REMISSION IN EPILEPSY: HOW LONG IS ENOUGH?

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Summary

Objective. The International League Against Epilepsy has proposed to expand the definition of remission to 10 year seizure-free with the last 5 years off AEDs. We examined if a 10-year remission is needed to predict the lowest recurrence risk.

Methods. The population-based study cohort consisted of 148 patients with childhood new-onset epilepsy living in the catchment area of Turku University Hospital. They were prospectively followed for 44 years (median). Patients in first remission were prospectively followed for the duration of remission or possible relapse at two years in remission with the last year without AEDs, at five years in remission with the last two years without AEDs and at 10 years with the last five years without AEDs. For comparison of the proportions of relapsed patients within each remission category exact Clopper Pearson 95% confidence intervals were used.

Results. The magnitude of the relapse rate estimates off AEDs did not significantly improve when remission increased from 2 to 5 and further to 10 years. However, 10YR was a more sensitive measure of no relapse than 2YR. Among patients with remission on or off AEDs, the ability to predict lower relapse rate increased markedly from 2 to 5 years, and again from 5 to 10 years. The risk of relapse was virtually the same estimated after 2YR off AEDs as after 10YR on or off AEDs, except for those with generalized epilepsy whose 2YR off AEDs was a weaker predictor than 10YR on or off AEDs.

Significance. Given the very modest differences in relapse rates between the 5 years seizure-free with last 2 years off medications definition and the 10 year seizure-free with last 5 years off medications, and the adverse impact of not being considered in remission, we propose that a return to the 5 year definition may be warranted.

Key words: Length of remission; long-term follow-up; population study; risk of relapse; remitted epilepsy

Key Point Box

- We assessed how long you have to wait before considering epilepsy to be in remission.
- We examined the lowest recurrence risk after 2-year, 5-year and 10-year remission.
- Relapse rates differed only modestly between the 5-year and the 10-year remission.
- Given these results, we propose that a return to the 5-year definition may be warranted.

INTRODUCTION

The question when epilepsy can be considered to be in remission is a challenging one. Outside of isolated age specific epilepsy syndromes such as Benign Epilepsy of Childhood with Centro-Temporal Spikes (BECTS)[1-3], can one ever be really sure that epilepsy will not recur? For many reasons including driving, employment in certain occupations, insurability etc., criteria for and estimates of the risk of recurrence are crucially needed, because these issues have a significant impact on people with epilepsy and their families. In most studies, so far, be they epidemiological outcome studies[4-7], studies of discontinuing antiepileptic drugs (AEDs) in remission on AEDs[8, 9], or following epilepsy surgery[10-13], either a 2-year or 5-year seizure free definition of remission on or off AEDs was used. More recently, The International League Against Epilepsy (ILAE) has proposed to expand the definition to 10 year seizure free, of which at least the last 5 are off AEDs[14]. This definition is, however, based on a consensus of expert opinion as there are few published data with 10-year seizure free outcomes available[15]. There are hardly any reports on 10-year terminal remission. Callenbach et al[16] followed up a cohort of 29 children with newly diagnosed benign childhood epilepsy with centro-temporal spikes. After 12–17 years of follow-up, 96% had entered 5-year and 89% 10-year terminal remission. Whether the subjects were on or off AEDs was not given. Berg et al reported that 5-year and 10-year remission, regardless of continued treatment, occurred more often in children with absence epilepsy initially treated with ethosuximide versus valproate[17]. In a study of 10-year remission including 5 years off AEDs, Berg et al[18] found 5-year remission off AEDs to be a meaningful but not absolute marker for continued remission.

But how long does one have to wait before considering epilepsy to be remitted? The lack of compelling evidence on this clinically relevant question prompted our study. More specifically, we addressed whether a remission of 2 years with at least one year off AEDs, 5 years with at least the last 2 off AEDs

or, as proposed by Fisher et al[14], 10 years with at least the last 5 off AEDs are needed to predict the lowest recurrence risk. However, there are no observational data on the prognostic value as a predictor of relapse risk for the definition of 10-year remission with the last five years without AEDs compared with 5-year remission with the last two years without AEDs.

The Turku Adult Childhood Onset Epilepsy (TACOE) study is based on a population cohort of childhood onset epilepsy which has now been prospectively followed for 50 years[7, 19]. This evidence provides a unique opportunity to compare the robustness of the different definitions of remission. Our purpose was to study whether the accuracy of prediction of seizure-free future increases when the duration of preceding remission is prolonged from 2 to 5, and further to 10 years.

SUBJECTS AND METHODS

The study cohort is previously described in several reports[6, 7, 19-24]. In brief, the cohort consisted of 245 child patients aged 15 years or less who were living in the catchment area of Turku University Hospital at the end of 1964 and had a diagnosed epilepsy, defined as two or more unprovoked seizures. Patients were either cases of new-onset epilepsy in 1961–1964 (n=150, incident cases) or had epilepsy diagnosed prior to 1961 and had at least one unprovoked seizure in 1961–1964 (n=95, prevalent cases). For the present study, the prevalent cases were excluded, and only patients with incident cases were included. Epileptic seizures and syndromes were later re-classified[25] to be in line with the updated ILAE definitions [26-28]. Children with new-onset epilepsy and born in the catchment area of Turku University Hospital were identified by reviewing all relevant files from inpatient and outpatient clinical and EEG records of any of hospitals and institutions in the catchment area of Turku University Hospital and any relevant hospitals or institutions in southern Finland; special schools in the area; and community general practitioners' offices and private offices' records. Ninety-one percent of 148 study

subjects were seen at the Turku University Hospital and the remaining 9% at other hospitals and institutions in southern Finland. The rule was – and still is – that every child who starts to have epileptic seizures is to be referred for evaluation. Additional EEG and neuroimaging investigations were performed on clinical grounds, if needed. Finally, to detect those not otherwise identified, the National Health Service Register data of reimbursed antiepileptic drugs for epilepsy were reviewed by permission of the public authorities. The registers of the national social security institution are based on the legislation effective since 1964 with the principles largely copied from the British National Health Service act. The registers are proved to be a reliable source of data for research purposes in many reports. The review of all the above mentioned records including EEG statements and clinical examinations of the 150 children included in the study were made by one child neurologist (M.S.). Two children died before the end of 3-year follow-up, the minimum required for detecting a 2-year remission period. Thus, 148 subjects remained for the present analysis. Sixty-four children had focal epilepsy and all but two of the remaining 84 had what used to be called primary generalized. The mean follow-up time was 39.1 years (SD 10.1, median 44.0, range 6–47 years).

The cohort was followed up regularly every fifth year for seizure status until the end of 2007, death or emigration, using mainly semi-structured questionnaires. In addition, by signed permission of the patients, data were also collected from hospital and institution files. Patients who had entered remission were prospectively followed for the duration of remission or possible relapse at two years in remission with the last year without AEDs, at five years in remission with the last two years without AEDs and at 10 years with the last five years without AEDs (later referred to as “2YR”, “5YR” and “10YR”, respectively). For the present study, only the first remission of 2 years, 5 years and 10 years, respectively, was considered for each patient (Fig.1). For example, an individual patient in the “2YR” category who continued to be in remission for five years or later attained 5-year remission, would also

be included in the "5YR" category, and likewise a patient who continued to be in 5YR and later attained 10YR, would be included in the "10YR" category. As a consequence, the 2YR, 5YR, and 10YR groups are not mutually exclusive or independent because the same individual patient may be included in more than one remission period as defined above. Patients in remission were regularly advised by MS about the risks and benefits of stopping AEDs in remission.

Insert Fig 1 here

Statistical analysis. As outlined above, the remission groups are not independent or mutually exclusive. Subsequently, we cannot use customary statistical tests. For comparison of the different remission categories, we assessed the proportions of relapsed patients within each remission category. Uncertainty of the estimates was controlled for by using exact Clopper Pearson 95% confidence intervals (CI) from the binomial distribution[29]. The rates and their CIs are presented as a forest plot. If the CIs of the estimates were not overlapping, the relapse rates were considered to be distinct between the categories. Kaplan-Meier graphs are given for the cumulative probabilities of time to relapse for the first 2YR, 5YR and 10YR categories, respectively, with regard to AEDs. The data are given for all 148 patients and separately for the subgroup of 84 patients with generalized epilepsy. Statistical analyses were done with SAS System for Windows, release 9.4 (SAS Institute, Cary, NC, USA) and R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics. The Institutional board approved the study design (Diary No. 120/2008/26.1.2009 §454). Written consent was obtained from the study subjects. We confirm that we have read the Journal's position on the issues involved in ethical publication and affirm that this report is consistent with the guidelines.

RESULTS

At the median 44-year follow-up, 117 (79%) of 148 subjects were in 5-year remission ever on or off medications and 98 (66%) of 148 subjects in 5-year terminal remission, respectively. Table 1 summarizes the number of patients in the different relapse categories and the relapse rates among the 148 incident patients with childhood onset epilepsy, and the 84 with generalized epilepsy. Limiting the analysis to those with primary generalized epilepsy did not change the results. About 50% reduction in the relapse rate is seen when the duration of remission increases from two to five years and, again, from five years to 10 years, and even more so when the patients remain in remission without AEDs. Being able to discontinue AEDs is a stronger predictor than longer duration of remission in lowering the risk of future relapse.

Insert Table 1 here

Fig. 2a shows the Kaplan-Meier estimates of the cumulative probability of time from achieved remission to relapse and proportions of relapsed patients at first 2-year, 5-year and 10-year remissions. When first 2YR, 5YR, or 10YR has been attained, five further years of follow-up appear to be enough to reasonable well approximate the risk of relapse (Fig. 2a). The shape of the curves remains similar when only patients with generalized epilepsy are considered (Fig. 2b). Note that due to the study design, patients with late relapse in the shorter remission groups are also included in the longer remission groups.

Insert Figs 2a and 2b here

Fig. 3. presents the overall relapse risk in the different remission categories during the total follow-up period, when the timing of relapse is not considered. Overlapping of 95% confidence intervals between the remission categories off AEDs meant that the accuracy of the relapse rate estimates did not significantly improve when the time in remission increased from 2 to 5 and further to 10 years. However, within the 95% confidence level, 10YR was a more sensitive measure of no relapse than 2YR. Among patients with remission on or off AEDs, the ability to predict lower relapse rate increased markedly when the premise of preceding remission time was raised from 2 to 5 years, and again from 5 to 10 years. Strikingly, the risk of relapse was virtually the same estimated after 2YR off AEDs as after 10YR on or off AEDs, except for those with generalized epilepsy whose 2YR off AEDs was a weaker predictor than 10YR on or off AEDs.

Insert Fig 3 here

DISCUSSION AND CONCLUSIONS

Our population-based study of incident childhood onset epilepsy aimed at determining if there is any relevant difference between the commonly used criteria of either 2-year remission with the last year off AEDs, 5-year remission with the last two years off AEDs, or 10-year remission with the last five years off AEDs, when predicting whether epilepsy can be considered to remain in remission without relapse.

A well-known US population study[30] retrospectively found 76% of all 457 patients of all ages with incident epilepsy, irrespective of etiology, to have achieved at least one five-year remission period

during 20-year follow-up. The remission was sustained at the end of follow-up in 70%. In a recent retrospective Italian population study of 747 subjects of all ages with either prevalent or incident epilepsy, during follow-up of 20 years, 50% had started a period of five-year remission and 43% were in sustained or terminal remission.[31] In a recent prospective observational general-practitioner-based cohort study from the UK[32], 318 people with incident epilepsy were followed-up for 25 years. Five-year remission ever was achieved by 81% and 5-year terminal remission by 80% of 178 subjects with complete follow-up. The present remission data of childhood onset epilepsy are well in line with those three studies with regard to 5-year remission ever (present 79% vs. previously reported 50–81%) or 5-year terminal remission (present 66% vs. previously reported 43–80%). Unlike our study, the US, Italian and UK studies did not, however, compare 2-year, 5-year or 10-year terminal remission rates.

There are three main findings of clinical relevance. First, we might, for the first time, give study-based data on the impact of the 10-year remission with the last five years off AEDs on the risk of relapse and compare the results between the previously used definitions of 5 years remission with 2YR off AEDs, and 2YR with the latter off AEDs, respectively. Second, in spite of the anticipated decrease in relapse risk after longer remission times, the relapse rates differed only between 10YR vs. 2YR among patients off AEDs at the end of follow-up for a median 44 years since their first seizure before the age of 16 years. In patients on or off AEDs, a reduction in the relapse rate was however seen with increasing duration of remission from 2YR to 5YR and further from 5YR to 10YR. Third, although discontinuation of the AEDs was considered as a better predictor than longer duration of remission in lowering the risk of future relapse, the risk of relapse was not higher, whether predicted by 10YR on or off AEDs than 2YR off AEDs, respectively. This finding is in line with clinical experience that many young adults who have no more seizures and medical indications for continued antiepileptic treatment

still want to continued antiepileptic treatment still want to continue on AEDs, mostly in fear of re-emergent seizures and their adverse social consequences.

Taken together, and answering the study question, our data indicate that epilepsy can only be predicted to remain in remission with the lowest risk of relapse on or off AEDs when ten years have passed without relapse while risk assessment based on 2YR and 5YR is less reliable. However, in patients with remission off AEDs, prolongation of follow-up time from five to ten years did not improve the predictability of relapse risk. The risk is between 10% and 30% for patients on or off AEDs after 10 years remission and between 5% and 20% for patients off AEDs after 5 years in remission.

Although our population-based study has the advantage of a very long median follow-up of 44 years of incident new-onset epilepsy in childhood, it also has its limitations. These include the fact that modern treatment including newer AEDs, relevant surgery, vagus nerve stimulation, or electric therapy were not available for most of the long-term study that began in the 1960s. The small sample size did not allow for reliable subgroup analyses for relapse risk. Despite limitations, our long-term study has three clinically important implications. First, our study could, for the first time, compare the former and the newly introduced criteria and determine the lowest risk of future relapse in those entering first remission. This is important for the management and research of epilepsy as most people with epilepsy fortunately enter remission[21, 33], yet we had to rely mostly on expert opinion that was not based on prospective evidence from an ultra long-term population-based study (see introduction). Secondly, our study showed that long term remission can be predicted after 5-year remission with the last 2 years without AEDs with no need to wait for the results of 10-year remission. This information is clinically important and supports the results of earlier studies with shorter follow-up studies of remission off AEDs[17, 34]. Thirdly, our study – or any other study – cannot provide absolute criteria for predicting life-

time remission, for being seizure free for 10 years or more even off AEDs may still be followed, in a small subpopulation of patients, by re-development of seizures after long periods of remission[33, 35]. Further, better recognition and delineation of initial epilepsy through increased awareness, and new diagnostic investigations may allow for earlier and more effective treatment in the future that was not available when our study started 50 years ago.

The definition of remission has major implications for patients´ perception of themselves, employability especially in certain professions and potentially on insurability. The traditional definition was based on 5 years. It is clear that the longer one is in remission, the better the chances of remaining so but that, with the exception of the age specific syndromes such as benign epilepsy of childhood with centro-temporal spikes, the rate never goes to zero. Given the very modest differences in relapse rates between the 5 years seizure free with last 2 years off medications definition and the 10 year seizure free with last 5 years off medications, we propose that a return to the 5 year definition which is supported by multiple prospective studies may be warranted.

None of authors has any relevant conflicts of interest to disclose.

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Table 1. Proportions of relapsed patients after 2-year (2YR), 5-year (5YR) and 10-year (10YR) remissions on or off AEDs or off AEDs among all 148 patients with childhood onset epilepsy and in a sub-group of 84 patients with generalized epilepsy. Relapse proportions are given with 95% confidence intervals (95%CI). Md=median.

Remission category	Attained remission		Remission length, years	Relapsed		
	n	%	Md (range)	n	%	95% CI
All patients						
2YR, on/off AEDs	132	89	5 (2–46)	93	70	61.9–78.1
5YR, on/off AEDs	117	79	28 (5–46)	48	41	32.0–50.5
10YR, on/off AEDs	101	68	36 (10–46)	19	19	11.7–27.8
2YR, 1y off AEDs	99	67	32 (2–46)	20	20	12.8–29.5
5YR, 2y off AEDs	85	57	38 (5–46)	10	12	5.8–20.6
10YR, 5y off AEDs	82	55	38 (14–46)	4	5	1.3–12.0
Generalized epilepsy						
2YR, on/off AEDs	80	95	6 (2–46)	49	61	49.7–71.9
5YR, on/off AEDs	76	90	34 (5–46)	24	32	21.4–43.3
10YR, on/off AEDs	72	86	38 (10–46)	10	14	6.9–24.1
2YR, 1y off AEDs	73	87	34 (2–46)	17	23	14.2–34.7
5YR, 2y off AEDs	66	79	38 (5–46)	9	14	6.4–24.3
10YR, 5y off AEDs	65	77	38 (14–46)	3	5	1.0–12.9

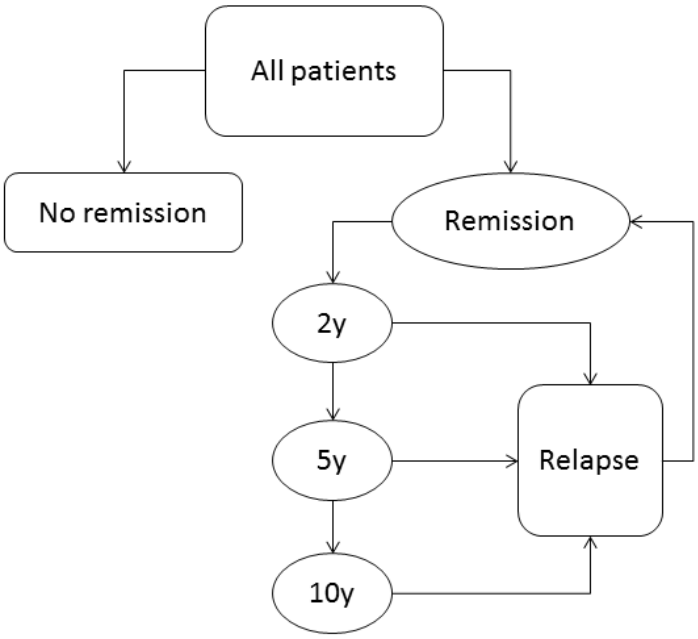
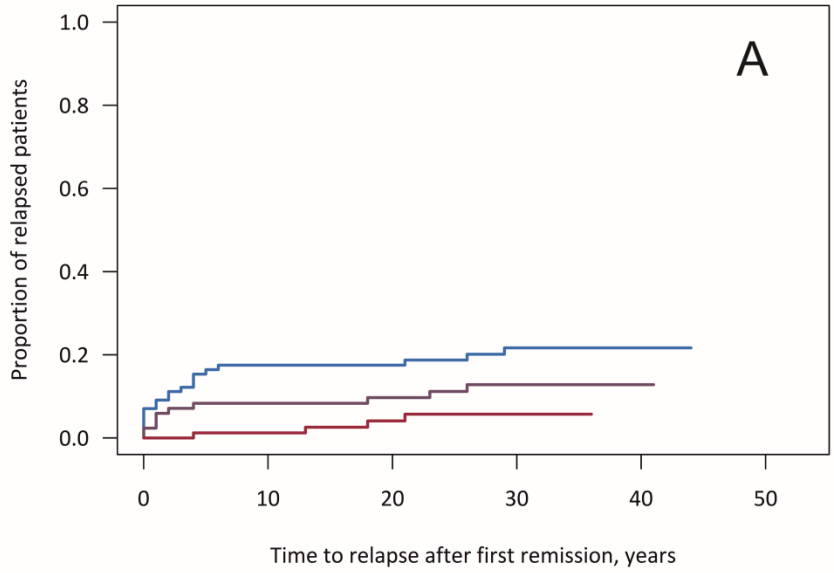


Fig. 1. Process chart of 148 patients with new-onset childhood epilepsy. Sixteen patients never entered 2-year remission. For each patient, the first 2-, 5-, and 10-year remission, respectively, was included in the analyses. During 44-year follow-up, an individual patient could belong to one or more of the 2-year, 5-year and 10-year remission categories. The number of patients in each category is given in Table 1. Of the 148 patients, 144 (97%), 135 (91%), 122 (82%), and 97 (66%) were followed up over 10, 20, 30, and 40 years, respectively.



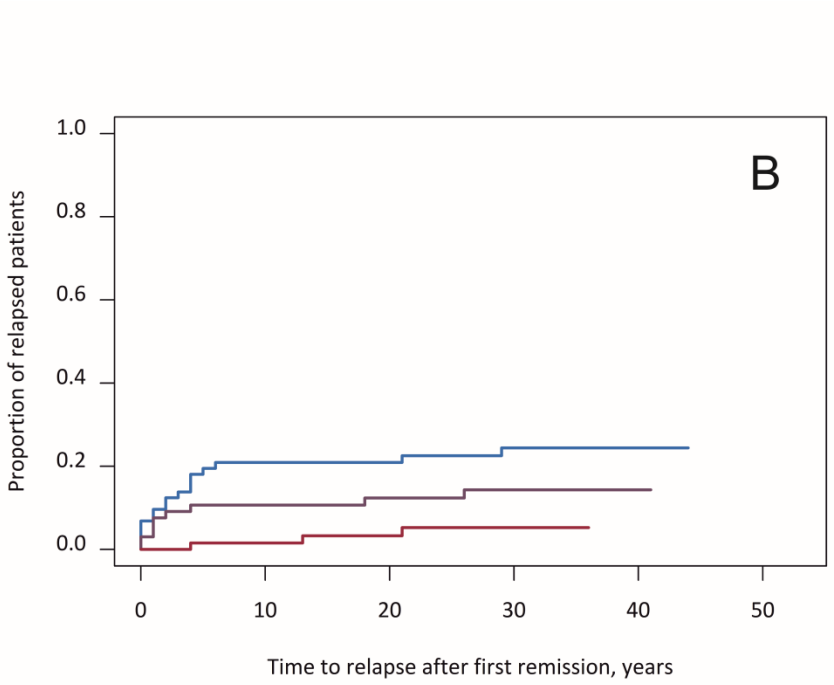


Fig. 2. Kaplan-Meier estimates of the cumulative probability of relapse and proportions of the relapsed after first 2-year, 5-year and 10-year remission off AEDs among 148 patients with new-onset childhood epilepsy (A) and among the sub-group of 84 patients with generalized epilepsy (B) during long-term follow-up. Blue lines: 2-year remission with the last year off AEDs; purple lines: 5-year remission with the last two years off AEDs; red lines: 10-year remission with the last five years off AEDs.

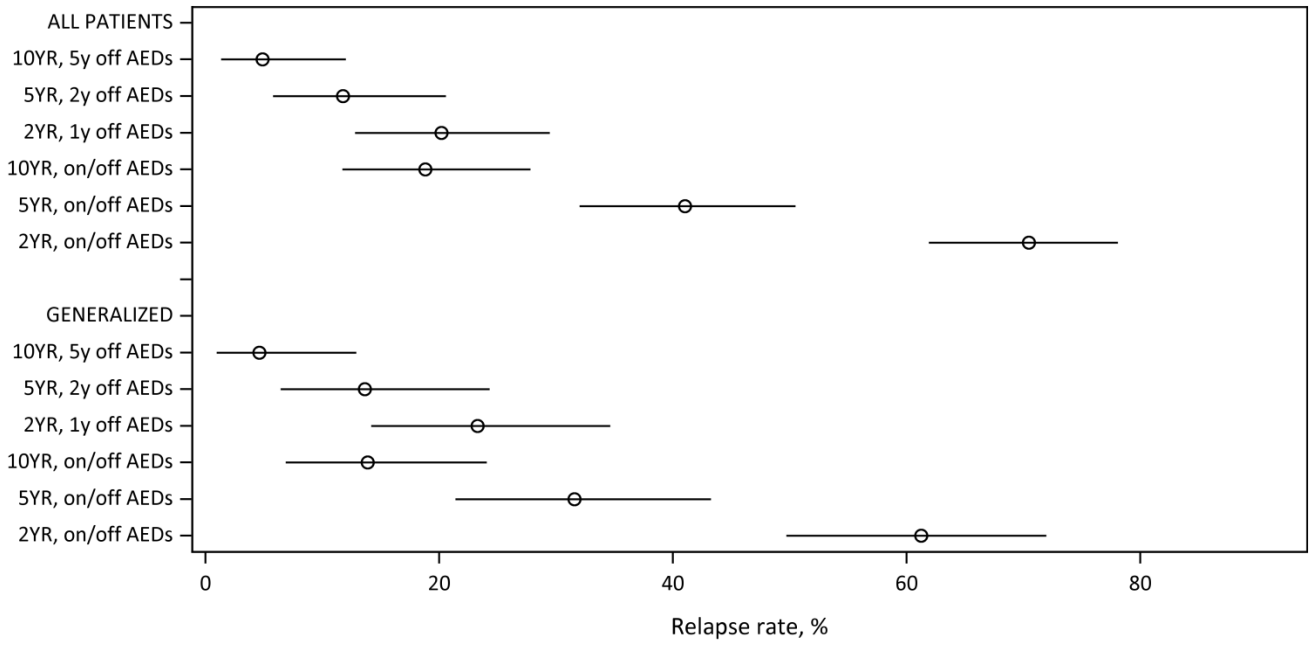


Fig. 3. Forest plot of relapse rates with exact Clopper Pearson 95% confidence intervals for patients in 2-year, 5-year and 10-year remission categories. The relapse rates decrease as the duration of remissions gets longer. Non-overlapping confidence intervals indicate different relapse rates between the remission groups.