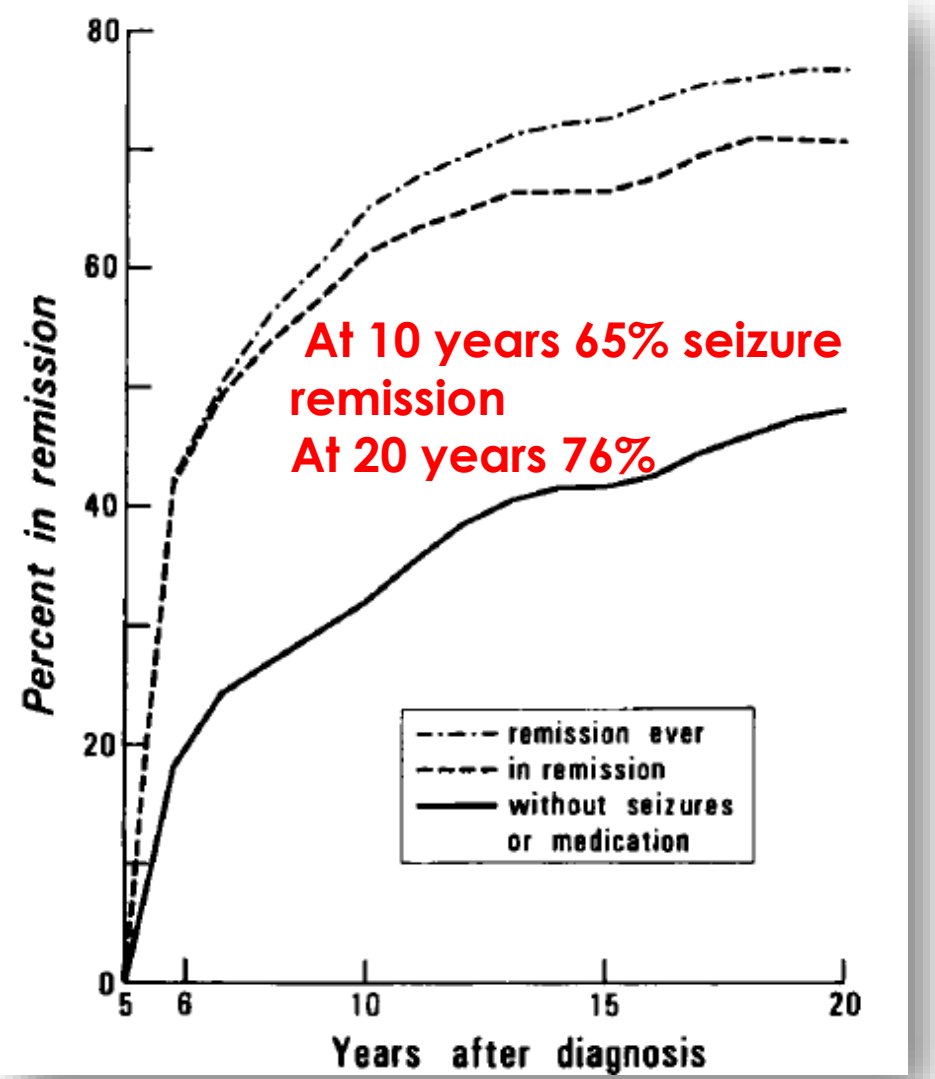
- **Based on 3 longitudinal community-based studies with long-term follow up**

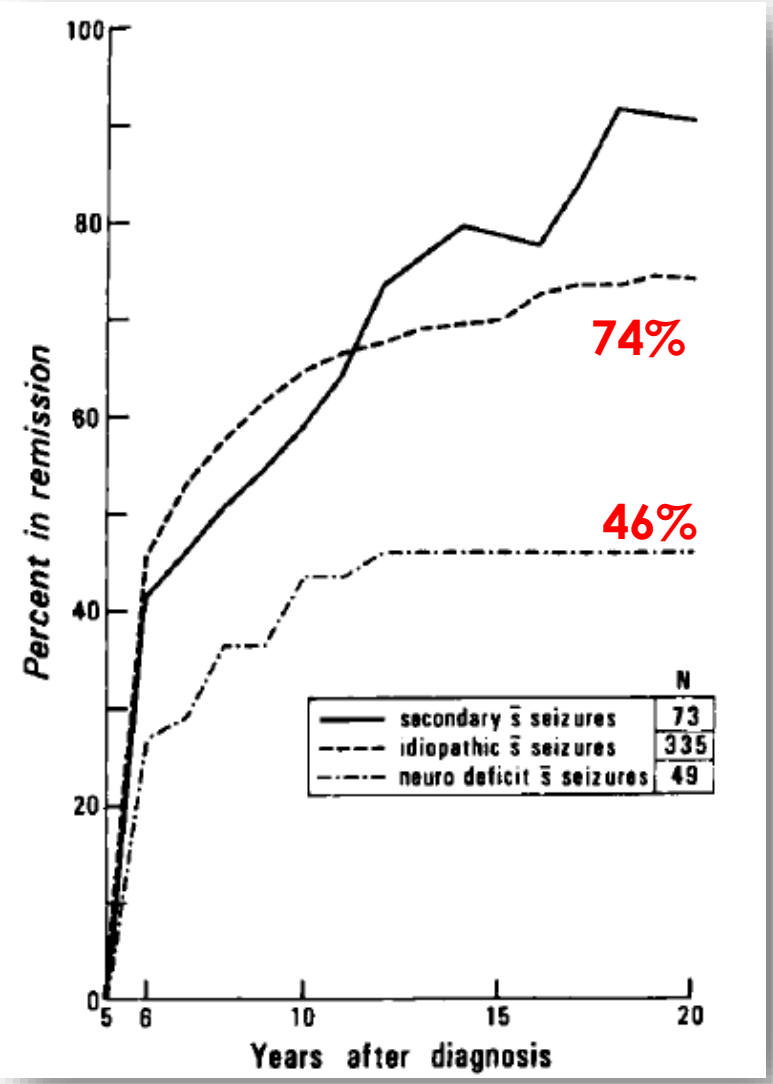
  - Mayo Clinic Record linkage study (US)

  - Tonbridge study (UK)

  - Turku study (Finland) (childhood-onset epilepsy)

Mayo clinic study (20 years follow up)

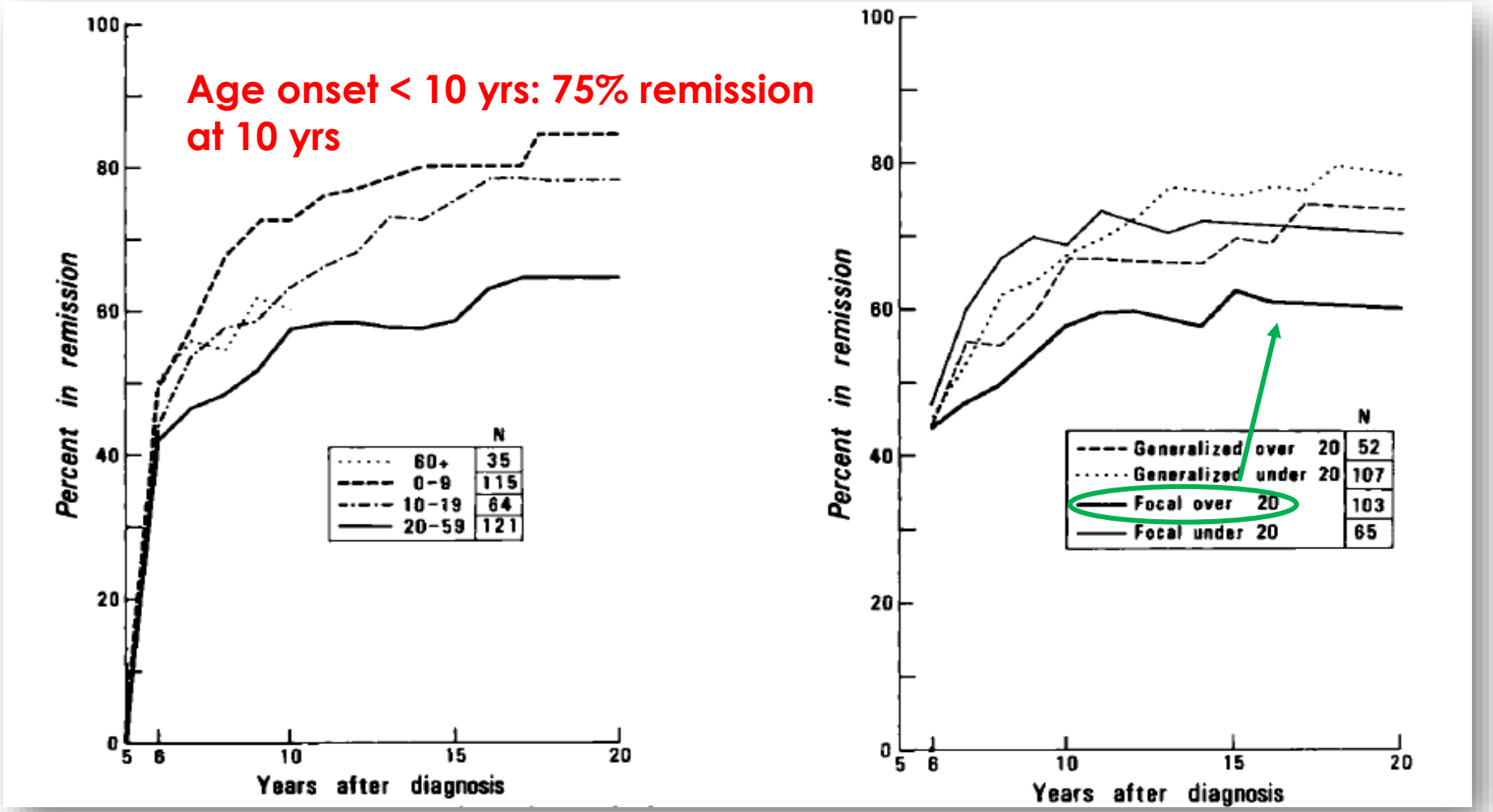




- 475 pts followed at least 5 yrs
- 141 pts > 20 yrs

Annegers et.al; Epilepsia 1979

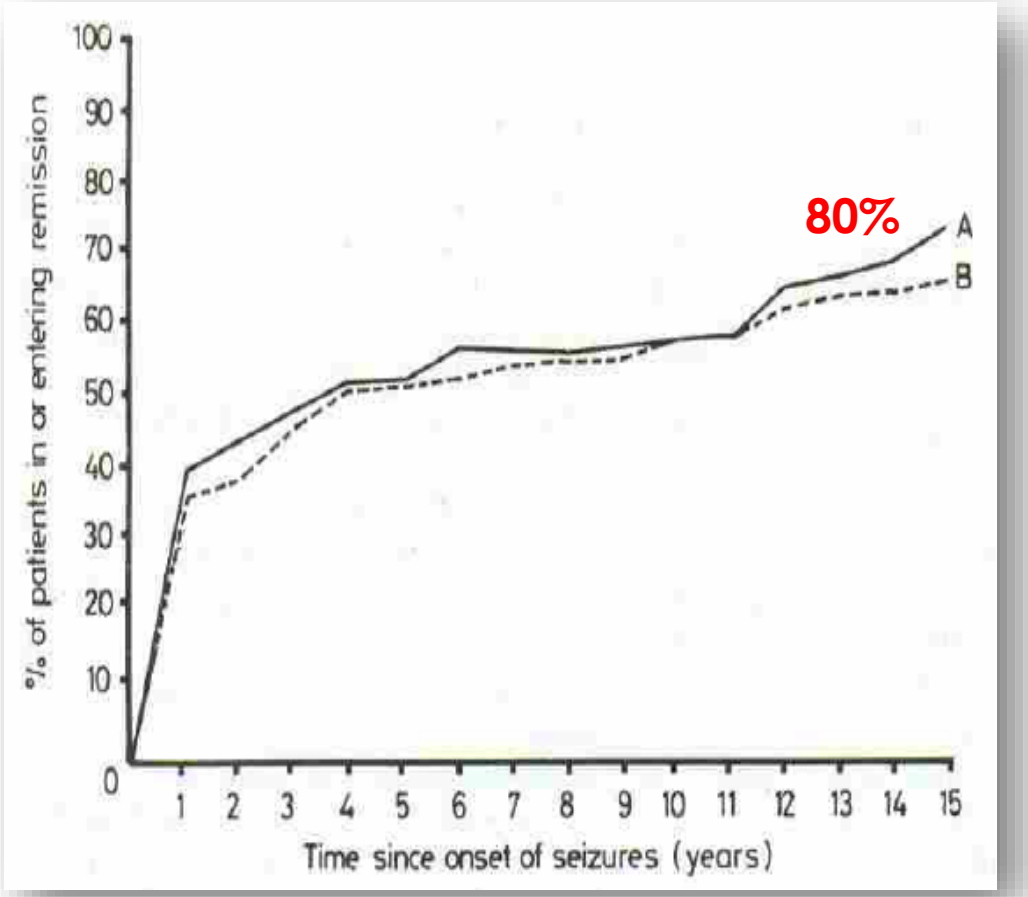
Mayo clinic study

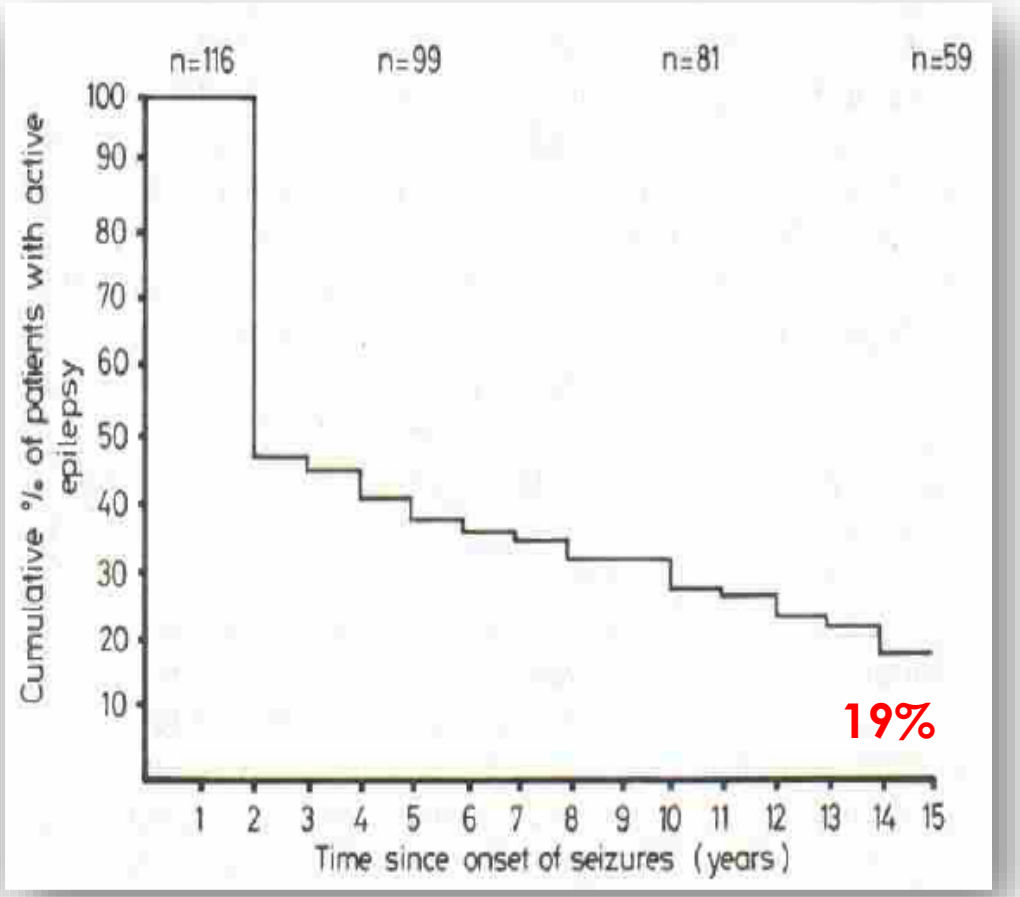


Higher remission: generalized-onset seizure diagnosed < 10 yrs

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)

Goodridge and Shorvon; BMJ 1983

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”

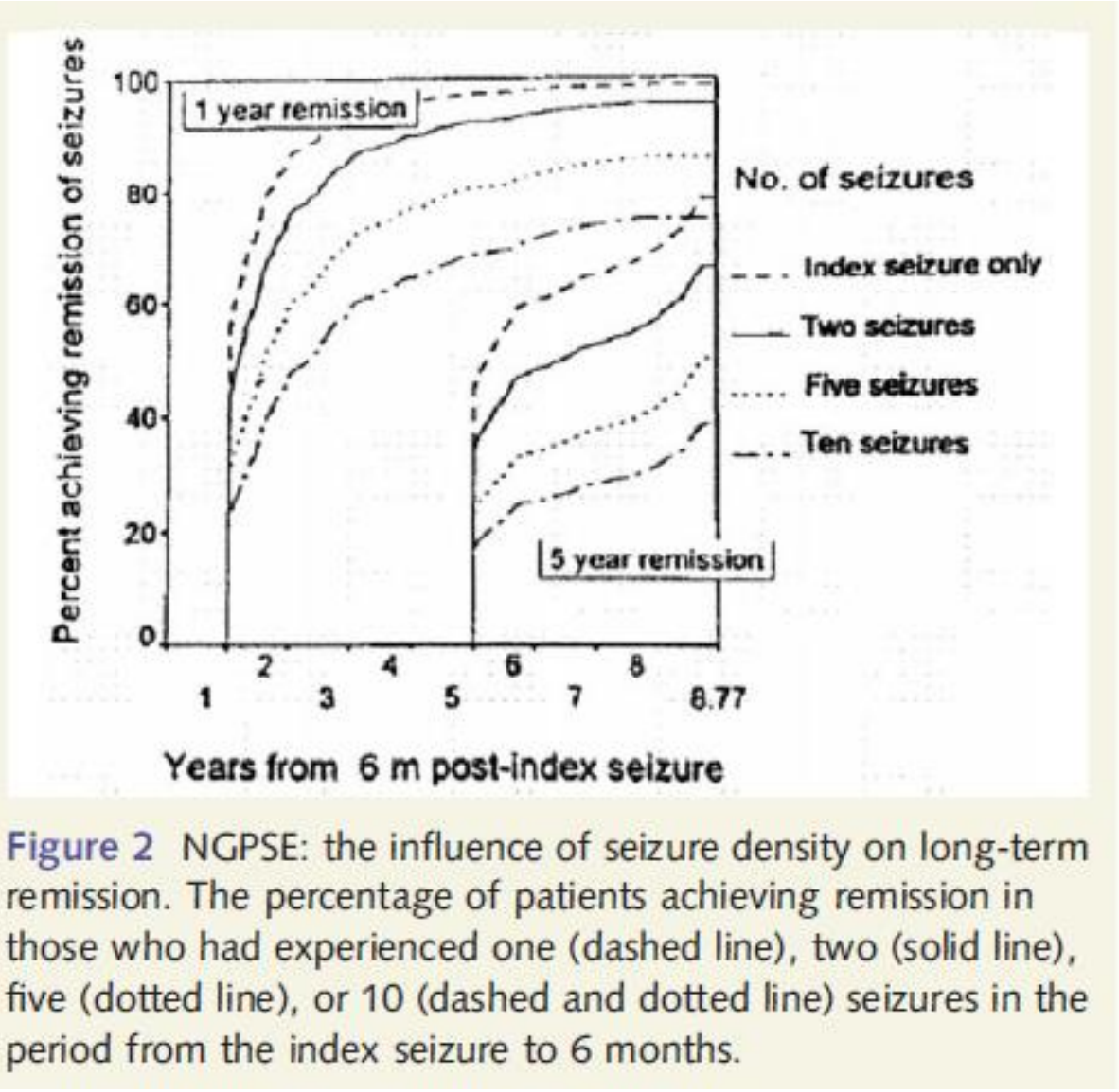


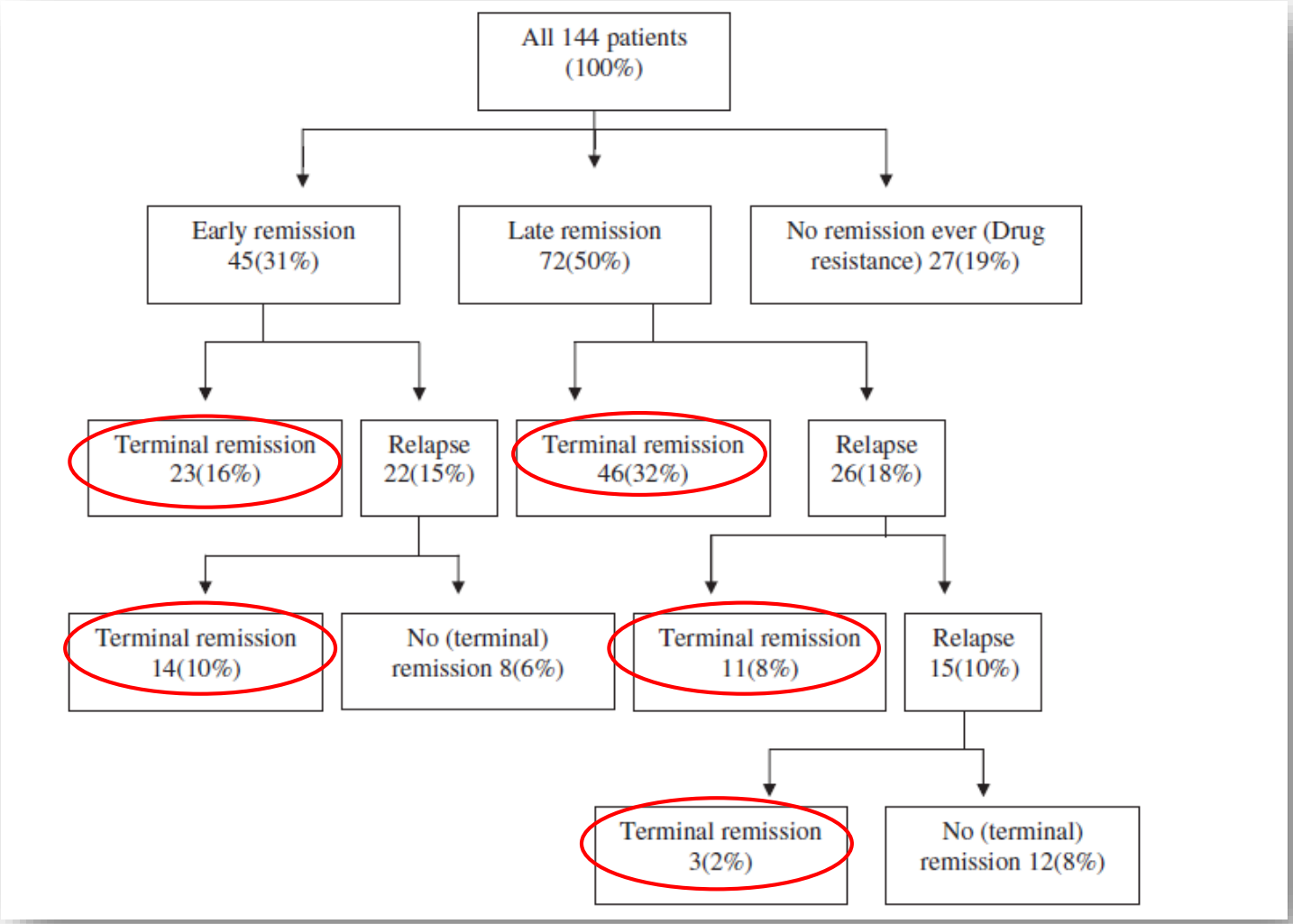
Figure 2 NGPSE: the influence of seizure density on long-term remission. The percentage of patients achieving remission in those who had experienced one (dashed line), two (solid line), five (dotted line), or 10 (dashed and dotted line) seizures in the period from the index seizure to 6 months.

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

MacDonald BK et.al; Ann Neurol 2000

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

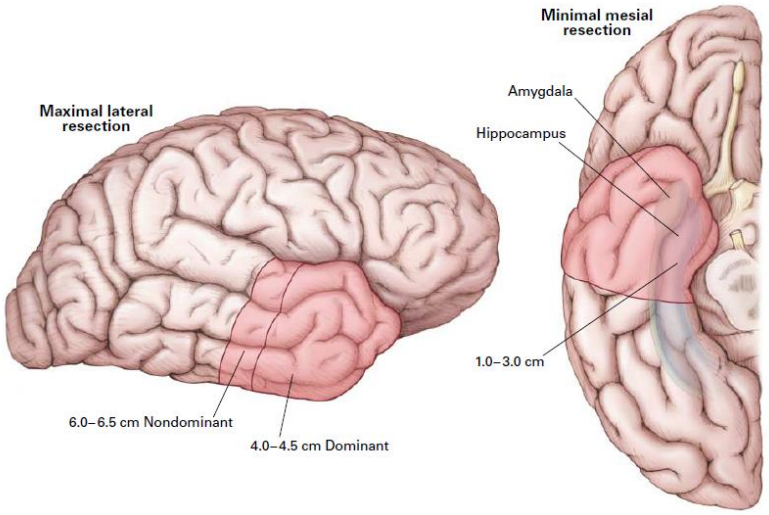
Sillanpaa M and Schmidt D; Brain 2006

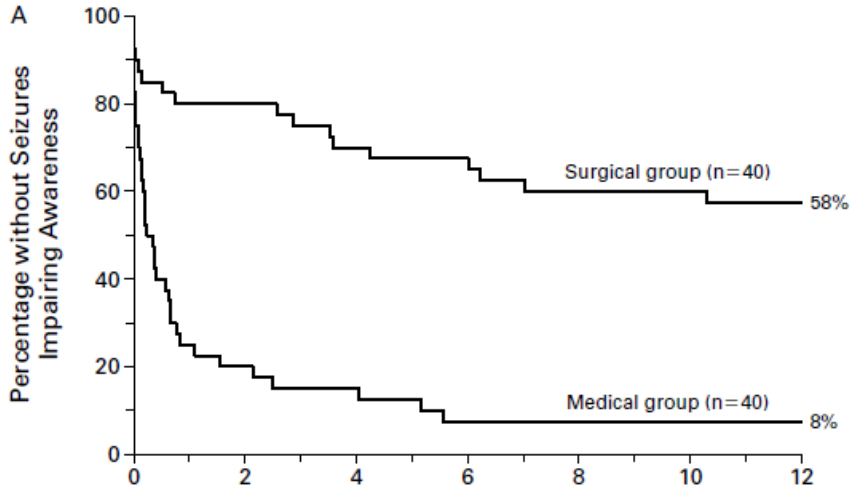
Conclusion

- **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**
- **Neurological deficits, age onset, seizure type, number of early seizure influence on long-term remission rate**

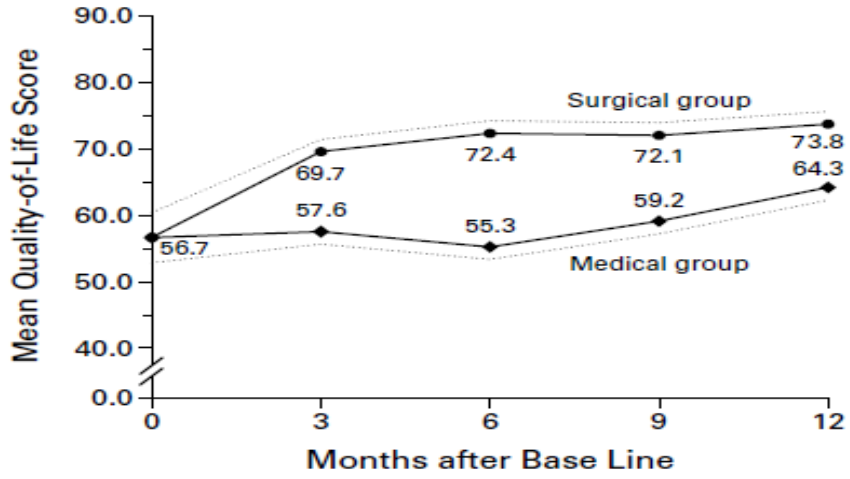
Natural course and prognosis of medically intractable epilepsy with surgeries

RCT of surgery for temporal lobe surgery



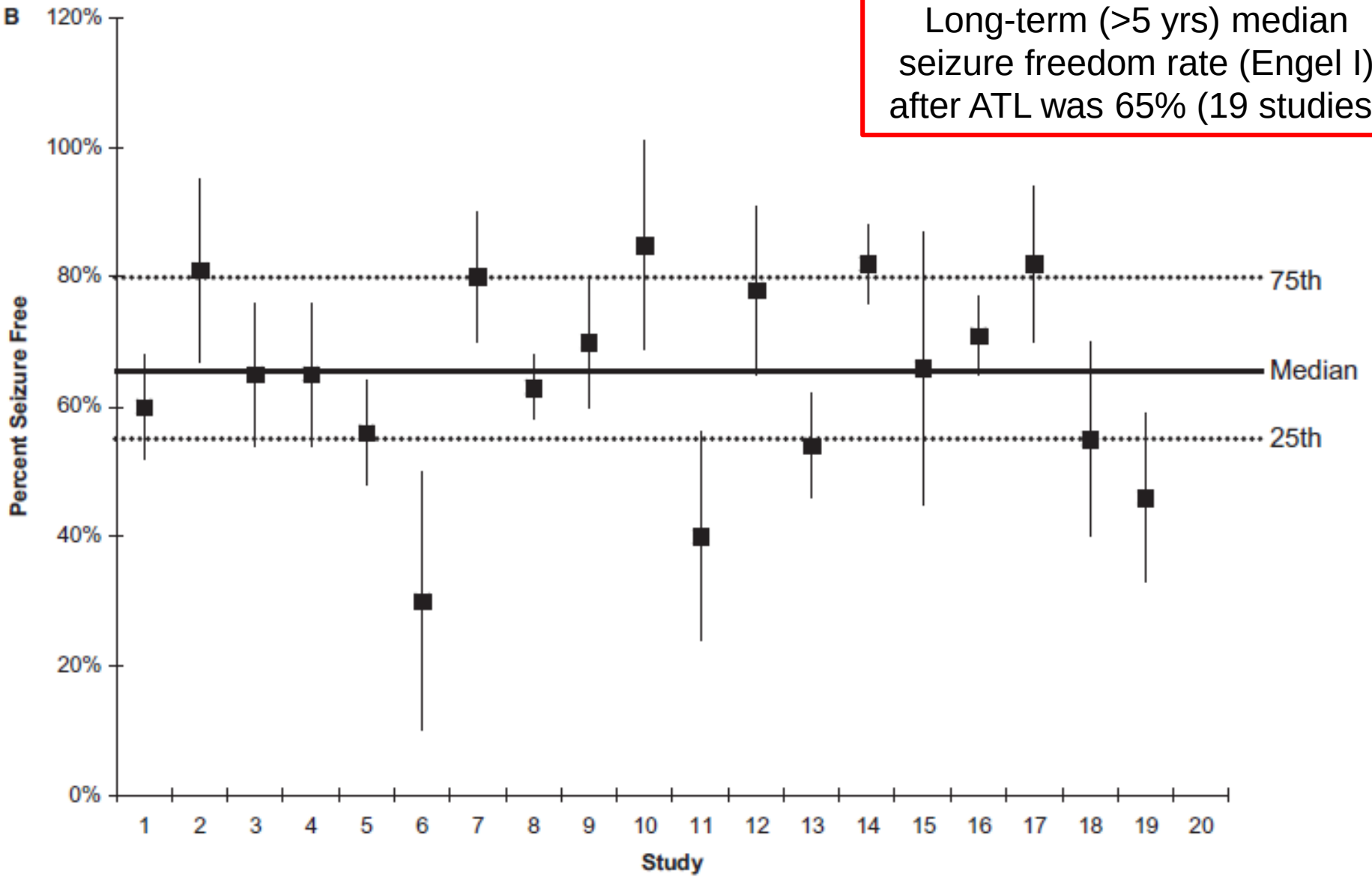


The patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life (P<0.001 for both comparisons) than the patients in the medical group

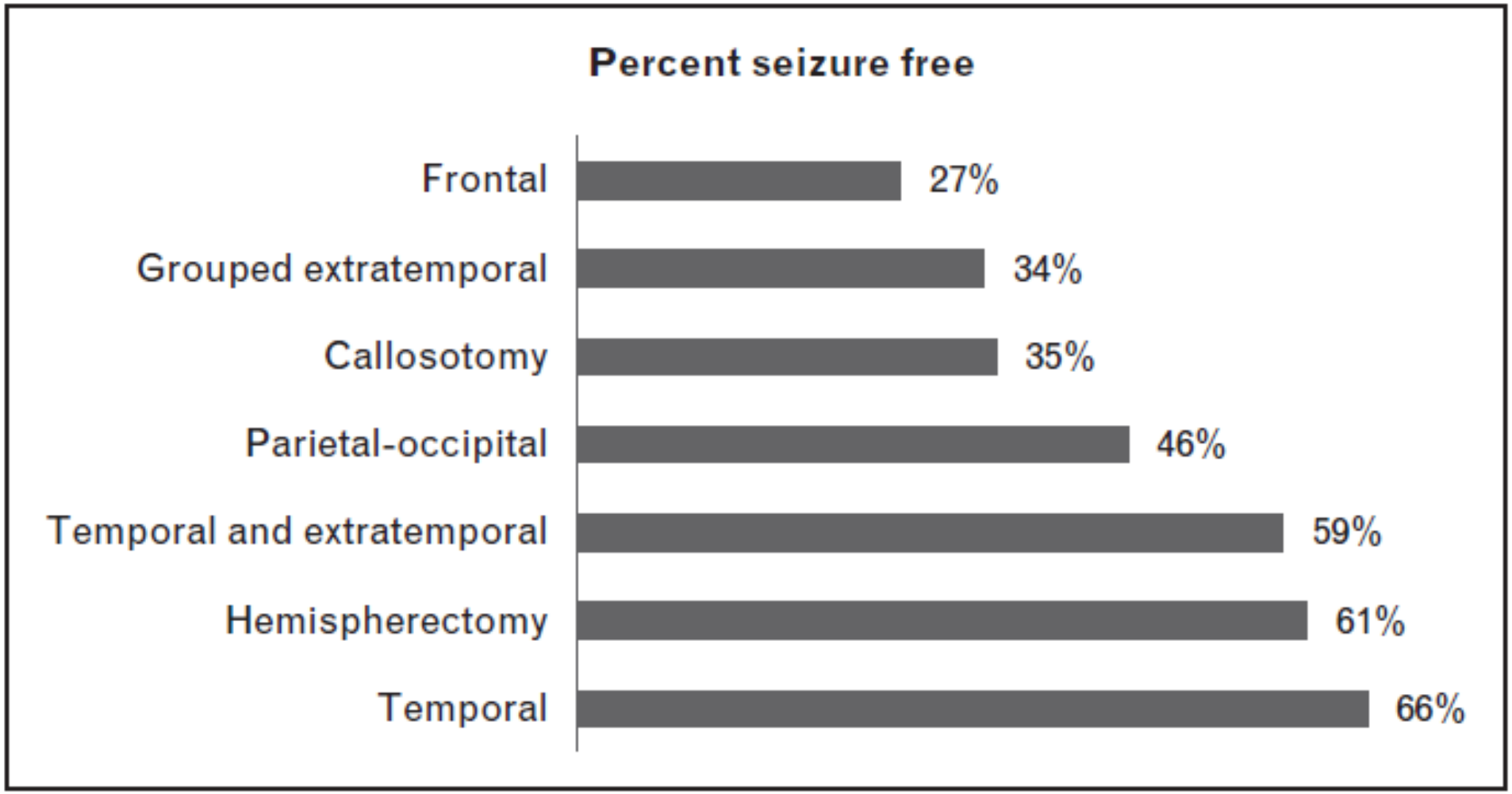


Wiebe S et.al; NEJM 2001

Long-term (>5 yrs) median seizure freedom rate (Engel I) after ATL was 65% (19 studies)

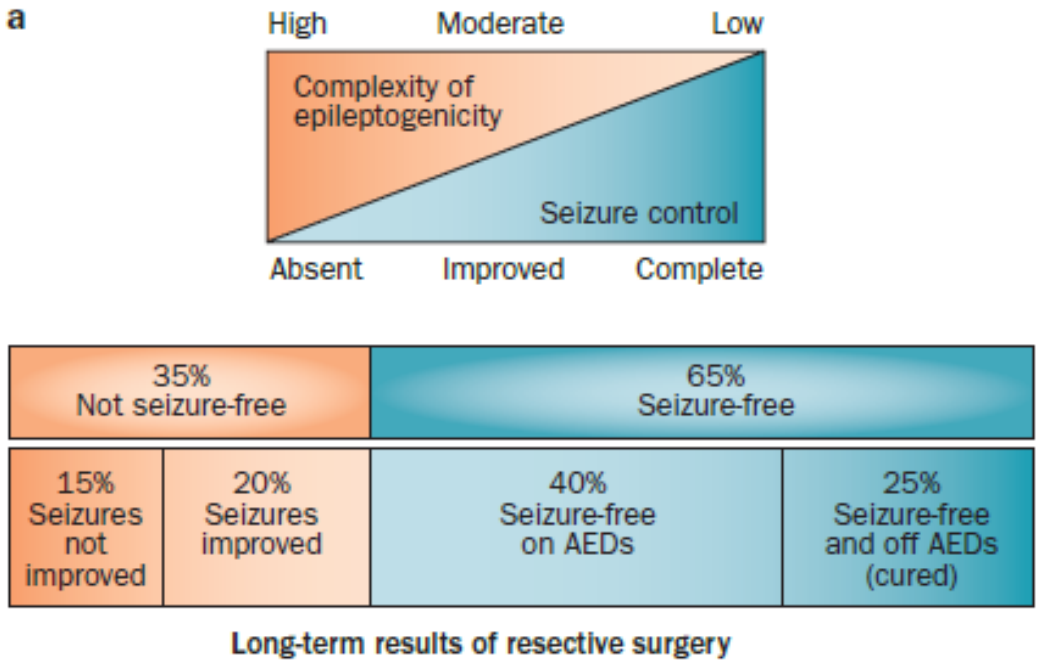


Tellez-Zenteno JF et.al; Brain 2005

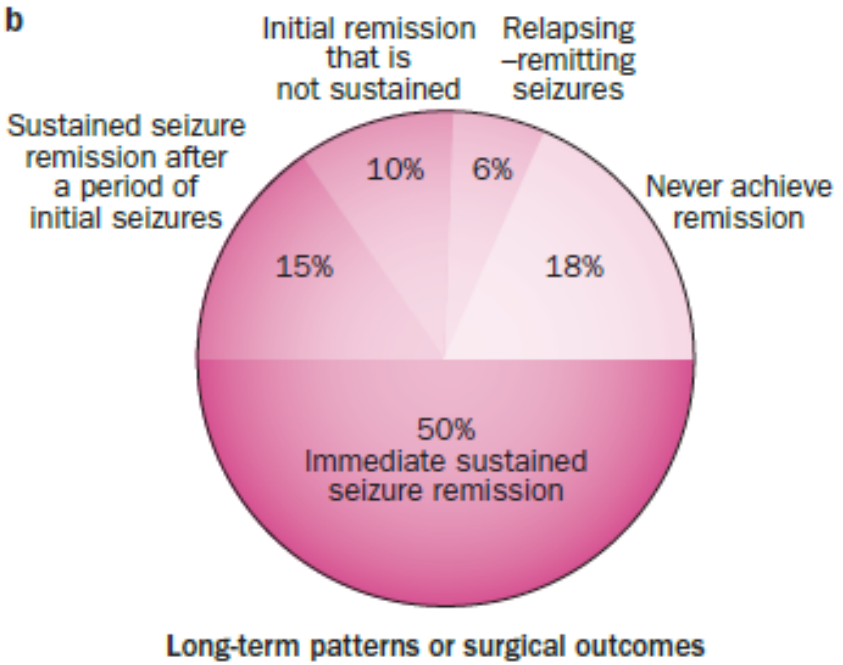


Tellez-Zenteno JF et.al; Brain 2005
Weibe S and Jette N; Curr Opin Neurol 2012

The outcome of surgical treatment in patients with epilepsy



Long-term results of resective surgery



Long-term patterns or surgical outcomes

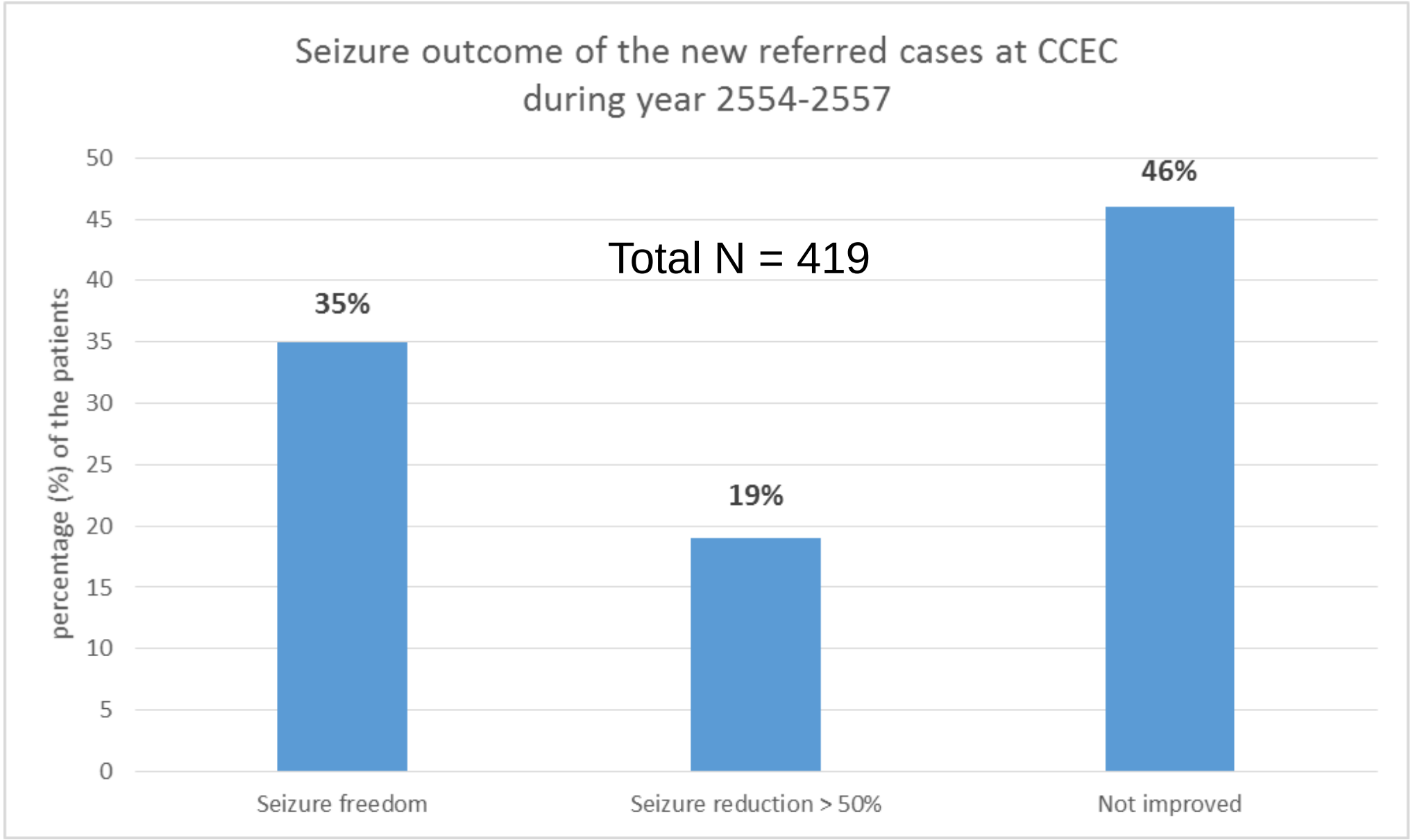
Wiebe S and Jette N; Nat Rev Neurol 2012

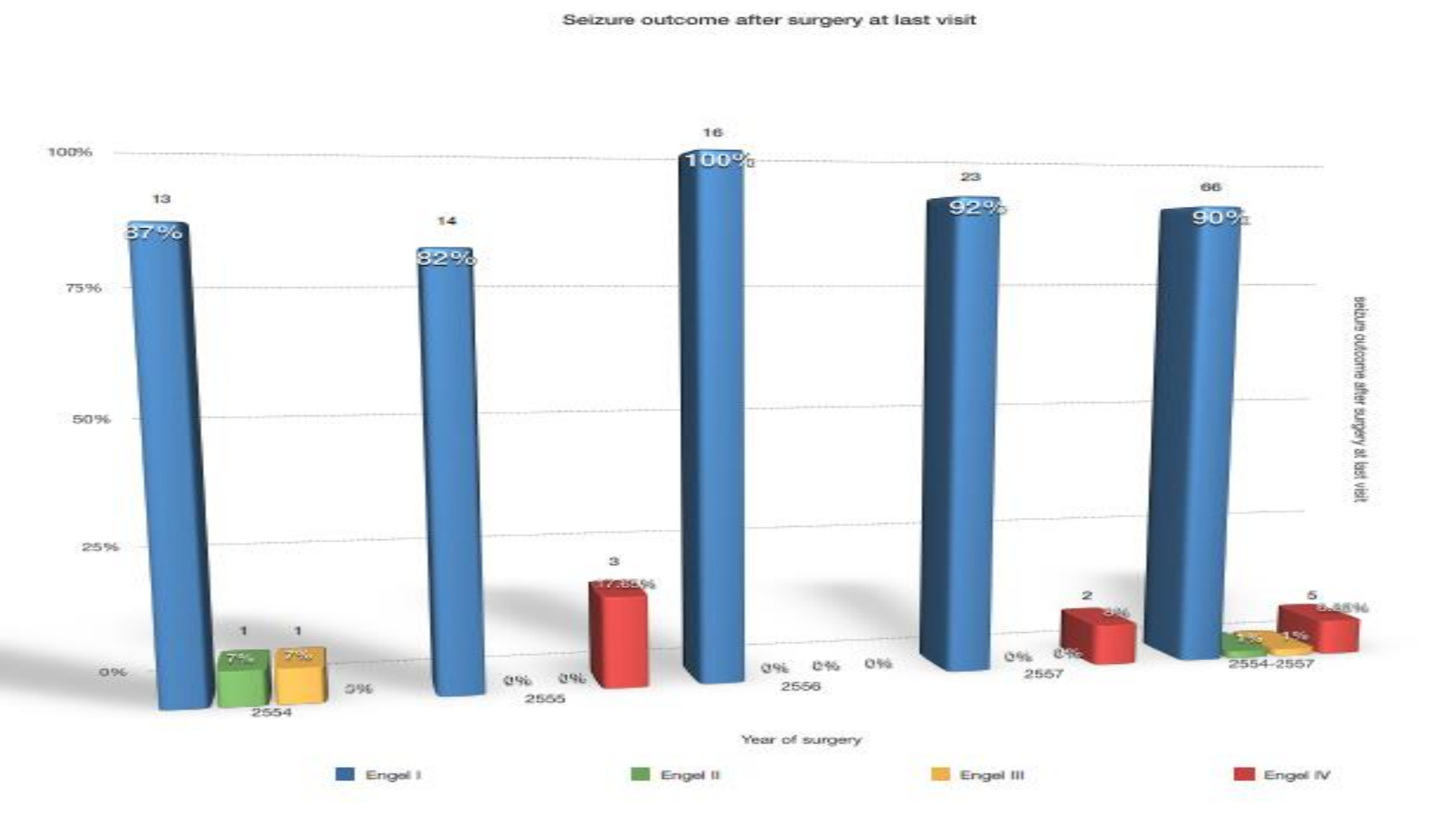
Referred cases at CCEC

Continuing seizures due to inadequate AEDs adjustment

Medically intractable TLE

Difficult surgical cases requiring extensive investigations


Seizure outcome of the new referred cases at CCEC during year 2554-2557
Total N = 419
percentage (%) of the patients
50
45
40
35
30
25
20
15
10
5
0
35%
19%
46%
Seizure freedom
Seizure reduction > 50%
Not improved


Seizure outcome after surgery at last visit
100%
75%
50%
25%
0%
13
87%
1
7%
1
7%
0%
2554
14
82%
0%
0%
2555
3
16
100%
0%
0%
0%
2556
23
92%
0%
2557
2
8%
66
90%
1%
1%
5
2554-2557
Seizure outcome after surgery at last visit
Year of surgery
Engel I
Engel II
Engel III
Engel IV

Long-term courses of Juvenile myoclonic epilepsy (JME)

JME

- Original report on JME, published in 1957, Janz and Christian highlighted the **rarity of spontaneous remission**, as well as the **high risk of relapse after AED discontinuation**
- Further studies with follow-up periods not longer than 5 years confirmed the initial observation
- Based on 3 recent population-based studies with long-term follow up varying from 25 to 63 years after epilepsy onset
  - 24, 31, and 66 patients respectively (2009, 2012, 2013)
  - 78%, 67.7%, and 59.1% achieved seizure remission
  - **25%, 28.6%, and 28.2% were seizure-free off medication for at least the last 5 years**

Camfield CS and Camfield PR; Neurology 2009
Geithner J et.al; Epilepsia 2012
Senf P et.al; Neurology 2013

Predictors for seizure recurrence

- **Additional absence seizure at onset of JME**
- **GTCs preceded by bilateral myoclonic seizures**
- **A long duration of epilepsy with unsuccessful treatment**
- **AED polytherapy**
- **Occurrence of photoparoxysmal responses**

Thank you for your attention