Insight into the pathophysiology of cardiometabolic diseases using multiple omics approaches

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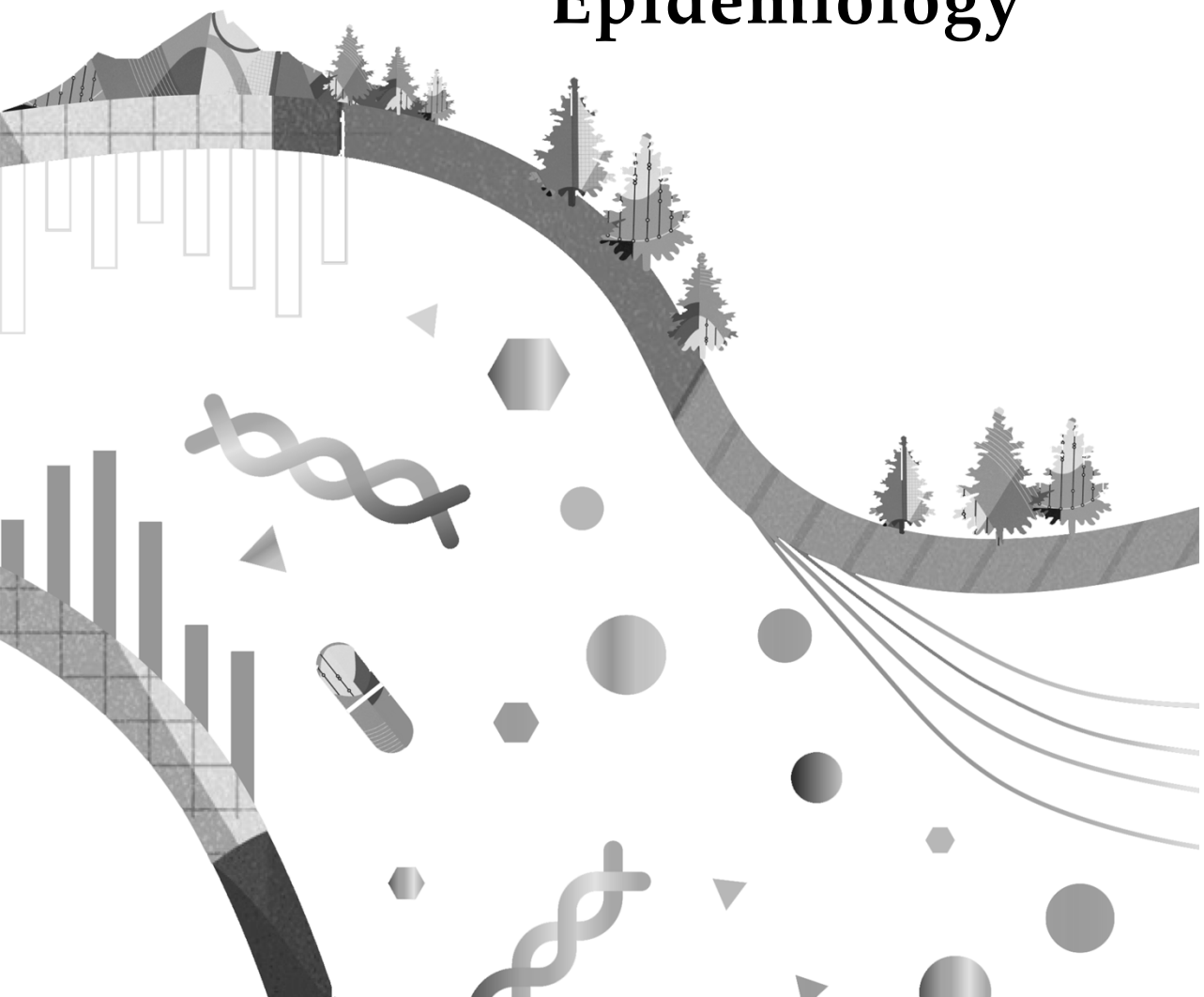
Part IV

Integration of Pharmacometrics and Epidemiology



Chapter 6

A novel approach for pharmacological substantiation of safety signals using plasma concentrations of medication and administrative/healthcare databases: A case study using Danish registries for an FDA warning on lamotrigine

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Abstract

PHARMACOM-EPI is a novel framework to predict plasma concentrations of drugs at the time of occurrence of clinical outcomes. In early 2021, the U.S. Food and Drug Administration (FDA) issued a warning on the antiseizure drug lamotrigine claiming that it has the potential to increase the risk of arrhythmias and related sudden cardiac death due to a pharmacological sodium channel-blocking effect. We hypothesized that the risk of arrhythmias and related death is due to toxicity. We used the PHARMACOM-EPI framework to investigate the relationship between lamotrigine's plasma concentrations and the risk of death in older patients using real-world data. Danish nationwide administrative and healthcare registers were used as data sources and individuals aged 65 years or older during the period 1996 – 2018 were included in the study. According to the PHARMACOM-EPI framework, plasma concentrations of lamotrigine were predicted at the time of death and patients were categorized into non-toxic and toxic groups based on the therapeutic range of lamotrigine (3-15 mg/L). Over 1 year of treatment, the incidence rate ratio (IRR) of all-cause mortality was calculated between the propensities score matched toxic and non-toxic groups. In total, 7286 individuals were diagnosed with epilepsy and were exposed to lamotrigine, 432 of which had at least one plasma concentration measurement The pharmacometric model by *Chavez et al* was used to predict lamotrigine's plasma concentrations considering the lowest absolute percentage error among identified models (14.25%, 95% CI: 11.68-16.23). The majority of lamotrigine associated deaths were cardiovascular-related and occurred among individuals with plasma concentrations in the toxic range. The IRR of mortality between the toxic group and non-toxic group was 3.37 [95% CI: 1.44-8.32] and the cumulative incidence of all-cause mortality exponentially increased in the toxic range. Application of our novel framework PHARMACOM-EPI provided strong evidence to support our hypothesis that the increased risk of all-cause and cardiovascular death was associated with a toxic plasma concentration level of lamotrigine among older lamotrigine users.

Introduction

Recent research has emphasized that the incorporation of information on plasma concentrations is important for effective pharmacoepidemiological research when performing pharmacological substantiation of clinical outcomes. [1–3] Thus far, the integration of data on plasma concentrations in pharmacoepidemiological research has been limited due to the lack of available approaches for performing this task. We have recently developed a novel framework, PHARMACO-EPI, to integrate pharmacometrics into pharmacoepidemiological research with the final goal of predicting plasma concentrations at the time of occurrence of clinical outcomes for their pharmacological substantiation, especially for newly discovered associations from signal detection activities. However, this framework has not been tested yet in real-life cases where regulatory agencies have detected new safety signals.

In early 2021, the U.S. Food and Drug Administration (FDA) issued a warning indicating that lamotrigine has the potential to increase the risk of arrhythmias and related sudden cardiac death. [4] These adverse events may be related to lamotrigine's sodium channel blocking effect and related alteration of the QRS complex of the electrocardiogram, and delay in ventricular conduction is associated with enhanced risk of ventricular arrhythmias and sudden cardiac death in susceptible patients. [4–6] As lamotrigine's sodium channel-blocking effects are dose-dependent [7], this risk may be higher in older epileptic patients aged 65+ exposed to lamotrigine as they have an increased risk of reaching toxic plasma concentration. [8]

We used PHARMACO-EPI [1,2,9,10], to predict the plasma concentration of lamotrigine at death and investigate the association between toxic plasma concentrations and death in older individuals exposed to lamotrigine by using Danish nationwide real-world data.

Method

Data source

Danish nationwide administrative and healthcare registers were used as data sources. Based on a unique personal identification number for each Danish citizen that linked Danish registers, we collected information on residents' date of birth, sex [11], hospital admission/ambulatory visit [12], medication redemptions in community pharmacies [13], and deaths. [14] Additionally, by using the Danish Register for Laboratory Results for Research, we collected information about plasma concentrations of antiseizure medications and results of immunological and biochemical tests performed in Danish patients. [15]

In Denmark, plasma concentration measurements are commonly used in Therapeutic Drug Monitoring (TDM) to optimize the dosage of antiepileptic medication. TDM helps ensure that the medication is within the therapeutic range and that the patient is receiving an effective and safe dose.

Study population

All residents in Denmark aged 65 years or older during the period 1996 – 2018, that were diagnosed with epilepsy, and that have redeemed their first prescription of lamotrigine were included in the study population. The first prescription of lamotrigine following epilepsy diagnosis was used as the index date from which we followed up individuals in the registers. Individuals that redeemed any antiseizure medications twelve months before the index date were excluded. Individuals were classified as having epilepsy if they had been hospitalized or had been in outpatient care with an epilepsy diagnosis (International Classification of Disease code, ICD-8 code 345, ICD-10 codes G40). The diagnosis codes for epilepsy in the Danish registers have been previously validated with a positive predictive value of 81% (95% Confidence Interval (CI): 75%–87%). [16]

Follow-up period & study outcome

The study population was followed from the index date for 365 days until the occurrence of the study outcome (i.e., death) or censoring due to

permanent emigration or end of the data coverage. The study outcome was all-cause of mortality within the follow-up period. We have selected 1-year follow-up based on the consideration that it was expected that the majority of dose-dependent events occurred during the early stages of the treatment.[17]

Identification of accessible pharmacometric models

We used PHARMACOM-EPI [1] to determine the fraction of deaths that are pharmacologically substantiated by toxic plasma concentrations at the time of death or the end of follow-up. According to PHARMACOM-EPI [1], pharmacometric models of lamotrigine developed on the adult population from the most recent systematic reviews [18] of population pharmacokinetic models of lamotrigine were identified. The same systematic review query was used to update the review and identify models that were not previously included in the systematic review. Detailed processes concerning systematic review are shown in Appendix 1.

Application of pharmacometric models to real-world data

Before applying the pharmacometrics model, we characterized them by extracting relevant socio-demographic characteristics of the populations on which the models were developed and parameters from the models including fixed parameters, equations for estimated parameters, inter-individual variability, residual variability, covariates tested, and software and number of compartments. The analytical dataset for pharmacometric models was structured according to the format requirements of NONMEM software [19]. By applying pharmacometric models to real-world data, we obtained population predictions and individual predictions of lamotrigine plasma concentrations for each model. Possible missing covariates required in the pharmacometric models were imputed using published data from similar populations. Missing value in height and weight were imputed based on published Danish reference data for men and women, respectively. [20] Blood urea nitrogen/serum creatinine ratio was imputed based on a normal distribution having a mean 11 and SD 2. Body surface area was calculated using following equation (Body Surface Area$= 007184 * Height(m)^{0.725} * Weight(kg)^{0.425}$). Glomerular filtration rate was estimated by equation published by *Levey AS et al*. [21] Similarly, genetic polymorphisms were imputed based on the allele frequencies of genotypes satisfying Hardy-

Weinberg equilibrium obtained from the NCBI database of genetic variation. [22] Daily doses of antiseizure medications were imputed using the Sessa Empirical Estimator [23–26] and missing dosing times were replaced with fixed times, assuming that the latest dose was taken at 8:00 a.m. on the same day of the measurement of plasma concentration. The models' performance was assessed by plotting observed versus predicted population/individual concentrations as two-dimensional density plots with contour lines where each contour shows aggregated data for more than 5 individuals. Trend lines were drawn using local polynomial regression fitting. In addition, the absolute percentage error of population concentration prediction and individual concentration prediction for each model was calculated to identify the pharmacometrics model with the lowest absolute percentage error. The absolute percentage error for population and individual prediction of each pharmacometric model was plotted using a boxplot.

Statistical analysis

Characteristics for the study population at the baseline were reported as mean with standard deviation (SD) for continuous variables and percentage for categorical variables separately between individuals with and without available plasma concentrations of lamotrigine.

To predict lamotrigine plasma concentration at death using individual predictions from pharmacometrics models, we used data from individuals with available plasma concentrations among those included in the study population. To infer the results from individuals with lamotrigine plasma concentration to those without plasma concentrations measurements, we performed propensity score matching. The propensity score for receiving or not a plasma concentration measurement was obtained based on risk factors of the outcome including age, sex, comorbidities, and co-medications according to the Elixhauser Comorbidity Index [27] using a logistic regression model. The Elixhauser Comorbidity Index [27] is a validated index that include clinical conditions associated with mortality. For each individual with available plasma concentration measurements, we matched four individuals without lamotrigine concentration using the greedy nearest neighbor method with a maximum caliper distance of 0.2 of the logit of the propensity score. The density plots of the propensity scores before and after matching were plotted. We considered it possible to infer the results from individuals with available plasma concentration to individuals without

plasma concentration if there was at least a 70% overlap of the propensity scores distributions.

To investigate the association between plasma concentration, when available, and the study outcome, we used the pharmacometric model with the lowest absolute percentage error to predict trough concentrations at death or at the end follow-up. Plasma concentrations were categorized into non-toxic and toxic groups based on the reference therapeutic range for lamotrigine (3-15 mg/L). [28] The cumulative incidence rate for all-cause mortality versus lamotrigine plasma concentration was plotted and the incidence rate ratio (IRR) of all-cause mortality between non-toxic and toxic group was calculated. The hazard functions of individuals within the non-toxic range and those with toxic plasma concentration were computed using a Cox regression model and plotted as cumulative hazards functions curves. All the analyses were implemented in R (version 4.0.0, RStudio, Austria).

Ethics

In Denmark, ethical committee approval or individual patient consent is not required according to Danish law, which implies that it is not required to obtain consent for participants in studies based on register data in Denmark.

Results

Study population characteristics

In total, 7286 individuals were diagnosed with epilepsy and were exposed to lamotrigine, 432 of which had at least one plasma concentration measurement. For the whole population, 49.7% of the individuals were men with an average age of 70 (SD: 10.5) years. The population with plasma concentration measurement had a greater mean age [72.7 (SD: 8.1) years] and a higher proportion number of males (53.5%) compared with the population without plasma concentration which had 49.4% of men and a mean age of 69.8 (SD: 10.6) years (**Table 1**). Within those individuals with at least one plasma concentration measurement, frequencies of comorbidities, age and sex did not differ significantly between those in the non-toxic group (n=290) and those who reached toxic ranges (n=142) suggesting comparability between the two groups (**Table 2**).

Table 1 Characteristics of epileptic patients with and without lamotrigine concentration measurements

Variable	Level	Patients without plasma concentration (n= 6849)	Patients with plasma concentration (n=432)	Total (n=7286)
Sex	Male	3385 (49.4)	234 (53.7)	3619 (49.7)
Age	Mean (SD)	69.8 (10.6)	72.7 (8.1)	70 (10.5)
Diabetes	Yes	717 (10.5)	56 (13.0)	773 (10.6)
Cancer	Yes	764 (11.2)	74 (17.1)	838 (11.5)
Arthritis	Yes	264 (3.9)	15 (3.5)	279 (3.8)
Coronary Heart Disease	Yes	1262 (18.4)	82 (19.0)	1344 (18.4)
Dementia	Yes	587 (8.6)	58 (13.4)	646 (8.9)
Respiratory Disorders	Yes	1665 (24.3)	131 (30.3)	1797 (24.7)
Ulcer	Yes	396 (5.8)	33 (7.6)	429 (5.9)
Cerebrovascular Disorders	Yes	3531 (51.6)	233 (53.9)	3765 (51.7)
Dyslipidaemia	Yes	982 (14.3)	95 (22.0)	1077 (14.8)
Depression	Yes	506 (7.4)	29 (6.7)	536 (7.4)
Renal Disorders	Yes	303 (4.4)	33 (7.6)	336 (4.6)
Pacemaker implanted	Yes	2373 (34.6)	99 (22.9)	2474 (34.0)

Data are reported as mean (SD) or frequency (%).

Table 2. Characteristics of epileptic patients within and over lamotrigine therapeutic range

Variable	Level	Non-toxic (n=290)	Toxic (n=142)	P
Sex	Male	159 (54.8)	73 (51.4)	0.57086
Age	Mean (SD)	72.8 (8.4)	72.5 (7.4)	0.68085
Diabetes	Yes	44 (15.2)	12 (8.5)	0.07165
Cancer	Yes	57 (19.7)	17 (12.0)	0.06358
Arthritis	Yes	8 (2.8)	7 (4.9)	0.37992
Coronary Heart Disease	Yes	55 (19.0)	27 (19.0)	1.00000
Dementia	Yes	3.8 (13.1)	20 (14.1)	0.89598
Respiratory Disorders	Yes	84 (29.0)	47 (33.1)	0.44339
Ulcer	Yes	23 (7.9)	10 (7.0)	0.89349
Cerebrovascular Disorders	Yes	153 (52.8)	80 (56.3)	0.54959
Dyslipidaemia	Yes	63 (21.7)	32 (22.5)	0.94615
Depression	Yes	18 (6.2)	11 (7.7)	0.69209
Renal Disorders	Yes	17 (5.9)	16 (11.3)	0.07279
Pacemaker implanted	Yes	70 (24.1)	29 (20.4)	0.45855

Data are reported as mean (SD) or frequency (%).

Pharmacometric models

Seven pharmacometric models satisfying inclusion and exclusion criteria that describe the population pharmacokinetics of lamotrigine were identified, one of which was derived from the systematic search and the rest were from the review paper [18]. Characteristics of the study population for each model were provided in **Supplementary Table 1**.

Application of pharmacometric models to real-world data

Four pharmacometric models successfully predicted individual and population lamotrigine concentrations, while three models failed to perform prediction due to convergence issues. Compared with population prediction, the individual prediction had a stronger correlation with observed plasma concentration as the density closely follows the trend line (**Figure 1**). The individual prediction had a lower absolute percentage error compared with population prediction (**Figure 2**) for all the models. Therefore, the individual prediction was prioritized for the pharmacological substantiation of lamotrigine-related death. Among these four pharmacometric models, the

model by *Chavez et al* [29]had the lowest absolute prediction error for individual prediction with 14.25% [95% CI: 11.68-16.23] and, therefore, it was used to predict plasma concentrations at death/end of the follow-up.

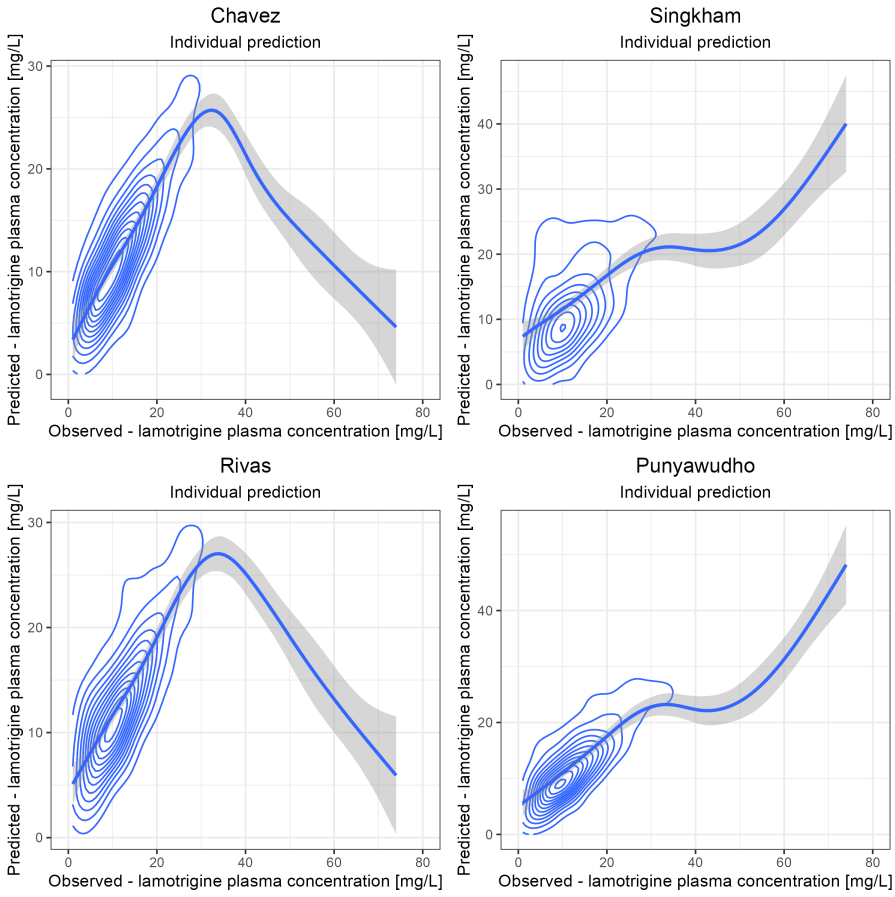

Figure 1. Two-dimensional density plots with contour lines and trend lines of population/individual predictions versus observed plasma concentrations of lamotrigine for four pharmacometric models.

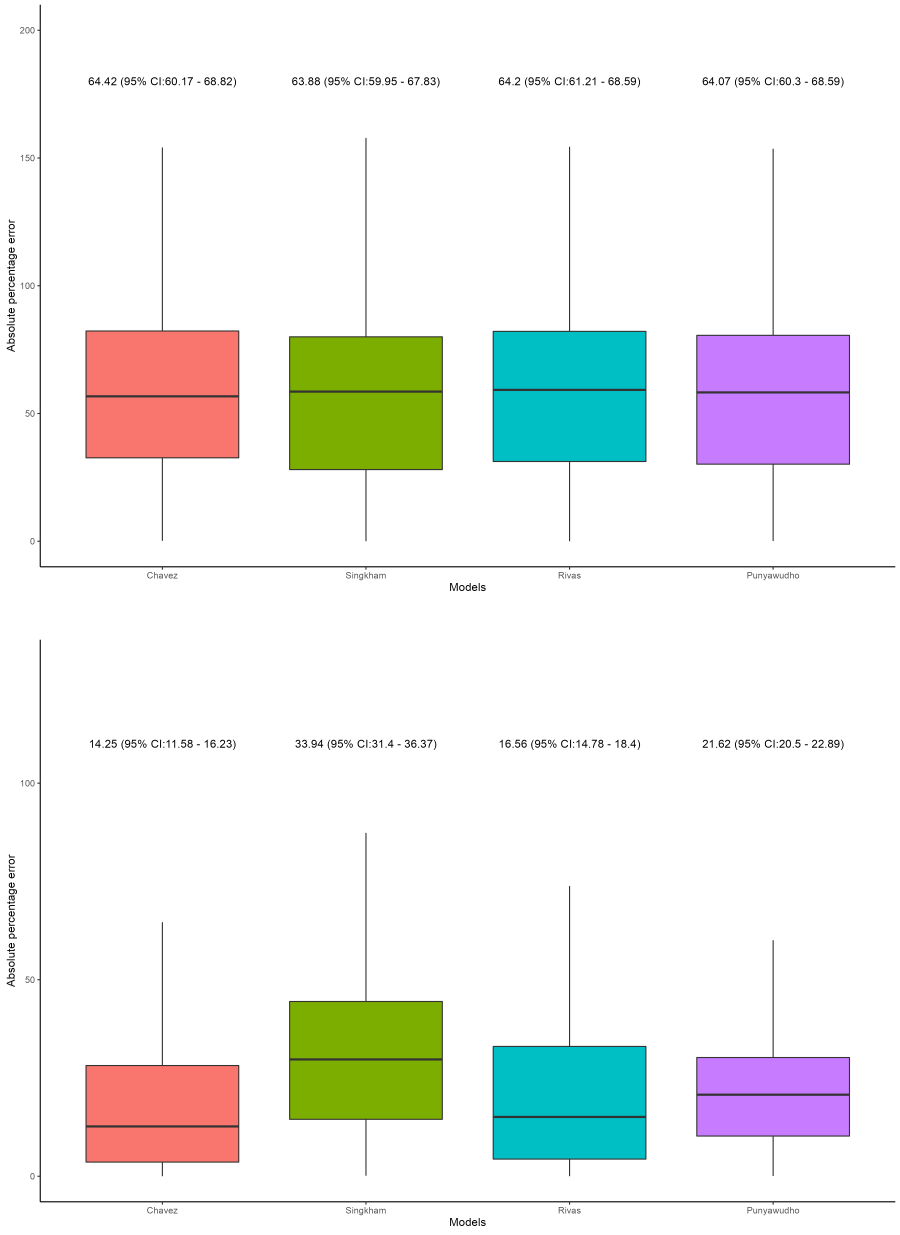

Figure 2. Bar plots of absolute percentage error for population (up) and individual (down) prediction of four pharmacometric models.

Pharmacological substantiation

Based on the individual prediction derived from the model by *Chavez et al*[29], among individuals who died, 10 were in the non-toxic range (n=290, 3.45%) and 16 in the toxic one (n=142, 11.27%). The median plasma concentration for the group within the non-toxic range was 9 mg/L (interquartile range: 6-12 mg/L) and for the group within the toxic range was 21 mg/L (interquartile range: 16-28 mg/L). Cardiovascular diseases were the cause of death in 44% and 60% of people who died in the non-toxic and toxic groups, respectively. The IRR of mortality between the toxic group and non-toxic group was 3.37 [95% CI: 1.44-8.32] and the cumulative incidence of all-cause mortality exponentially increased outside the therapeutic range (**Figure 3**). The cumulative hazard of all-cause mortality was significantly higher in the toxic compared with the non-toxic group (**Figure 4**). After propensity score matching of individuals (i.e., overlapping 99%) with lamotrigine concentration and those without, the densities between the two groups nearly fully overlapped compared with the overlapping before matching of 70% (**Supplementary figures 1 and 2**).

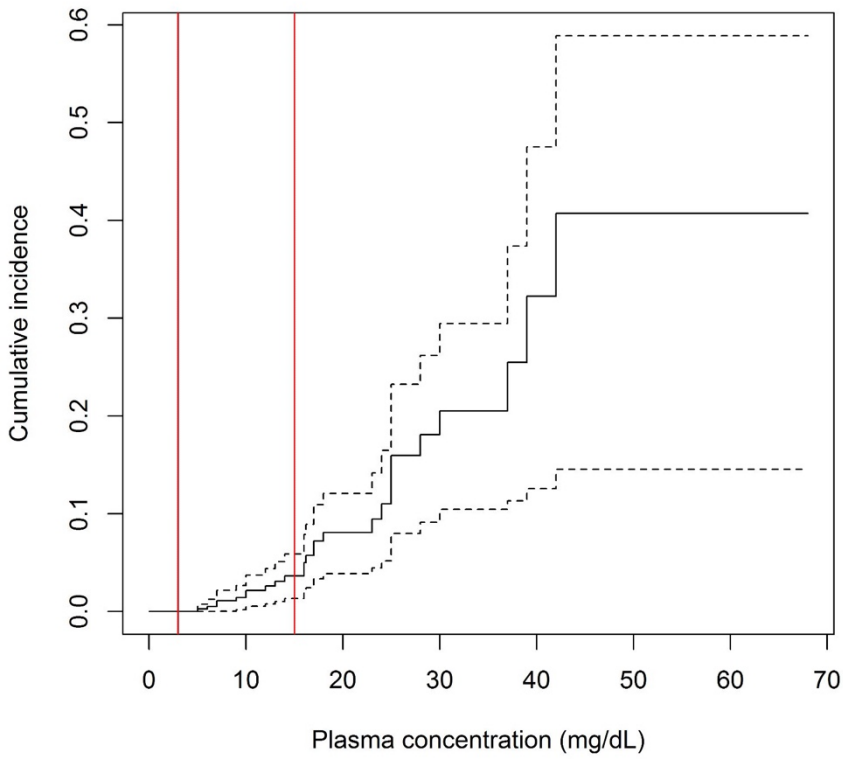

Figure 3. Cumulative incidence curve of all-cause mortality versus plasma concentration. The left horizontal red line indicated lower bound of therapeutic range of lamotrigine (3 mg/L) and the right horizontal red line indicated upper bound of therapeutic range of lamotrigine (15 mg/L). Dotted line = 95% Confidence interval.

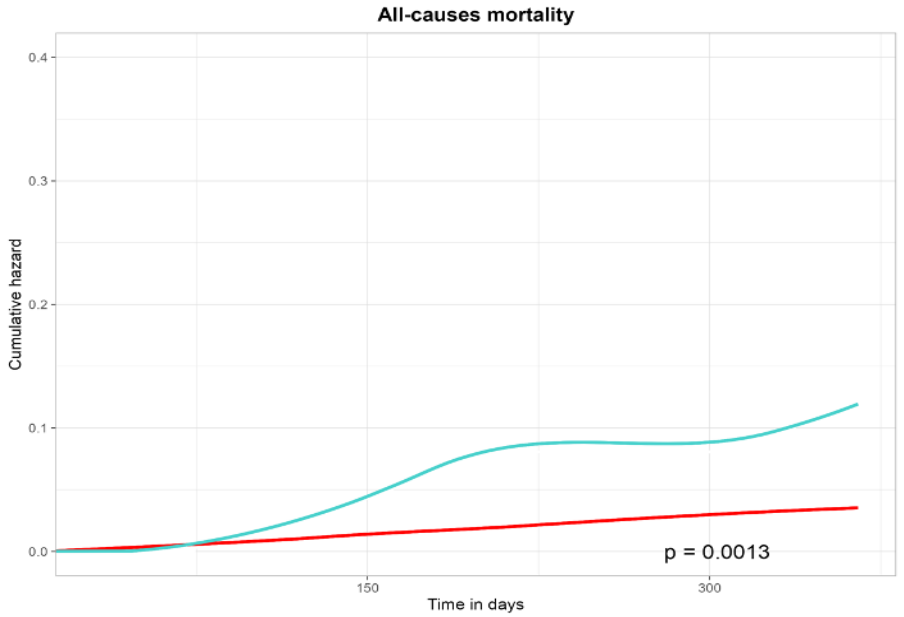

Figure 4. Cumulative hazard of all-cause mortality over time. The red curve is for individuals with therapeutic range and the blue curve is for individuals with toxic range.

Discussion

In this study, we applied a novel framework, PHARMACOM-EPI to real-world data to predict individual plasma concentrations of lamotrigine, which were subsequently categorized into non-toxic and toxic groups for individuals with plasma measurements. We found that individuals within the toxic group had a higher incidence of all-cause and cardiovascular mortality compared with individuals within the non-toxic group. For the first time, it was feasible to use data on plasma concentration levels and a new framework to confirm toxicity hypotheses with administrative and real-world healthcare data. The approach was applied to a case of lamotrigine's triggered cardiovascular death, which had not been previously clarified.
This result suggests that QRS alterations are mainly related to the dose-dependent inhibiting effects of lamotrigine on the sodium channel. [30] In the heart, sodium channels modulate the voltage threshold and the duration of action potentials, thus contributing to conduction and cellular excitability. [31] A key difference between neuronal and cardiac action potentials is their duration: in humans, in the central nervous system, it is between 1 and 10 ms [32], whereas in cardiac ventricles it may vary up to 450 ms. [33] Therefore, any sodium channel isoform sensitive to lamotrigine in the heart will have a much longer inactivation time. In individuals with tachycardia, this mechanism of action enhances an anti-arrhythmic effect. However, in individuals without tachycardia, the increase in the refractory period may cause bradycardia and other related cardiac arrhythmias. Concurrently, late sodium current contributes to longer QT intervals and may thus trigger arrhythmias. [31]

The warning of the FDA on lamotrigine [4] warranted clinical studies: multiple studies on healthcare registries were then performed. However, their results did not clarify whether there was an increased risk of the overall-mortality compared to other antiseizure medications, both in the general adult population [34–36] and in older individuals. [37,38] Our study is the first observational study to use nationwide real-world data for predicting plasma concentration to investigate the association between plasma concentrations of lamotrigine and its related toxicity [39,40]. We found that some patients experienced fatal effects within the therapeutic range, which may be explained by inter-patient variability. [41] Several individual features such as body weight, gender, duration of therapy, and genetic polymorphisms can influence serum levels of lamotrigine, which is why therapeutic drug monitoring of antiepileptic drugs is strongly recommended.

[18] The importance of inter-individual variability among patients might explain the better prediction we found of individual-patient pharmacometric models, which considered individual demographic characteristics reported in our sample.

Strengths and limitations

One of the strengths of our study is the application of a novel framework along with real-world data. Our analysis can therefore be considered appropriate to better explore issues raised by Health Authorities. For instance, we were able to include a wide sample of individuals aged over 65 years (mean age 70 years) and this criterion was based on the FDA's warning concerning the increased risk of arrhythmias and cardiac death mostly in patients with heart diseases. [4] Individuals aged over 65 years that use lamotrigine and have pre-existing cardiovascular disorders are preferable for investigating our aims for the following reasons. 1) The incidence of epilepsy has a bimodal distribution with the highest risk in the older people. [42] 2) In the older population, cerebrovascular diseases (e.g. stroke) are the most common cause of epilepsy and seizures. [43] 3) Age-related changes in body composition and function and the co-existence of epilepsy with other chronic diseases complicates clinical treatment and increases the risk of clinically relevant drug-drug interaction and pharmacokinetics issues which, in turn, increase the risk of reaching toxic plasma concentrations. [44–46].

The major limitation of our study is that we could not assess the relationship between mortality and plasma concentration in all patients using lamotrigine in the Danish registry, since only 432 cases had at least one serum measurement. Therefore, the results indicating the toxic range of lamotrigine associated with a higher incidence of mortality should be inferred cautiously to individuals aged over 65 years without plasma measurements in the Danish register-based cohort. Moreover, in real-world data, there usually are missing covariates such as genetic profiles, but we were able to impute them based on available literature and multiple imputation.

Conclusion

By using our novel framework PHARMACOMEPI, we found strong evidence to support our hypothesis that the increased risk of all-cause and cardiovascular death among older lamotrigine users was associated with a toxic plasma concentration of lamotrigine.

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