New statistical method for analysing time to first seizure: example using data comparing carbamazepine and valproate monotherapy.

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Abstract (248 words)

Introduction: Time to first seizure is a common outcome in antiepileptic drug (AED) studies. Previous studies have typically failed to find statistically significant differences between carbamazepine (CBZ) and valproate (VPS). We re-analysed a meta-analysis comparing CBZ and VPS monotherapy with new powerful statistical methods which incorporate baseline seizure rate information.

Methods: Individual patient data were available on 1,265 patients from a meta-analysis of 5 trials. The outcome measure was time to first seizure after randomisation, adjusted for background variables and baseline seizure rate.

Results: We found strong evidence of an interaction between treatment and epilepsy type, and between treatment and age. For generalized onset seizures VPS was statistically significantly better than CBZ: VPS delayed the first seizure after treatment 58%, 52%, 44% and 36% longer than CBZ for individuals aged 10, 20, 30 or 40, respectively. For partial onset seizures in individuals older than 30, CBZ was significantly better then VPS; CBZ delayed the time to first seizure by 9%, 25%, 44% and 66% longer than VPS for individuals aged 20, 30, 40 or 50, respectively.

Discussion: The results show clear age-varying differences between the effectiveness of CBZ and VPS for generalized onset and partial onset seizures, which have not been identified in previous studies using standard statistical methods. In future trials of AED monotherapy or add-on where time to first or N^{th} seizure is an outcome, methodology which can incorporate baseline seizure rate information would allow more powerful comparisons between treatments or between treatment and placebo.

Introduction

Antiepileptic drug (AED) treatment choices should be based upon reliable evidence derived primarily from randomized controlled trials (RCTs). Such trials should use appropriate methods of analysis. In this paper we present a new statistical model that uses baseline seizure counts in the statistical modelling of the outcome time to first seizure after randomization (Cowling et al., 2006). Time to first seizure is an outcome recommended by the International League against Epilepsy for monotherapy trials (International League Against Epilepsy Commission on Antiepileptic Drugs, 1998), and is also being advocated as an outcome for add-on therapy trials.

We examine data on a large cohort of epilepsy patients from a meta-analysis of RCTs comparing carbamazepine (CBZ) and valproate (VPS) monotherapy, which are recommended as first line treatments (Scottish Intercollegiate Guidelines Network., 2003, Wallace, 1997) despite uncertainty about their relative effects. A reanalysis of these data using our new methodology (Cowling et al., 2006) has detected clinically important differences between CBZ and VPS that were not detected in a previous meta-analysis of these data (Marson et al., 2002). Furthermore, the new methodology allows appropriate estimation of effects even though the assumptions of the proportional hazards model are not met. The new methodology, the results and their interpretation are presented for a clinical readership.

Subjects and Methods

We analysed data on 1,265 individuals from five clinical trials comparing CBZ with VPS monotherapy in children and adults (de Silva et al., 1996, Heller et al., 1995, Mattson et al., 1992, Richens et al., 1994, Verity et al., 1995). Forty patients with

inadequate information on post-randomization seizures could not be included in the analyses, and a further 39 patients with unknown pre-randomization seizure counts and three with unknown ages were excluded, leaving 1,183 (94%) patients with complete data. Sensitivity analyses showed that 12 (1%) individuals with very high (>200) 6-month pre-randomization seizure counts were overly influential on the results, and these individuals were excluded leaving 1171 individuals for analysis.

The outcome of interest was the time from randomization to a first seizure. A typical analysis might use a Cox proportional hazards model, which would assume that the risk of first seizure on CBZ and VPS are proportional, that is have the same ratio at all times, and would adjust for the 6-month pre-randomization seizure count as an important explanatory variable. However the assumption of proportional hazards is not satisfied in these data (Kwong and Hutton, 2003). In contrast, accelerated failure time models, which assume instead that the times to first seizure are proportional, have been found to fit these data well (Kwong and Hutton, 2003). Accelerated failure time models assume that the times to event (rather than the risk) are themselves proportional, so that one group has proportionally accelerated times to event compared to baseline.

We have developed methodology to allow appropriately for the uncertainty in observed seizure counts (Cowling et al., 2006). The model is represented graphically in Figure 1, where the arrows indicate that both the pre-treatment seizure count and post-treatment time to first seizure depend on unobserved seizure rates, therefore both of these variables are outcomes, or dependent, variables. Conventional analyses using proportional hazards and accelerated failure time models would allow the post-treatment time to be predicted by the observed pre-treatment count, whereas our model specifies

that both are predicted by (unobserved) seizure rates. Our model allows for seizure rates to vary depending on baseline characteristics including age, sex, epilepsy type and trial (Figure 1). Under the new model, each patient was assumed to have a constant underlying seizure rate before the initiation of anti-epileptic therapy. Our model further specifies that each patient's post-therapy underlying seizure rate was reduced relative to the baseline rate, with a greater reduction in seizure rate resulting in a longer (decelerated) time to first post-randomization seizure, which indicates a better therapy. The degree of acceleration or deceleration in the time to first seizure can be obtained from the estimated regression coefficients and is usually referred to as the 'acceleration factor'. Using outcome data on the pre-treatment seizure count and the post-treatment time to first seizure, we estimate the relative importance of the background information and the treatment administered on the reduction in seizure rate due to therapy. Therefore our model estimates not only the effects of background information on the baseline seizure rate but also the effects of both background and treatment effects on the change in seizure rate due to therapy. A further advantage of the new methodology is that it incorporates uncertainty in the (unobserved) baseline seizure count, whereas a typical proportional hazards model would include the seizure count as a proxy for baseline rate ignoring the uncertainty.

Both the number of seizures recorded in the 6 months prior to randomization, and the time to first seizure after randomization are outcome ('dependent') variables in the new methodology. The explanatory ('independent') variables used included age, sex, trial, and seizure type (generalized-onset or partial-onset). Seizures were classified as generalized or partial-onset by the original trialists using the International League Against Epilepsy Classification of seizures.

We investigated the goodness of fit of the model by plots of the residuals. To explore the influence of the patients with high seizure rates (>100 and >50 in 6 months) on the results, we conducted sensitivity analyses by excluding these patients. We performed all analyses using R version 2.1.0 (The R Foundation for Statistical Computing, Vienna). Further technical details may be found in (Cowling et al., 2006).

Results

Of the 1171 patients included in the analyses, 784 (384 CBZ and 400 VPS) individuals, of whom 570 (73%) were males, had their seizures classified by the original trialists as partial onset seizures including simple partial, complex partial and secondary generalized tonic clonic seizures. The remaining 387 (197 CBZ and 190 VPS) individuals, including 193 (50%) males, had seizures classified by the original trialists as generalized onset seizures, all of whom had tonic clonic seizures. Although some patients may have had other generalized seizure types such as absence or myoclonus, only tonic clonic seizures were recorded during follow-up and baseline and results apply to tonic clonic seizures only. Individuals with generalized onset seizures had median 3 (interquartile range (IQR): 2, 4) seizures in the 6 months prior to randomization, while individuals with partial onset seizures had median 4 (IQR: 2, 7) seizures. The Kaplan-Meier estimates of the time to first seizure are shown in Figure 2, without adjusting for pre-randomization seizure rates. For generalized-onset tonic clonic seizures, the median time to first seizure after randomization was 321 days in the CBZ arm and 339 days in the VPS arm. For partial-onset seizures, the median times to first seizure after randomization were 116 days and 56 days in the CBZ and VPS arms, respectively.

When fitting the new model to the epilepsy data, we found no effect of gender on the underlying seizure rate or as an effect modifier on the reduction in seizure rate by the treatments, so omitted this variable. Age and seizure type (partial versus generalized onset) were both important in explaining the variability in seizure rates between individuals, and both modified the effect of the treatments. Seizure rates were also adjusted for the effects of study.

The results of a gamma accelerated failure time model are shown in Table 1, and contrasted with the estimated regression coefficients of the new model. Under the gamma model, which has previously been shown to fit these data well (Kwong and Hutton, 2003), VPS was superior for generalized onset seizures in children and young adults, while CBZ was superior for partial onset seizures (Table 1), however the gamma model did not have the power to detect statistically significant differences. Under the new model, younger individuals and those with partial-onset epilepsies had typically higher baseline seizure rates, and they benefited from a higher reduction in seizure rate after treatment (Table 1). The interactions between treatment and epilepsy type, and treatment and age, were both highly statistically significant. Comparing regression coefficients reveals that the new method finds a substantial benefit for VPS in generalized onset seizures, and a benefit for CBZ in older patients with partial onset seizures. The regression coefficients of the gamma model and the new methodology may be directly compared, and Table 1 shows that the estimated effects are of similar direction and magnitude under both models. For example, patients with partial-onset seizures had higher seizure rates than those with generalized-onset seizures, as shown by the regression coefficient of 0.700 under the gamma model, whereas patients with partial-onset seizures had much higher baseline seizure rates (regression coefficient

1.304) which were attenuated but still higher than patients with generalized-onset seizures after treatment (1.304 – 0.787 = 0.517) under the new model. Residual differences between these estimates of the effects of seizure type are likely accounted for in the differences between the estimated effects of age, given the high degree of correlation between age and seizure type (12). The increased statistical power of the new methodology is also apparent from the smaller p-values for similar effect sizes (Table 1).

To aid interpretation of the new model, the regression coefficients for the treatment effect and interaction terms may be presented as acceleration factors (AF) for CBZ vs VPS, which are the relative acceleration (<1) or deceleration (>1) in time to first seizure for individuals treated with CBZ rather than VPS (Table 2). The results show that the median time to first seizure for a patient aged 10 with generalized onset seizures would be 58% shorter (AF=0.42) if CBZ were assigned rather than VPS. In contrast, the median time to first seizure for a patient aged 40 with partial onset seizures would be 44% longer (AF=1.44) for CBZ compared to VPS. These estimates are consistent with the empirical patterns in time to first seizure shown in Figure 2.

We examined residual plots and found that the fit of the model was satisfactory. Sensitivity analyses showed that the relative effects of the treatments were not changed if 49 patients with more than 50 seizures or 11 patients with more than 100 seizures in the 6 months prior to randomization were excluded (appendix table).

Discussion

The results show a clear preference for VPS over CBZ for all patients with generalized onset tonic clonic seizures. Conversely, the results support the use of CBZ rather than VPS for most patients with partial onset seizures. It is unclear, however, which is the best treatment for patients under the age of 30 with partial-onset seizures. The results show a strong dependence of time to first seizure on prior seizure rates, age, and epilepsy type. While the Kaplan-Meier estimates of time to first seizure were initially similar for generalized-onset epilepsies, the curves later diverge showing a clear advantage of VPS (Figure 2). After adjusting for prior seizure rates, age, and epilepsy type, the new methodology estimates that VPS can approximately double the expected time to first seizure for a typical patient aged 20, compared to CBZ (Table 2). In contrast for partial-onset epilepsies the Kaplan-Meier estimates of time to first seizure showed a clear advantage of CBZ (Figure 2), and after adjusting for prior seizure rates, age, and epilepsy type, the new methodology estimates that CBZ can increase by 44% the expected time to first seizure for a typical patient aged 40, compared to VPS (Table 2).

A potential limitation of our study is the assumption of constant seizure rate, since seizures can occur in clusters. A moderate degree of clustering would result in a typically longer time to first post-randomization seizure than predicted by our model (except for a few patients in the midst of a cluster of seizures at randomization, who would have much shorter times to first seizure than predicted), and the absolute reduction in seizure frequency estimated by our model would be slightly optimistic. However, the relative differences between CBZ and VPS (Table 2) should be maintained even under clustering, because of the randomization of treatments. Without

data on the dates of each seizure it is impossible for us to assess or allow for clustering in these data, and we would recommend that future trials record the precise dates of seizures before and after randomization. A caveat of the new methodology is that the estimated regression coefficients can be somewhat sensitive to outlying values; we found that a small number of patients with very high baseline seizure counts could be influential to the results. Therefore we recommend that care should be taken when applying the new methodology, and in particular the influence of outliers should be investigated.

A further limitation in our study is the quality of data. While our data contain the standardized outcome of seizures in the 6 months prior to randomisation, the original trialists collected some data in different formats (i.e. time from first seizure to randomisation and number of seizures in this period) before the data were converted to a consistent format for the meta analysis (Marson et al., 2002). Extrapolation or interpolation of these data to the standardised outcome used in our study may have biased the estimated treatment effects, although randomization should have attenuated this bias somewhat. We note that in our model it is straightforward to incorporate data on time from first seizure to randomisation when these are available. A separate issue with the data quality concerns the classification of epilepsy type by the original trialists, since further analysis (Williamson et al., 2002) has suggested that misclassification may have affected the results, particularly inflating the treatment-age interaction since age is a proxy for epilepsy type.

It should also be noted that time to first seizure is only one of the recommended outcomes for assessing the efficacy of AEDs (International League Against Epilepsy

Commission on Antiepileptic Drugs, 1998). In particular, consideration of safety profiles is important.

In future AED trials, methodology which can incorporate baseline seizure rate information would allow more powerful comparisons between treatments. The example chosen in this paper included data from comparative monotherapy trials, and illustrates increased statistical power compared to standard statistical analyses. This approach would also be valid for regulatory add-on trials in which a new drug or placebo is added to a stable base of other AEDs. Some are advocating trials using time to first seizures to screen for effective drugs, and the methods outlined in this paper would help maximise the power of such studies.

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References

Cowling BJ, Hutton JL, Shaw JEHS (2006) Joint modelling of event counts and survival times. *Applied Statistics,* 55(1):31-9.

de Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Neville BG, et al. (1996) Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet,* 347(9003):709-13.

Heller AJ, Chesterman P, Elwes RD, Crawford P, Chadwick D, Johnson AL, et al. (1995) Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *Journal of Neurology, Neurosurgery & Psychiatry,* 58(1):44-50.

International League Against Epilepsy Commission on Antiepileptic Drugs (1998) Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. *Epilepsia,* 39(7):799-803.

Kwong GPS, Hutton JL (2003) Choice of parametric models in survival analysis: applications to monotherapy for epilepsy and cerebral palsy. *Applied Statistics,* 52(2):153-68.

Marson AG, Williamson PR, Clough H, Hutton JL, Chadwick DW, Epilepsy Monotherapy Trial G (2002) Carbamazepine versus valproate monotherapy for epilepsy: a meta-analysis. *Epilepsia,* 43(5):505-13.

Mattson RH, Cramer JA, Collins JF (1992) A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *New England Journal of Medicine,* 327(11):765-71.

Richens A, Davidson DL, Cartlidge NE, Easter DJ (1994) A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Adult EPITEG Collaborative Group. *Journal of Neurology, Neurosurgery & Psychiatry,* 57(6):682-7.

Scottish Intercollegiate Guidelines Network. (2003) *Diagnosis and management of epilepsy in adults : a national clinical guideline*. Edinburgh: Scottish Intercollegiate Guidelines Network.

Verity CM, Hosking G, Easter DJ (1995) A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. The Paediatric EPITEG Collaborative Group. *Developmental Medicine & Child Neurology,* 37(2):97-108.

Wallace H (1997) *Adults with poorly controlled epilepsy*. London: Royal College of Physicians.

Williamson PR, Clough HE, Hutton JL, Marson AG, Chadwick DW (2002) Statistical issues in the assessment of the evidence for an interaction between factors in epilepsy trials. *Statistics in Medicine,* 21(18):2613-22.

Table 1. Estimated regression coefficients under the gamma accelerated failure time model and the new methodology.

Factor[a]	gamma model		New methodology			
			Baseline seizure rate		Difference in rate after treatment	
	Regression coefficient[b]	p-value	Regression coefficient[c]	p-value	Regression coefficient[d]	p-value
CBZ	reference		reference		reference	
VPS	-0.622	0.288	-	-	-1.007	<0.001
Generalized-onset epilepsy	reference		reference		reference	
Partial-onset epilepsy	0.700	0.007	1.304	<0.001	-0.787	<0.001
Age at randomization (in decades)	-0.248	<0.001	-0.012	0.592	0.074	0.008
Log(number of seizures)	0.501	<0.001	-	-	-	-
VPS * partial-onset epilepsy	0.471	0.167	-	-	0.815	<0.001
VPS * age (in	0.175	0.032	-	-	0.139	<0.001

decades)

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[a] All models are also adjusted for study effects.

[b] A regression coefficient >0 (<0) would indicate a quicker (slower) time to first seizure relative to the reference group.

[c] A regression coefficient >0 (<0) would indicate an increased (decreased) pre-treatment seizure rate relative to the pre-treatment seizure rate in the reference group.

[d] A regression coefficient >0 (<0) would indicate an increased (decreased) post-treatment seizure rate, relative to the post-treatment seizure rate in the reference group.

Table 2. Predicted relative changes (acceleration factors) in time to first seizure for individuals with different ages and epilepsy type, assigned to treatment with carbamazepine (CBZ) compared to sodium valproate (VPS).

Age	Generalized onset		Partial onset	
	Acceleration factor (AF)[a]	95% CI for AF	Acceleration factor (AF)[a]	95% CI for AF
Age 10[b]	0.420[c]	(0.331, 0.533)		
Age 20	0.483	(0.371, 0.629)	1.090	(0.912, 1.303)
Age 30	0.555	(0.416, 0.740)	1.253	(1.034, 1.518)
Age 40	0.638	(0.467, 0.870)	1.440	(1.174, 1.767)
Age 50[b]			1.655	(1.333, 2.055)

[a] An acceleration factor <1 would indicate an accelerated, i.e. shorter, time to first seizure for patients taking CBZ rather than VPS.

[b] Predictions are not made for individuals aged 50 with generalized onset epilepsies, or aged 10 with partial onset epilepsies, since the data contained few such individuals.

[c] The proportional change in seizure rate on VPS vs CBZ (which is equivalent to the acceleration factor in time to first seizure on CBZ vs VPS) for an individual with generalized-onset seizures and aged 10 can be calculated from the coefficients in Table 1 via exp(-1.007+0.139) = 0.420.

Figure 1. A model for epilepsy data showing how data on pre-treatment seizure counts may be incorporated to allow more precise estimation of the effect of anti-epileptic therapy in reducing the pre-treatment seizure rate. Traditional analyses would include the pre-treatment count as an independent variable rather than as a second dependent variable.

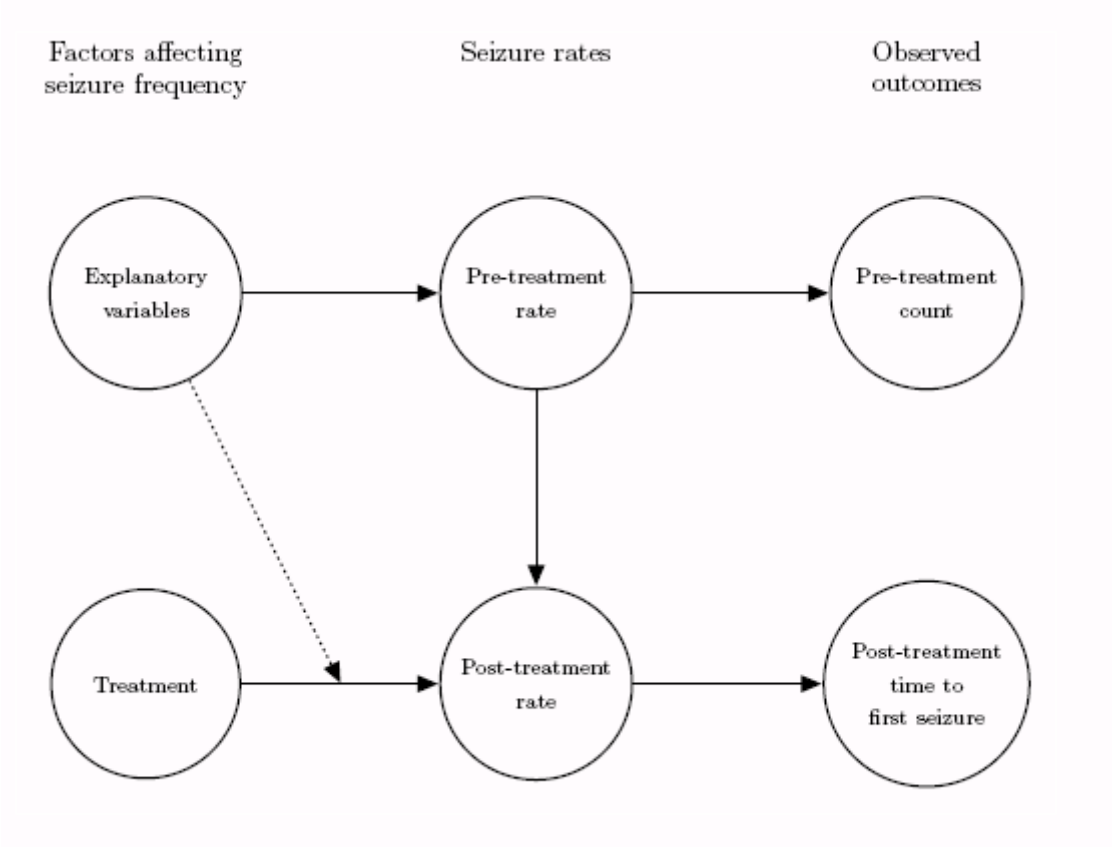
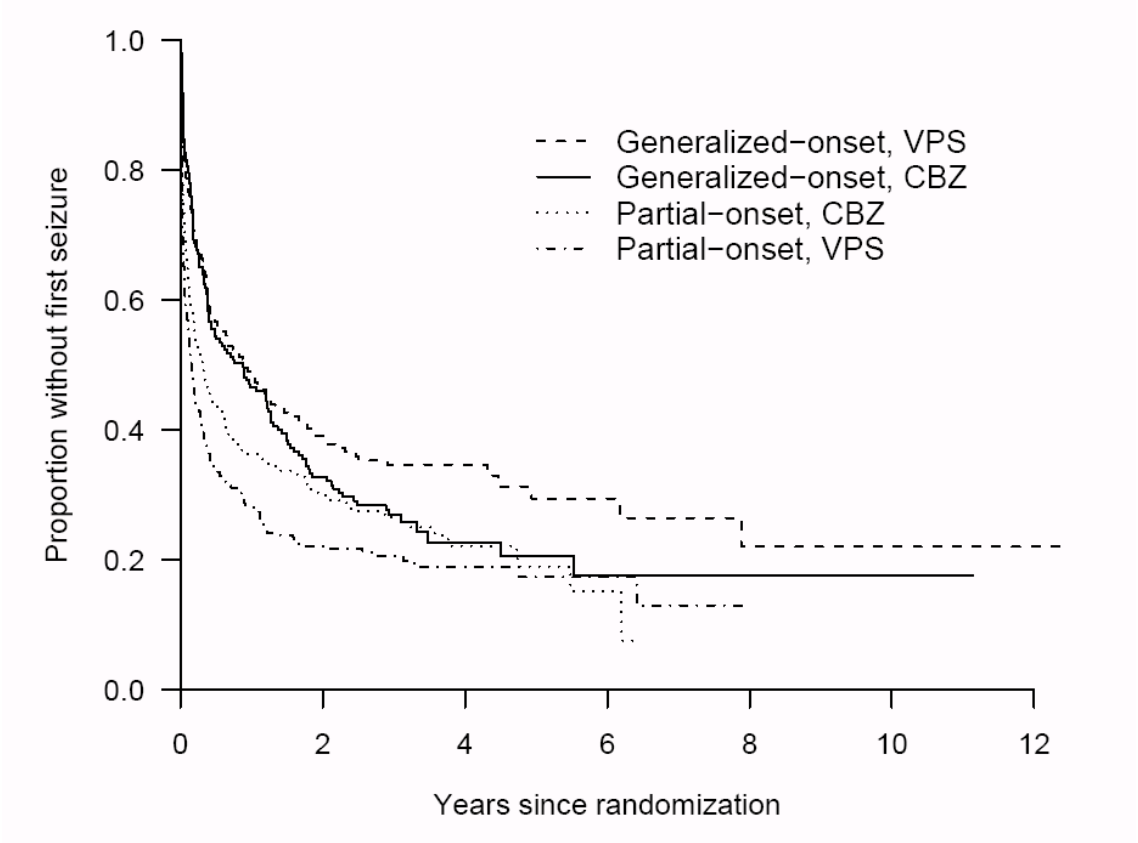


Figure 2. Time to first seizure by epilepsy type and treatment.



Appendix table: Sensitivity analysis of results of joint model to the exclusion of individuals with high seizure counts. The results for individuals with ≤200 seizures have been selected for presentation in Table 2.

Inclusion criteria	N	Generalized onset seizures							
		Age 10		Age 20		Age 30		Age 40	
		AF	95% CI for AF	AF	95% CI for AF	AF	95% CI for AF	AF	95% CI for AF
All data	1183	0.079	(0.065, 0.096)	0.098	(0.077, 0.125)	0.123	(0.093, 0.162)	0.153	(0.112, 0.209)
≤200 seizures	1171	0.420	(0.331, 0.533)	0.483	(0.371, 0.629)	0.555	(0.416, 0.740)	0.638	(0.467, 0.870)
≤100 seizures	1160	0.459	(0.367, 0.573)	0.524	(0.405, 0.678)	0.599	(0.448, 0.800)	0.684	(0.497, 0.941)
≤50 seizures	1122	0.498	(0.406, 0.610)	0.556	(0.433, 0.715)	0.622	(0.465, 0.830)	0.694	(0.502, 0.960)
		Partial onset seizures							
		Age 20		Age 30		Age 40		Age 50	
		AF	95% CI for AF	AF	95% CI for AF	AF	95% CI for AF	AF	95% CI for AF
All data	1183	1.186	(0.994, 1.417)	1.479	(1.224, 1.787)	1.844	(1.509, 2.253)	2.298	(1.861, 2.838)
≤200 seizures	1171	1.090	(0.912, 1.303)	1.253	(1.034, 1.518)	1.440	(1.174, 1.767)	1.655	(1.333, 2.055)
≤100 seizures	1160	1.319	(1.095, 1.589)	1.508	(1.240, 1.833)	1.723	(1.405, 2.113)	1.968	(1.592, 2.434)
≤50 seizures	1122	1.626	(1.329, 1.990)	1.817	(1.480, 2.231)	2.030	(1.648, 2.501)	2.268	(1.835, 2.803)